PREPARE-ABC

SupPoRtive Exercise Programmes for Accelerating REcovery after major ABdominal Cancer surgery (PREPARE-ABC)

A multicentre, 3 arm, parallel randomised controlled trial of standard care alone versus standard care plus supervised hospital based exercise and standard care plus supported home-based exercise pre and post hospital discharge in cancer patients awaiting curative colorectal cancer surgery.

Version	8.0
Date	23 June 2020
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust
Trial registration	ISRCTN82233115
NRES #	16/EE/0190

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1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 3. It describes the PREPARE-ABC trial, sponsored by Norfolk and Norwich University Hospitals NHS Foundation Trust and co-ordinated by NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at NCTU.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template includes the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials (Chan et al 2013). The SPIRIT Statement Explanation and Elaboration document can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP), the UK Data Protection Act and General Data Protection Regulation (GDPR), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach if necessary within the Sponsors timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

Norfolk and Norwich University Hospitals NHS Foundation Trust is the trial sponsor and has delegated the overall management of the PREPARE-ABC trial jointly to the Co-CIs and NCTU. Queries relating to sponsorship of this trial should be addressed to the Co-CIs, Director, NCTU, or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN82233115
Date of Registration in Primary Registry	07/07/2016
Secondary Identifying Numbers	NIHR HTA 14/192/53 NNUH Ref Number: 200804 REN Number: R200647 NU Ref: RPJ01780
Source of Monetary or Material Support	This trial is funded by NIHR Health Technology Assessment Programme
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust
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Contact for Clinical Queries	Mr James Hernon James.hernon@nnuh.nhs.uk 01603 287688 Consultant General and Colorectal Surgeon General Surgery Norfolk and Norwich University Hospitals NHS Foundation Trust Norwich Research Park, Norwich, NR4 7UY, UK
Contact for Information on the Exercise Interventions	Prof John Saxton john.saxton@northumbria.ac.uk 0191 227 3371 Head, Department of Sport, Exercise and Rehabilitation Faculty of Health and Life Sciences Room 259, Northumberland Building Northumbria University Newcastle Upon Tyne, NE1 8ST, UK
Public Title	SupPoRtive Exercise Programmes for Accelerating REcovery after major ABdominal Cancer surgery (PREPARE-ABC)
Scientific Title	SupPoRtive Exercise Programmes for Accelerating REcovery after major ABdominal Cancer surgery (PREPARE-ABC) – A multicentre, 3 arm, parallel randomised controlled trial of standard care alone versus standard care plus supervised hospital based exercise and standard care plus supported home-based exercise pre and post hospital discharge in cancer patients awaiting curative colorectal cancer surgery.
Countries of Recruitment	United Kingdom and Ireland
Health Condition(s) or Problem(s) Studied	Post-operative recovery in patients awaiting curative colorectal cancer surgery.
Intervention(s)	**Arm A** Hospital-Based Supervised exercise programme consisting of: Pre-surgery: Initial 45 minute exercise counselling incorporating behaviour modification techniques. Patients will be offered three sessions per week of aerobic interval exercise on a cycle ergometer over 3-4 weeks prior to their procedure (aim is to achieve 12 sessions). In

	addition, patients will undertake twice weekly resistance exercise. Exercise programmes will be tailored to each patient, taking previous level of activity, mobility and any barriers to exercise into consideration. Post-surgery: 6 weeks post-surgery to 12 months post-randomisation: Patients will be encouraged to comply with current physical activity recommendations: 150 minutes of moderate intensity aerobic exercise per week (brisk walking / cycling) and two sessions of resistance exercise per week. They will also be sign posted to local exercise facilities and receive monthly supervised 'booster' exercise sessions. **Arm B** Home-Based Supported exercise Pre-surgery: Initial 45 minute exercise counselling incorporating behaviour modification techniques. Patients will then be encouraged to comply with current physical activity recommendations, which will form the basis of the home exercise programme: a minimum of 150 minutes of moderate intensity aerobic exercise per week (brisk walking / cycling) and two sessions of resistance exercise. Exercise programmes will be tailored to each patient, taking previous level of activity, mobility and any barriers to exercise into consideration. Patients will receive weekly 15 minute telephone support from a member of the Trial Intervention Team to encourage compliance with the exercise programme. Post-surgery: 6 weeks post-surgery to 12 months post-randomisation: Patients will be encouraged to comply with current physical activity recommendations and sign posted to local exercise facilities and receive monthly 15 minute motivational telephone calls from a member of the Trial Intervention Team. **Arm C** Standard care/Treatment as Usual Treatment as Usual (TAU) comprising the patient information leaflet only. No other information relating to peri-operative exercise will be offered, consistent with current practice.
Key Inclusion and Exclusion Criteria	Target population: NHS patients awaiting a curative elective colorectal resection for cancer. **Inclusion Criteria:** 1. Male and female participants ≥ 18 years old 2. Awaiting a curative elective colorectal resection for cancer

	3. American Society of Anaesthesiologists physical status I-III (ASA, 2014) 4. Able and willing to provide informed consent 5. Understand verbal and written instructions in English 6. Patients who are already participating (or have participated) in other trials may be eligible, but this must be agreed in advance by the relevant trial teams. Trials where there is already an agreement in place, are listed in section 5.3.1.4 **Exclusion Criteria:** 1. Contra-indications to exercise (e.g. lower limb amputation without prosthesis, bone, joint or muscle problem which may be exacerbated by exercise, chronic lung disease causing desaturation with exercise or shortness of breath at rest, severe psychiatric health problems) 2. Cardiovascular contra-indications (e.g. unstable angina, acute left ventricular failure, uncontrolled cardiac arrhythmias, uncontrolled hypertension, cardiac event in the previous 6 weeks, cerebral vascular disease resulting in transient ischaemic attacks) 3. Participation in other treatment trials, where this has not been agreed in advance with both trial teams.
Study Type	A multi-centre, single blind (assessors only), 3-arm randomised controlled trial recruiting cancer patients awaiting curative colorectal cancer surgery from colorectal units in the UK and Ireland
Date of First Enrolment	1 November 2016
Target Sample Size	1146 patients
Primary Outcome(s)	Two primary outcomes will be used: **Short term outcome:** Morbidity for standard care versus hospital based and standard care versus home based exercise interventions (both exercise interventions are in addition to treatment as usual). Assessed by Clavien-Dindo classification of post-operative complications Measured 30 days post-operatively **Long Term Outcome:** Health-related quality of life at 12 months for standard care versus hospital based and standard versus home based exercise interventions. Assessed by the Medical Outcomes Study Short-Form Health Questionnaire (SF-36) 12 months post-randomisation.

Key Secondary Outcomes	The following secondary outcomes will be assessed for standard care versus hospital based and standard care versus home based exercise interventions: **Pre-operative outcomes** The following outcomes will evaluate response to the intervention in the pre-operative phase of the study only. Outcome: Pre-operative change in cardiopulmonary exercise test (CPET). Metric: Change in cardiopulmonary fitness variables, as measured using an incremental CPET between 4 weeks prior to surgery and shortly before surgery (e.g. peak VO2; anaerobic/ventilatory threshold; VE/VCO2; oxygen pulse). Outcome: Pre-operative change in grip strength. Metric: Change in grip strength as measured using a standard digital grip strength dynamometer **Post-operative outcomes:** Outcome: Length of hospital stay Metric: Duration of stay from date of operation to discharge immediately following operation Outcome: Fitness for discharge Metric: Patients will be considered fit for discharge if they meet the following criteria: oral intake established to meet nutritional needs; independence (or return to previous level of function) in washing, dressing and mobility; post-operative pain control met with oral analgesia; passing flatus. Clinical teams managing the patient's post-operative care and blinded to treatment intervention will be responsible for assessing fitness for discharge. Outcome: Morbidity at discharge Metric: Measured by Clavien-Dindo classification of post-operative complications, assessed by the clinical / research team who are blinded to the treatment intervention. Outcome: 90-day all cause re-admission rate Metric: 90-day all cause re-admission will be recorded by the local research teams, from date of operation. Outcome: 90-day post-operative mortality, Metric: Defined as percentage of patients who died on or up to 90 days following date of operation. Outcome: Post-operative change in grip strength. Metric: Change in grip strength as measured using a standard digital grip strength dynamometer

	The following outcomes will be evaluated at baseline, 6 months and 12 months post-randomisation: Outcome: Physical activity behaviour Metric: Measured using modified Godin Leisure Time Exercise Questionnaire (modified) Outcome: Psychological health status, Metrics: Measured using Hospital Anxiety and Depression Scale (HADS) Outcome: Self-efficacy and motivation for exercise, Metric: Measured using four brief questionnaires: Self-Efficacy for Exercise scale, Behavioural Regulation in Exercise Questionnaire (BREQ-3), Exercise Identity Scale (EIS) Outcomes: cost effectiveness and quality of life Metric: Patient reported health resource use costs Hospital reported costs Metric: Health related Quality of Life (HRQoL) as reported using EuroQol EQ5D-5L

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
James Hernon	NNUH	Co-Chief Investigator
John Saxton	Northumbria University	Co-Chief Investigator
Ann Marie Swart	NCTU	NCTU Director
Erika Sims	NCTU	NCTU Operations Manager
Juliet High	NCTU	NCTU Senior Trial Manager
Allan Clark	NCTU	Statistician
David Turner	NCTU	Senior Health Economist
Lisa Irvine	NCTU	Health Economist
Megan Jones	NCTU	NCTU Trial Manager
Edward Pring	LNWUH	Ancillary Study Co-investigator
Ian Jenkins	LNWUH	Ancillary Study Co-investigator/Site PI
Katrina Knight	NHS GGC	Ancillary Study Co-investigator
Campbell Roxburgh	NHS GGC	Ancillary Study Co-investigator/Site PI

1.4.2 Role of trial sponsor

Name	Affiliation	Role
Julie Dawson	NNUH	Sponsors Representative
Professor Alastair Forbes	UEA & NNUH	Chief of Research and Innovation

1.4.3 Trial Team

Name	Affiliation	Role
James Hernon	NNUH	Co-Chief Investigator
John Saxton	Northumbria University	Co-Chief Investigator
Megan Jones	NCTU	NCTU Trial Manager
Gregory Howard	NCTU	NCTU Trial Manager
Erika Sims	NCTU	NCTU Operations Manager
Juliet High	NCTU	NCTU Senior Trial Manager
Kerry Dresser	NCTU	NCTU Trial Assistant
Martin Pond	NCTU	Head of Data Management
Antony Colles	NCTU	Senior Data Programmer
Katharine Goodall	NCTU	Data Assistant
Elena Hojas Garcia	NCTU	Monitoring and Safety Coordinator
David Turner	NCTU	Senior Health Economist
Allan Clark	NCTU	Senior Statistician
Susan Stirling	NCTU	Statistician
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Jamie Murdoch	NCTU	Process Evaluation Lead
Jane McCulloch	NCTU	Process Evaluation Research Associate
Anna Varley	NCTU	Process Evaluation Research Associate

Jenni Naisby	Northumbria University	Process Evaluation Research Associate
Katherine Baker	Northumbria University	Process Evaluation Research Associate
Laura Thomas	Liverpool John Moores University	Exercise Psychologist

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
James Hernon	NNUH	Co-Chief Investigator and clinical lead
John Saxton	Northumbria University	Co-Chief Investigator and exercise physiology lead
Ann Marie Swart	NCTU	NCTU Director; Overall responsibility for trial delivery at NCTU
David Turner	NCTU	Senior Health Economist. Overall responsibility for health economic evaluation.
Allan Clark	NCTU	Senior Statistician. Overall responsibility for statistical design and analysis.
Lisa Irvine	NCTU	Health Economist. Responsible for conducting health economic evaluation.
Jamie Murdoch	NCTU	Process Evaluation lead. Responsible for design, conduct and analysis of interviews, focus groups and observations undertaken as part of the process evaluation.
Erika Sims	NCTU	NCTU Operations Manager; responsible for operational oversight of the trial
Anna Wordley	CHU	Nurse Consultant (GI Cancer Services). Principal Investigator and Co-Applicant
Neil Smart	RDEH	Principal Investigator and Co-Applicant
Robert Dennis	PSH	Principal Investigator and Co-Applicant
Paul Ziprin	ICL	Principal Investigator and Co-Applicant
Seamus Kelly	NHC	Principal Investigator and Co-Applicant
Samson Tou	DTH	Principal Investigator and Co-Applicant
Jonathan Lund	UoN	Principal Investigator and Co-Applicant
Alan Stephens		Public and Patient Involvement Representative and Co-Applicant
Nicola Fearnhead	CUH	Principal Investigator and Co-Applicant
Simon Bach	QEHB	Principal Investigator and Co-Applicant
Jurgens Nortje	NNUH	Principal Investigator and Co-Applicant
Laura Thomas	Northumbria University	Exercise Psychologist
Ann Russell		Public and Patient Involvement Representative

1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Professor Dean Harris	Singleton Hospital	Independent Chair
Dr Anna Campbell	Edinburgh Napier University	Independent Member
Jessica Whibley	The Royal Marsden NHS Foundation Trust	Independent Member

1.4.6 Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Mr Dale Vimalachandran	Western Cheshire Primary Care NHS Trust	Chair
Dr Mona Kanaan	University of York	Statistician
Dr Jane Hook	Leeds Teaching Hospitals NHS Trust	Member

2 Trial Diagram

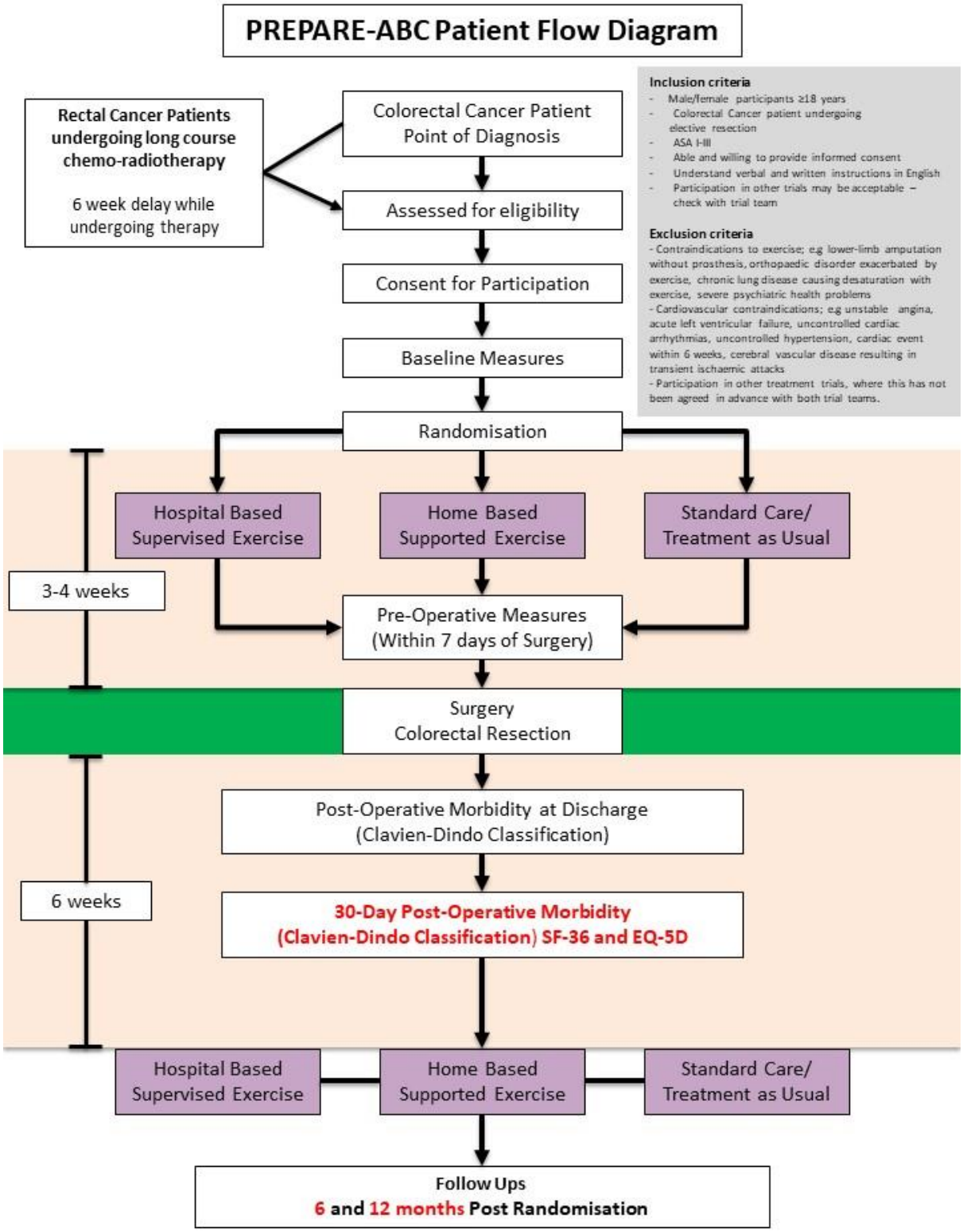

Figure 1. PREPARE-ABC patient flow diagram.

3 Abbreviations

AE	Adverse Event
ASA	American Society of Anaesthesiologists
CHU	Colchester Hospital University NHS Foundation Trust
CI	Chief Investigator
Co-CI	Co Chief Investigator
CPET	Cardiopulmonary Exercise Test
CRF	Case Report Form
CRP	Serum C-Reactive Protein
CSRI	Client Service Receipt Inventory
CTA	Clinical Trial Authorisation
CUH	Cambridge University Hospitals NHS Foundation Trust
CWT	Cancer Waiting Times
DTH	Derby Teaching Hospitals
eCRF	Electronic Case Report Form
EU	European Union
GCP	Good Clinical Practice
HEAP	Health Economics Analysis Plan
HR QoL	Health Related Quality of Life
HRR	Heart rate reserve
ICH	International Conference on Harmonisation
ICL	Imperial College London
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ITT	Intention to Treat
LCRN	Local Clinical Research Networks
LNWUH	London North West University Healthcare NHS Trust
mGPS	Modified Glasgow Prognostic Score
MHRA	Medicines and Healthcare products Regulatory Agency
NCRN	National Cancer Research Networks
NCTU	Norwich Clinical Trials Unit
NHC	Northumbria Healthcare NHS Foundation Trust
NHS GGC	NHS Greater Glasgow and Clyde
NIHR	National Institute for Health Research
NLR	Neutrophil : lymphocyte ratio
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
PI	Principal Investigator
PIS	Participant Information Sheet
POM	Post-Operative Morbidity
PSH	Peterborough and Stamford Hospitals NHS Foundation Trust
PSSRU	Personal Social Services Research Unit
QA	Quality Assurance
QC	Quality Control
QALYs	Quality Adjusted Life Years
QEHB	Queen Elizabeth Hospital Birmingham
QMMP	Quality Management and Monitoring Plan
REC	Research Ethics Committee
RDEH	Royal Devon and Exeter Hospital
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIR	Systemic Inflammatory Response
SSA	Site Specific Approval
TAU	Treatment as usual
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UEA	University of East Anglia
UoN	University of Nottingham

4 Introduction

4.1 Background and Rationale

Colorectal cancer is the fourth commonest cancer in the UK with 40,000 patients diagnosed per year (CRUK, 2015). The current standard, and best-proven, treatment for this patient group is a surgical resection with approximately 25,000 patients in the UK undergoing a major abdominal resection each year. A colorectal resection, while offering the best chance of cancer survival, results in significant post-operative mortality (3-5%) (ACPGBI, 2014) and reduced quality of life (Santa Mina et al, 2014).

Post–Operative Morbidities (POMs) following major abdominal surgery place a significant psychological and health burden on patients, while impacting greatly on available healthcare resources. The increased utilization of healthcare is evident in both primary and secondary care. POM results in a significant elevation in the required level of inpatient care, with extended stays in the intensive care unit, the need for multiple returns to theatre for re-operation, increased radiological interventions and an increase in the average length of hospital stay from 5-7 days, to weeks and months. Post-discharge, patients have increased rates of post-discharge re-admission to hospital and require greater input from district and community stoma care nurses and primary care physicians.

Complication rates within the reported literature vary as a function of patient selection within studies, time/intensity of follow up, and definition of complication. Grocott et al (2007) showed that in patients undergoing major abdominal surgery, 78% have a POM / complication at day 5 with 50% continuing at day 8. They indicate that morbidity at or beyond day 5 results in longer post-operative stays and increased resource utilisation. A review of 1200 gastrointestinal procedures (389 colorectal) to determine the cost burden of complications in the US demonstrated a complication rate of 53.8% at day 30 (Vonlanthen et al., 2011). The most recently reported UK colorectal trial of patients undergoing open vs. laparoscopic resectional colorectal surgery - EnROL (Kennedy et al., 2014) reported a total complication rate of 34%. This lower complication rate may be attributable to differences in the severity of the study population as EnROL required patients to be suitable for laparoscopic surgery. The 2014 National Bowel Cancer Audit (NBOCA, 2014) indicates that in England and Wales only 50% of elective colorectal resections are performed laparoscopically. It is therefore likely that the complication rate in EnROL may not be equally comparable to an unselected group of patients undergoing a colorectal resection. A recent small scale feasibility study comprising of a 3 month consecutive review of patients (98 elective) undergoing a colorectal resection (either open or laparoscopic) demonstrated that 55% of elective patients had a significant POM within 30 days.

Post-surgical complications significantly increase the cost of patient care and have marked financial implication to the NHS, in some cases costing five times as much, where complications lead to POMs, compared to patients undergoing a similar operation with no complications (Vonlanthen et al., 2011). Individual patient level costing provided by the NNUH places the average cost of a colorectal resection at £7,500. Estimates suggest that a post-surgical complication could conservatively double the cost of post-operative care. Therefore interventions to reduce post-surgical complications could provide significant cost-savings to the NHS.

Considerable research has focussed on improving post-surgical outcomes. The Improving Surgical Outcomes Group reported a correlation between the level of cardiopulmonary fitness and post-operative clinical outcomes (ISOG, 2005). This suggests that maximising pre-operative cardiopulmonary fitness could improve post-surgical outcomes. Systematic review evidence suggests that exercise training can improve

cardiopulmonary fitness in the short period available prior to surgery (Santa Mina et al., 2014, Singh et al., 2013) and can reduce the risk of post-operative complications following major cardiac and abdominal surgery (Valkenet, 2011). However, most studies to date have been of low to moderate quality and more robust definitive randomized controlled trials are needed.

The Anaesthesia and Perioperative Care Priority Setting Partnership (May 2015), a collaborative involving patients, the public and clinical professionals, identified 'How can pre-operative exercise or fitness training, including physiotherapy, improve outcomes after surgery' as one of the top 10 priorities for peri-operative care research (NIAA, 2015).

The health benefits of physical activity for cancer patients are recognized by the National Cancer Survivor Initiative (NCSI), a partnership between NHS England and Macmillan Cancer Support (NCSI, 2014). The NCSI places the promotion of post-operative physical activity as one of its four main pillars in the rehabilitation of cancer patients. However lifestyle / exercise advice is not yet routinely given to cancer patients. This is, in the main, due to reluctance of health professionals to discuss lifestyle factors with cancer patients due to limitations in knowledge and an inadequacy in the available evidence (Miles et al., 2010).

The role of pre-operative exercise 'prehabilitation' in improving pre-operative cardiopulmonary fitness and its impact on surgical outcomes remain poorly defined, as does the effectiveness of different exercise delivery methods (e.g. hospital-based supervised programmes vs. supported home-based exercised programmes). While self-directed home-based exercise can be delivered in a more cost effective manner, a more intensive exercise intervention (hospital-based supervised) may be required to evoke the clinically meaningful changes required to impact on post-operative morbidity and HR QoL. (Unpublished pilot study REC: 13/EE/0319, IRAS Project ID 129902)

4.1.1 Rationale for choice of interventions

Two interventions will be evaluated. Intervention 1 is pre- and post-operative hospital-supervised exercise training. Intervention 2 is pre- and post-operative home-supported exercise training.

The hospital based exercise will comprise, in the pre-operative period, a 45 minute exercise counselling session followed by 12 aerobic interval exercise sessions 3-4 weeks prior to surgery and two home-based resistance exercise sessions per week. Post-hospital discharge there will be monthly booster supervised sessions up to 12 months post-randomisation and patients will be encouraged to comply with the NHS England Chief Medical Officer current physical activity recommendations throughout this time period.

The home based exercise intervention will comprise, in the pre-operative period, a 45 minute exercise counselling session followed by a home-exercise programme where participants will be encouraged to comply with current physical activity recommendations: a minimum of 150 minutes of moderate aerobic exercise per week, in the 3-4 weeks prior to surgery and two resistance exercise sessions per week. Post-hospital discharge participants should continue their exercise regime and will receive monthly telephone support from a member of the Trial Intervention Team up to 12 months post-randomisation.

Systematic review evidence suggests that the optimal aerobic exercise intensity for inducing cardiorespiratory adaptations in sedentary older adults is 66-73% heart rate reserve (HRR; ~66-73% VO2 max; Borg RPE Scale: 13-15) (Huang et al., 2015). As aerobic interval exercise programmes (incorporating interpolated rest intervals) enable a greater volume of higher intensity exercise to be achieved, this system of exercise training can help elderly individuals who are less accustomed to physical exertion to maintain

exercise intensity in the optimal range for cardiorespiratory adaptations. This is supported by our recent feasibility work, which showed that cancer patients tolerate and respond well to pre-operative aerobic interval training programmes at 60-80% HRR (Borg RPE Scale: 13-15) using a cycle ergometer, with improvements in anaerobic threshold and peak VO2 being evident after a median of 6 exercise sessions over 3-4 weeks.

Cardiopulmonary exercise testing (CPET) will be used as an objective method of evaluating oxygen transport and utilization during a dynamic exercise challenge and it reflects the ability of the cardiopulmonary system to deliver oxygen to the tissues under conditions of stress. Evidence from systematic reviews and more recent studies suggests that CPET variables can reliably predict patients at increased risk of post-operative complications and morbidity following major surgery for abdominal cancers, aortic aneurysm repair, thoracic surgery and colonic surgery (Benzo et al., 2007, Smith et al., 2009, Thompson et al., 2011, West et al., 2013).

Small-scale feasibility studies have reported improvements in functional outcomes following supported home-based aerobic exercise in conjunction with progressive resistance exercise in cancer patients before surgery (Timmerman et al., 2011, Carli et al., 2010, Li et al., 2013). There is also evidence that such programmes can be successfully continued soon after major cancer surgery (Li et al., 2013, Gillis et al., 2012) and patients who engaged in structured exercise programmes before and after their operation had significantly better functional capacity up to 8 weeks post-surgery (Li et al., 2013). A recent prospective study using similar methodology, pre-operative aerobic interval training, delivered as a hospital based intervention for colorectal cancer patients following post-chemoradiotherapy demonstrated changes in physical fitness following a short programme (6 weeks) of exercise and reported over 90% compliance (West et al., 2015).

The potential role of post-operative exercise programmes for helping to optimise long-term recovery after major abdominal cancer surgery has also been recognized. Preliminary evidence suggests that pre-operative exercise promotes better adherence to post-operative exercise (Gillis et al., 2012) and epidemiological data shows that a physically active lifestyle after curative colorectal cancer treatment enhances survival (Meyerhardt et al., 2006).

This trial aims to produce definitive evidence of the clinical efficacy of pre- and post-operative exercise training on short and longer-term recovery outcomes in cancer patients undergoing major lower-gastrointestinal surgery. In addition, the trial will provide valuable cost-effectiveness data to underpin new clinical guidance on how to implement exercise programmes for cancer patients awaiting and recovering from major abdominal surgery.

4.1.2 Explanation for choice of comparator

The comparator for both Intervention 1 and Intervention 2 is standard care/treatment as usual. Patients are not given advice on exercise pre- or post-surgery other than what is routinely offered within the Trust.

4.2 Objectives

There are three trial arms:

- Arm A – Hospital based supervised exercise
- Arm B – Home based supported exercise
- Arm C – Standard care, treatment as usual

There are two primary research hypotheses:

- hospital-supervised exercise training in the pre- and post-operative period, in addition to standard care, leads to fewer post-operative complications by day 30 and improved HR-QoL, measured via SF-36, at 12 months post-randomisation versus standard care alone.

- home-supported exercise training in the pre- and post-operative period, in addition to standard care, leads to fewer post-operative complications by day 30 and improved HR-QoL, measured via SF-36, at 12 months post-randomisation versus standard care alone.

The exploratory research hypothesis is that pre- and post-operative hospital-supervised exercise training will lead to greater improvements in cardiopulmonary fitness and fewer post-operative complications, leading to greater improvements in HR-QoL, measured via SF-36, after 12 months, than pre- and post-operative home-supported exercise.

4.2.1 Primary objectives

1. To establish the effectiveness and cost-effectiveness of hospital-supervised and home supported pre-operative and post-hospital discharge exercise programmes in relation to short-term recovery outcomes and HR-QoL, measured via SF-36, at 12 months in cancer patients undergoing major colorectal cancer surgery.
2. To generate robust research and cost-effectiveness data that will underpin clinical guidance on how exercise programmes should be implemented in the routine management of patients undergoing major colorectal cancer surgery.

4.3 Trial Design

This is a multi-centre, 3-arm, randomised controlled trial, to investigate the clinical and cost effectiveness of exercise interventions for cancer patients awaiting curative, elected colorectal cancer surgery.

4.3.1 Internal Pilot Phase

An internal pilot phase has been designed to allow an assessment of stop/go criteria for progression to a full trial. At the end of this phase a decision will be made by the funder, in consultation with the TSC and IDMC, on whether or not to proceed with the trial. Recruitment will continue while data on patients in the internal pilot are analysed and reviewed by the TSC and IDMC and a funder decision is obtained. As an internal pilot, all data collected on study participants will be included in the further analyses.

The objectives of the internal pilot phase (to run for 1 year following 6 month site set-up) are to confirm feasibility of:

1. Site set-up
2. Site recruitment
3. Acceptability of the exercise intervention
4. Adherence to the respective exercise interventions

The stop/go criteria are:

1. Site set-up – 75% of sites open at recruitment month 12.
2. At least 30% of eligible patients recruited to the study. This will be closely monitored throughout the recruitment phase of the trial.

3. Recruitment – demonstrate that 50% of sites can reach recruitment rates sufficient to sustain the phase II study, i.e. 4-5 patients per month during recruitment months 10-12.
4. Meaningful adherence to the study arms (minimum of 6 pre-operative supervised sessions in at least 70% of patients and 50% of post-operative booster sessions in at least 70% of patients.

5 Methods

5.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this to the Co-Chief Investigators and NCTU.

5.1.1 Study Setting

Participants will be identified from colorectal units, at point of diagnosis. Initially the following sites will be opened, but with the intention to open further sites as the study progresses. The collaborating sites identified at study start-up are: Norfolk and Norwich University Hospitals NHS Foundation Trust, Northumbria Healthcare NHS Foundation Trust, Sheffield Teaching Hospitals NHS Foundation Trust, Cambridge University Hospitals NHS Foundation Trust, University Hospitals Birmingham NHS Foundation Trust, Derby Teaching Hospitals NHS Foundation Trust, Imperial College Healthcare NHS Trust, Royal Devon and Exeter NHS Foundation Trust, Western General Hospital Edinburgh, Central Manchester University Hospitals NHS Foundation Trust, Peterborough and Stamford Hospitals NHS Foundation Trust and Colchester Hospital University NHS Foundation Trust.

The exercise interventions will take place in hospitals and in the community depending on the treatment arm to which the participant is allocated.

5.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol, and at least one person to lead the Trial Intervention Team will be identified from each site to undergo intensive training on how to deliver the intervention.

To participate in the PREPARE-ABC trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the PREPARE-ABC Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician (surgeon, anaesthetist or physiotherapist) is committed to take Principal Investigator responsibility.
- Suitably trained staff are available to recruit participants, enter data and provide support
- A named Trial Intervention Team Lead available to fulfil the requirements of the trial
- A named lead to coordinate CPET testing (if available)
- The site is able to identify a suitable number of patients, this will vary depending on the location and size of the hospital, the study has been designed to include and represent a good cross section of sites. Recruitment targets will be discussed with each centre.
- The site is not currently delivering either the hospital supervised or home based intervention as standard care

Trial sites meeting eligibility criteria and that are accepted by the TMG as being suitable to recruit to the trial, will be issued with the PREPARE-ABC Trial Master File (TMF) documentation to use when applying for Site-Specific Approval (SSA) or local institutional approval as applicable.

5.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The Investigator(s) must be willing to sign an Investigator Agreement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

5.1.2.2 Resourcing at site

The Investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (i.e. the Investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to NCTU.

5.2 Site approval and activation

On receipt of the signed Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site activation. Sites will not be permitted to recruit any patients until a letter for activation has been issued. The trial manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and by the Research Ethics Committee (REC) who gave a favourable opinion and/or Institutional Review Board (IRB). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at NCTU.

A list of activated sites may be obtained from the trial manager.

5.3 Participants

5.3.1 Eligibility Criteria

There will be no exceptions (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

5.3.1.1 Participant Inclusion Criteria

1. Male and female participants ≥ 18 years old
2. Awaiting a curative elective colorectal resection for cancer
3. American Society of Anaesthesiologists physical status I-III (ASA, 2014)
4. Able and willing to provide informed consent
5. Understand verbal and written instructions in English
6. Patients who are already participating (or have participated within 4 weeks of randomisation) in other trials may be eligible, but this must be agreed in advance by the relevant trial teams. Trials where there is already an agreement in place, are listed in section 5.3.1.4

Where potential patients present with metastases, on the condition there is a potentially curative treatment plan (clinical intervention to treat primary and metastases with curative intent) the patient, may be approached for inclusion in the study providing all other eligibility criteria are met.

5.3.1.2 Participant Exclusion Criteria

1. Contra-indications to exercise (e.g. lower limb amputation without prosthesis, bone, joint or muscle problem which may be exacerbated by exercise, chronic lung disease causing desaturation with exercise or shortness of breath at rest, severe psychiatric health problems)
2. Cardiovascular contraindications (e.g. unstable angina, acute left ventricular failure, uncontrolled cardiac arrhythmias, uncontrolled hypertension, cardiac event in the previous 6 weeks, cerebral vascular disease resulting in transient ischaemic attacks)
3. Participation in other treatment trials, where this has not been agreed in advance with both trial teams.

The exclusion criteria outlined above are intended to exclude patients for whom exercise is unsafe. The conditions listed above are provided for example purposes only and are not an exhaustive list. It is the responsibility of the PI, or sub-investigator delegated the appropriate responsibility, to determine whether it is safe for a patient to exercise following a review of their medical history. Patients who are deemed to be in a stable condition following previous cardiovascular conditions (eg stable and treated arrhythmia such as atrial fibrillation) may be approached for the study providing they meet all other eligibility criteria.

5.3.1.3 Eligibility Criteria for Individuals Performing the Interventions

The Trial Intervention Team includes physiotherapists and any other staff responsible for delivery of exercise interventions/advice/motivation or phone calls relating to this must be identified on the delegation log and must have received study specific training to ensure consistency in the way exercise interventions are delivered at all sites. Training will be delivered through a training package including either an initial face to face session or remote training via training videos, slides and follow-up phone calls with the co-CI and exercise psychologist, refresher meetings and a physiotherapy manual.

For the purposes of the trial, a member of the Trial Intervention Team, is any member of the research team trained to deliver the trial intervention at site. These will include physiotherapists, registered nurses, exercise specialists, exercise scientists, exercise trainers, exercise practitioners or health care assistants. This list is not exhaustive, and other appropriately trained members of the team can deliver the intervention at the agreement of the Trial Intervention lead and PI of the site, and the co-CIs. A named Trial Intervention lead at each site must have responsibility for the delivery of the intervention at their site.

5.3.1.4 Co-enrolment Guidance

The exercise intervention is intended in addition, rather than to replace any current treatments, therapies or surgery. It is therefore appropriate to include participants who have previously or are currently participating

in other treatment trials. Participants in the trials listed below will be permitted to participate in PREPARE-ABC, providing they satisfy all other eligibility criteria. This is not an exhaustive list, if the patient has participated in another trial, within 4 weeks of entering this trial, not listed here, please contact NCTU to discuss this, prior to their recruitment. Participation in another trial includes follow-up visits regardless of whether the patient has discontinued trial treatment or not.

List of trials where co-enrolment has been agreed by both trial teams:

- Add-Aspirin: "A Phase III, double blind, placebo-controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours". EudraCT: 2013-004398-28
- ARISTOTLE: "A phase III trial comparing standard versus novel chemoradiation treatment (CRT) as a pre-operative treatment for magnetic resonance imaging (MRI)-defined locally advanced rectal cancer" EudraCT: 2008-005782-59
- ASPEN: "Asymptomatic Small Pancreatic Endocrine Neoplasms" NCT03084770
- BEST-2: "Evaluation of a Non-Endoscopic Immunocytological Device (Cytosponge) for Barrett's Esophagus Screening in a Case-Control Study" ISRCTN12730505
- CAPP3: "A randomised double blind dose non-inferiority trial of a daily dose of 600mg versus 300mg versus 100mg of enteric coated aspirin as a cancer preventive in carriers of a germline pathological mismatch repair gene defect, Lynch Syndrome. Project 3 in the Cancer Prevention Programme" ISRCTN: 16261285
- CHHiP: "A phase III, multicentre, randomised controlled trial to see whether hypofractionated radiotherapy schedules (fewer fractions in higher doses) for localised prostate cancer could improve the therapeutic ratio by either improving tumour control or reducing normal tissue side effects" ISRCTN: 97182923
- CIPHER: "UK Cohort study to Investigate the prevention of Parastomal HERnia (CIPHER) Phase A Protocol: Understanding surgery and current practice in stoma formation and developing Patient Reported Outcome Measures for Parastomal Hernia to inform Phase B of CIPHER" IRAS: 201605
- DALES: "Drug Allergy Labels In The Elective Surgical Population". 3-day snapshot study exploring the prevalence and impact of patient-reported drug allergies. IRAS: 232512
- ELGAR: "Optimising drinking following colorectal surgery: a feasibility study". IRAS: 247996
- EPIC-Norfolk: "The European Prospective Investigation of Cancer"
- EPOCH/TheraSphere: "An open-label, prospective, multicenter, randomized, Phase III clinical trial evaluating yttrium-90 transarterial radioembolization with TheraSphere® in patients with metastatic colorectal carcinoma (mCRC) of the liver who have failed first-line chemotherapy" NCT01483027.
- Ethicon Enseal X1: "A Prospective, Multi-Center Evaluation of the ENSEAL X1 Large Jaw Tissue Sealer" NCT03441178.
- University of Highlands /NHS Highland Feasibility Study: "Physical activity for people recovering from bowel cancer, or with inflammatory bowel disease who have a stoma" ISRCTN58613962
- IBD BioResource: Part of the NIHR BioResource for Translational Research. Nationally-accessible resource of over 100,000 volunteers from the general population and patients with common and rare diseases. REC Reference: 14/EE/1112.
- LABSS: The Lothian Bowel Symptoms Study.
- MAR-CUTIS: "Randomised, open-label, multicenter, comparator-controlled clinical study to compare MAR-CUTIS with Dermabond Advanced in closure of surgical incisions and lacerations ≤15 cm". NCT03688880.
- MINSTREL: "MRI in Staging Rectal Polyp Planes". NCT02532803.

- NeoART: “Phase II randomised, double blind, placebo controlled trial to determine if a 2 week course of pre-operative oral artesunate (an established antimalarial drug) can reduce the risk of cancer recurring after surgery in patients with Stage II/III operable bowel cancer” NCT02633098.
- OCCAMS : “Multicentre Study to determine predictive & prognostic biomarkers & therapeutic target for Oesophagael & junctional Adenocarcimona including genome sequencing”
- POLAR-A: “Preventive Treatment of OxaLiplatin Induced peripherAl neuRopathy in Adjuvant Colorectal Cancer” NCT04034355
- PQIP: “Perioperative Quality Improvement Programme” IRAS NUMBER 215928PREVENTT: “A randomised double-blind controlled phase III study to compare the efficacy and safety of intravenous ferric carboxymaltose with placebo in patients with anaemia undergoing major open abdominal surgery” EudraCT: 2012-002786-35
- PRISM: “A pragmatic randomised controlled trial of continuous positive airway pressure (CPAP) to prevent respirator complications and improve survival following major abdominal surgery” REC reference 15/LO/1595
- Quantifying Disease Burden: “Quantifying disease burden in patients with cancer using tumour-specific genomic rearrangements”. Wellcome Trust funded.
- RECREATE: “Development and evaluation of strategies to reduce sedentary behaviour in patients after stroke and improve outcomes”.
- ROSSINI 2 “Reduction of Surgical Site Infection using several Novel Interventions.” 16/31/123
- SAILOR: “Surgery alone in rectal cancer” ISRCTN02406823
- SCOTTY: “Detailed genetic analysis of blood and tissue removed from tumours from individuals who have developed bowel cancer at a young age and also blood samples from each of their parents”. IRAS ID 200475
- SCOVIDS: Scottish Vitamin D Study.
- SOCCS3: Study looking at genes of people in Scotland who have developed bowel cancer, to see if the information can identify other people at risk of developing the disease and fully understand the genetic basis of bowel cancer" REC reference: 11/SS/0109.
- STAMPEDE: “Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy”. NCT00268476.
- SuMMiT-D: “Support through mobile messaging and digital health technology for diabetes.” ISRCTN13404264.
- TARGET FAL01: “Translational Analysis and Research in Gynaecological Epithelial Tissues – Fallopian Tubes.”
- TRACC: “Tracking mutations in cell free tumour DNA to predict Relapse in early colorectal cancer”. NCT00827671
- TRIGGER: “Magnetic Resonance Tumour Regression Grade (mrTRG) as a Novel Biomarker to Stratify Management of Good and Poor Responders to Chemoradiotherapy: A Rectal Cancer Multicentre Randomised Control Trial” NCT02704520. **Please note:** only patients randomised to the **TRIGGER control arm** are eligible for co-enrolment on PREPARE-ABC.
- University of Birmingham: “Tracking mutations in cell free tumour DNA to predict relapse in early colorectal cancer”. IRAS ID 210641100,000 Genomes Project: https://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project/
- VODECA: “Volatile Organic Compounds for Detection of Colorectal Cancer.” CRUK

List of trials where both trial teams have agreed **co-enrolment is not permitted**:

- ALLEGRO: "A placebo controlled randomised trial of intravenous lidocaine in accelerating gastrointestinal recovery after colorectal surgery"ISRCTN52352431.
- STAR-TREC: "Can we save the rectum by watchful waiting or transanal surgery following (chemo)radiotherapy versus total mesorectal excision for early rectal cancer?" EudraCT: 2016-000862-49

The above list is current to the date on the front of this protocol, please contact NCTU for the most recent list.

5.4 Interventions

There are three trial arms:

- Arm A - Hospital based supervised exercise
- Arm B - Home based supported exercise
- Arm C – Standard care, treatment as usual

Patients undergoing curative surgery for colorectal cancer are not routinely investigated with a CPET to assess cardiopulmonary fitness, or given any advice/support with respect to exercise prior to surgery.
All patients, once consented to the trial, will have a baseline CPET and another CPET immediately prior (within 7 days) of their planned colorectal surgery.

Data on planned type of surgery (laparoscopic or open) and tumour histological stage data at 30 days post-surgery will be collected and recorded on the relevant pages of the eCRF. If a patient is found to have had a benign tumour post-operatively, they may continue to participate in the study as per protocol.

If the patient is undergoing rectal cancer long course chemo-radiotherapy, this should be carried out before the patient is consented to the trial. There would then be a 6 week delay to their participation whilst they undergo chemo-radiotherapy. Once chemo-radiotherapy is complete, the patient will be approached for informed consent and a baseline assessments performed.

Patients will then receive, in addition to treatment as usual, the interventions below, depending on their treatment arm allocation during randomisation.

5.4.1 Arm A – Hospital Based Supervised Exercise

Note: subject to temporary suspension, see Section 5.12 COVID-19 Impact and Adaptation.

Baseline CPET will be performed.
Pre-surgery: Initial 45 minute exercise counselling session, incorporating behaviour modification techniques. Patients will be offered three sessions per week of aerobic interval exercise on a on a cycle ergometer over 3-4 weeks prior to their procedure to achieve up to 12 one hour sessions. If there is a delay in surgery for any reason, patients will be offered more supervised exercise sessions up to the date of their operation. Exercise programmes will be tailored to each patient, taking previous level of activity, mobility and any barriers to exercise into consideration.

Each session will comprise 6 x 5 minute repetitions at 60-80% of heart rate reserve (~60-80% peak VO_2; Borg RPE Scale 13-15 (Borg 1970) with 2.5 minute rest intervals. There will also be 2 home-based resistance exercise sessions per week.

Pre-surgery CPET to be completed not more than 7 days prior to planned surgery.

6 weeks post-surgery to 12 months post-randomisation: patients will be sign posted to local exercise facilities and receive monthly 'booster' exercise sessions, incorporating aerobic interval exercise and resistance training (as in the pre-operative period). Patients will be encouraged to comply with current physical activity recommendations of completing 150 minutes of moderate intensity aerobic exercise per week (e.g. brisk walking, cycling etc.), measured at 13-15 on the Borg RPE Scale (Borg 1970), and two sessions of resistance exercise per week.

Patients will be provided with a pedometer to record step counts throughout the study in the exercise diary provided.

5.4.1.1 Modifications, Interruptions and Discontinuations

The exercise routine can be interrupted or discontinued if the trial team feel there are any contraindications to the patient continuing. Interruptions and discontinuations should be noted in the eCRF. Exercise intensity and duration will be closely controlled and will only be progressed through discussion with a member of the Trial Intervention Team.

5.4.2 Arm B – Supported Home Based Exercise

Baseline CPET will be performed.

Pre-Surgery: Initial 45 minute exercise counselling session, incorporating behaviour modification techniques, followed by a home exercise programme achieving a minimum of 150 minutes of moderate intensity aerobic exercise per week (e.g. brisk walking/jogging/cycling/swimming, etc.) measured at 13-15 on the Borg RPE Scale (Borg 1970) and two sessions of resistance exercise. This is in accordance with current Chief Medical Officer guidelines (DOH, 2011, UK Physical activity guidelines). Exercise programmes will be tailored to each patient, taking previous level of activity, mobility and any barriers to exercise into consideration. Patients will receive weekly 15 minute telephone support from a member of the Trial Intervention Team to encourage compliance with the exercise programme. If there is a delay in surgery for any reason, patients will be instructed to maintain their home exercise programme up to the date of their operation.

Pre-surgery CPET to be completed not more than 7 days prior to planned surgery.

6 weeks post-surgery to 12 months post-randomisation: Patients will be sign posted to local exercise facilities and receive monthly 15 minute motivational telephone calls from a member of the Trial Intervention Team to encourage completion of home exercise programme of 150 minutes of moderate intensity aerobic exercise per week, measured at 13-15 on the Borg RPE Scale (Borg 1970), and two sessions of resistance exercise.

Patients will be provided with a pedometer to record step counts throughout the study in the exercise diary provided.

5.4.2.1 Modifications, Interruptions and Discontinuations

The exercise routine can be interrupted or discontinued if the trial team feel there are any contraindications to the patient continuing. Interruptions and discontinuations should be noted in the eCRF. Exercise intensity

and duration will be closely controlled and will only be progressed through discussion with a member of the Trial Intervention Team.

5.4.3 Arm C – Standard Care, Treatment as Usual

Apart from two pre-surgery CPETs, patients randomised to the control arm of the study will follow the current standard care pathway – no further information or advice will be offered with respect to pre- or post-operative exercise outside of standard care for the Trust.

As part of the process evaluation, an assessment of current practice will be performed.

5.4.4 Compliance and Adherence

Although participants in the exercise groups will be encouraged to complete the trial according to the protocol, ultimately it will be the participant's own choice how dedicated they are to completing the exercise. Participants in the hospital based group will have their exercise visits recorded in the eCRF. For the home based group, general compliance questions will be asked during the scheduled phone calls and responses recorded in the eCRF. In addition, participants will record their self-directed exercise in an exercise diary, with daily step counts also being recorded via the pedometer.

Compliance will be reviewed at the pre-surgery visit immediately prior to operation and at 6 and 12 months post-randomisation, for patients in the intervention groups.

The exercise counselling sessions and supporting telephone calls will be designed to increase and maintain motivation for exercise.

During the initial consent process, participants will be offered the option of signing up to a subscription based email service that will be used to distribute newsletters with information on progress of the trial. The production and circulation of these updates will be coordinated by NCTU.

5.4.5 Concomitant Care

All patients will receive treatment as usual for their colorectal cancer surgery and after care, including treatment for post-operative morbidities regardless of randomisation into this trial.

5.4.6 Cancer waiting times (CWT) for trial participants

Department of Health Guidelines for Cancer Waiting Times (CWT) in the UK give strict requirements for time to first definitive treatment date for curative colorectal surgery. The date of consent given by a patient entering this trial will be the first definitive treatment date for this purpose, as clarified by the NIHR National Cancer Research Network (NCRN). The pre-operative intervention part of this study has been designed to fit within CWT targets. Surgery should not be unduly delayed as a result of entry into the study.

5.4.7 Trial participants with anaemia

Haemoglobin levels will be tested routinely as part of standard of care at the time of referral to the site (typically within 28 days of randomisation) and at the patients pre-operative assessment. Patients presenting with anaemia should be treated according to local policy and procedures.

For the purposes of this study, the date of test and haemoglobin level should be recorded on the relevant pages of the eCRF, at both baseline and pre-operatively, as well as details of any treatment for anaemia administered.

5.4.8 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable adverse event/s from the exercise intervention
- Inter-current illness that prevents further exercise
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

5.5 Outcomes

5.5.1 Primary Outcomes

Two primary outcomes will be used:

Short Term Outcome; 30-day morbidity

30-day morbidity will be assessed using the Clavien-Dindo classification of post-operative complications (Clavien et al. 2009), for standard care versus hospital based and standard care versus home based interventions. Data will be collected 30 days post-operation by the clinical team, who are blinded to treatment intervention, using a structured set of questions during the routine post-operative review.

Long Term Outcome; health related quality of life

Health-related quality of life will be assessed by the Medical Outcomes Study Health Questionnaire (SF-36) (Ware et al., 1992) (total score) at 12 months post-randomisation, for standard care versus hospital based and standard care versus home based interventions.

5.5.2 Secondary Outcomes

The following secondary outcomes will be assessed for standard care versus hospital based and standard care versus home based interventions:

Pre-operative outcomes

The following outcomes will evaluate response to the intervention in the pre-operative phase of the study only:

- Pre-operative change in cardiopulmonary exercise testing (CPET) variables (Smith et al., 2009)

The following parameters (at a minimum) will be determined using standard techniques at maximum exercise tolerance: peak VO2; Anaerobic/Ventilatory Threshold; VE/VCO2; maximal oxygen pulse (oxygen consumption per heartbeat).

- Pre-operative change in grip strength.

Change in grip strength as measured using a standard digital grip strength dynamometer

Post-operative outcomes

The following outcomes will evaluate the effects of pre- and post-operative exercise training on post-operative recovery outcomes:

- Length of hospital stay

Duration of stay as measured from date of operation to discharge immediately following operation. This will be recorded by the local research team.

- Health related quality of life subscales at 6 and 12 months

The mental and physical health scale from the SF-36.

- Fitness for discharge

Patients will be considered fit for discharge if they meet the following criteria: oral intake established to meet nutritional needs; independence (or return to previous level of function) in washing, dressing and mobility; post-operative pain control met with oral analgesia; passing flatus. Clinical teams managing the patient's post-operative care and blinded to treatment intervention will be responsible for assessing fitness for discharge.

- Morbidity at discharge

Measured by Clavien-Dindo classification of post-operative complications, assessed by clinical team who are blinded to treatment intervention. See appendix 1 for table showing classifications.

- 90-day all cause re-admission rate

90-day all cause re-admission will be recorded by the local research teams (from date of operation)

- 90-day post-operative mortality

Defined as percentage of patients who died on or up to 90 days following date of operation.

- Post-operative change in grip strength

Change in grip strength as measured using a standard digital grip strength dynamometer at 30 days following operation, 6 and 12 months post-randomisation.

Baseline, 6 and 12 months post-randomisation

The following measures will be recorded at baseline and at 6 and 12 months:

- Psychological health status

Measured using Hospital Anxiety and Depression Scale (HADS) (Zigmond et al., 1983), both anxiety and depression sub-scales.

- Self-efficacy and motivation for exercise

Measured using three brief questionnaires:
-Self-Efficacy for Exercise scale, focuses on the self-efficacy expectations for exercise for older adults;
-Behavioural Regulation in Exercise Questionnaire (BREQ-3), assess motives for physical exercise;
-Exercise Identity Scale (EIS), assesses extent to which motivation for exercise has been internalised into one's identity

- Physical activity behaviour

Measured using a modified Godin Leisure Time Exercise Questionnaire (Godin et al., 1985)

Cost effectiveness outcomes

- Health resource use

Community care monitored using a study-specific participant-completed questionnaire at baseline, 6 months and 12 months follow-up. Secondary care monitored from hospital records at 12 months follow-up.

- Health related Quality of Life (HR-QoL)

The EuroQol measures health related quality of life (HR-QoL) using questions in five domains (the EQ-5D-5L), plus the EuroQol visual analogue scale (Herdman et al 2011). EQ-5D measured at baseline, 30 days post-operation, 6 and 12 months post-randomisation

5.6 Participant Timeline

Table 1. Schedule of enrolment, interventions, and assessments.

	Pre-Surgery						Post-Surgery			Post randomisation	
Visit	**Screening (Diagnosis)**	**Baseline**	**Randomisation - 4 weeks to surgery**	**Pre-surgery -4 to -3 weeks**	**Pre-surgery ≤ 7 days**		**Post-surgery discharge ~ 5-7 days**	**Post-surgery 30 days[1]**	**Post-surgery 6 weeks**	**6 month follow up visit[2]**	**12 month follow up visit[2]**
Consent	X										
Eligibility	X										
Demographics		X									
Medical history		X									
Hb result and document treatment for anaemia.		X			X						
Tumour histological stage								X			
CPET		X			X						
SF36 Questionnaire		X						X		X	X
EQ-5D-5L Questionnaire		X						X		X	X
Hospital Anxiety and Depression Scale		X								X	X
Self-Efficacy for Exercise Scale		X								X	X
Behavioural Regulation in Exercise Questionnaire (BREQ-3)		X								X	X
Exercise Identity Scale (EIS)		X								X	X
Godin Leisure Time Exercise Questionnaire (modified)		X								X	X
Resource Use questionnaire		X								X	X
Grip Strength		X			X			X		X	X
Full blood count and liver function tests[3]		X									
CT scans (staging/cancer surveillance)[3]		X								X	X
Randomise to Intervention			X								
Exercise Intervention (or TAU Arm C)				⟷	⟷				⟷	⟷	⟷
Record Adverse Events where applicable		⟷	⟷	⟷	⟷		⟷	⟷	⟷	⟷	⟷
Record POMs in eCRF							⟷	⟷			
POM Clavien–Dindo Classification							X	X			
Blinded assessment of fitness for discharge							X				
Review of adherence to exercise interventions (if applicable)					X					X	X

Surgery

[1] The 30 Days post-surgery visits may take place within -3 days and +7 days of the schedule.

[2] The 6 and 12 Month follow-up visits should take place within ±6 weeks of the schedule

[3] Results/images of FBC, LFTs and CT scans taken during standard care assessments uploaded onto eCRF for sub-study analyses

5.6.1 Patient Assessments

5.6.1.1 Screening visit

Written informed consent to enter and be randomised into the trial must be obtained from participants, after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as usual standard of care.

If the PI or referring Co-I considers from a patient's medical notes that they may be eligible for the trial, the patient information sheet should be handed to the patient and they should be given adequate time to consider whether they wish to consent. This process must take place after diagnosis and once a decision to perform curative colorectal surgery has been reached, but should allow 3-4 weeks prior to surgery for the pre-surgery interventions to take place. If the patient is undergoing neo-adjuvant chemoradiotherapy, the treatment should be carried out before the patient is recruited to the study. If following the chemoradiotherapy clinical management plan is to proceed to a curative resection, the patient should then be approached for recruitment and randomisation to the study.

5.6.1.2 Baseline visit

Once the participant has given written informed consent, an initial CPET* should be performed.

If the participant is undergoing rectal cancer long course chemo-radiotherapy, this should be carried out before the baseline assessments.

All participants should have the following questions/questionnaires asked/administered; Quality of Life Questionnaires SF36 and EQ-5D-5L, Behavioural Regulation in Exercise Questionnaire (BREQ-3), Exercise Identity Scale (EIS), The Hospital Anxiety and Depression Scale, Self -Efficacy for Exercise Scale, modified version of Godin Leisure Time Exercise Questionnaire and Resource Use Questionnaire. Grip Strength should be measured using a standard digital grip strength dynamometer.

5.6.1.3 Randomisation

When the results of the CPET* are recorded and all baseline assessments have been completed, the option to randomise the participant will be available to the trial team. The participant should be randomised and this will decide the intervention they receive.

*Every effort should be made to ensure CPET data can be collected on each patient, but, if due to resource constraints or other exceptional circumstances, this would mean excluding a patient from the study, the patient may be randomised without CPET data. If a post-randomisation (within 7 days) baseline CPET is feasible prior to the start of the exercise intervention, the test should be completed and the results entered onto the eCRF at the baseline time point.

5.6.1.4 CPET guidance

For the purposes of this study, cardiopulmonary exercise tests should be completed as per standard local processes and procedures. However, the results should be uploaded onto the eCRF in breath-by-breath and/or 30 second average formats where possible.

If CPETs are carried out as part of standard care pre-surgical assessments, the results may be used for the baseline time point provided they are within 28 days of randomisation.

5.6.1.5 Pre-surgery treatment phase

Participants randomised to Arm A will receive:

Initial 45 minute exercise counselling session incorporating behaviour modification techniques, with the aim of raising awareness about the potential benefits of exercise and consequences of inactivity, decisional balance (positive/negative experiences of exercise, exercise preferences and overcoming fears about exercise, etc.), goal setting, self-regulation, safe physical exertion and practical advice for exercise. Patients will then be offered three sessions per week of aerobic interval exercise on a cycle ergometer over 3-4 weeks prior to their procedure to achieve up to 12 sessions. Patients are not required to attend a set minimum number of sessions but should be encouraged to attend as many pre-operative supervised exercise sessions as possible.

Each session will comprise 6 x 5 minute repetitions at 60-80% of heart rate reserve (~60-80% peak VO2; Borg RPE Scale 13-15 (Borg 1970), with 2.5 minute rest intervals. Heart rate, clinical signs, blood pressure and perceived exertion (via Borg RPE Scale) will be recorded regularly throughout exercise. The programme will be progressed as the patient becomes accustomed to exercise, by increasing the number of intervals to a maximum of 6 and /or adding further load to the cycle ergometer flywheel. Patients will receive instructions on how to complete an exercise diary for recording each exercise session (e.g. exercise modality, duration, intensity) and will be given a pedometer to record daily step counts.

There will also be 2 home-based resistance exercise sessions per week, using Thera-bands and body resistance, in accordance with current guidelines.

These sessions will be delivered by a member of the Trial Intervention Team who has had trial specific training to deliver these interventions consistently to all Arm A participants. Adherence to the exercise programme should be recorded in the eCRF, from pedometer data, patient participation/attendance and patient completed exercise diary. This is in addition to all other treatment as usual, offered prior to curative colorectal cancer surgery.

Participants randomised to Arm B will receive:

Initial 45 minute exercise counselling session incorporating behaviour modification techniques, with the aim of raising awareness about the potential benefits of exercise and consequences of inactivity, decisional balance (positive/negative experiences of exercise, exercise preferences and overcoming fears about exercise, etc.), goal setting, self-regulation, safe physical exertion and practical advice for exercise. This will be followed by a home exercise programme, aimed at achieving a minimum of 150 minutes of moderate intensity aerobic exercise per week (brisk walking/jogging/cycling/swimming, etc.), measured at 13-15 on the Borg RPE Scale (Borg 1970), and two sessions of resistance exercise (using Thera-bands and body weight, according to current guidelines). Exercise programmes will be tailored to each patient, taking previous level of activity, mobility and any barriers to exercise into consideration. Patients will also receive instructions on how to complete an exercise diary for recording each exercise session (e.g. exercise modality, duration, intensity) and will be given a pedometer to record daily step counts. Patients will receive weekly 15 minute telephone support from a member of the Trial Intervention Team to encourage compliance with the exercise programme.

These telephone calls will be made by a member of the Trial Intervention Team who has had trial specific training to deliver the intervention consistently to all Arm B participants. Adherence to the exercise programme will be recorded in the eCRF from pedometer data and patient completed exercise diaries. This is in addition to all other treatment as usual, offered prior to curative colorectal cancer surgery.

Participants randomised to Arm C will receive:
Other than the patient information leaflet, no other information relating to pre-operative exercise will be offered other than what is offered as part of standard care within the Trust. They will receive all other treatment as usual, offered prior to curative colorectal cancer surgery.

5.6.1.6 Within ≤7 days pre-surgery

All participants (all arms) must have their second CPET within 7 days prior to their curative surgery taking place, grip strength should be measured at the same time. If due to resource constraints or other exceptional circumstances, a second CPET is not possible, the patient can continue with data from one (or no) CPETs.

In the event that a patients surgery is postponed, the patient should continue with the exercise intervention, if randomised to an intervention arm, and proceed to surgery following rescheduling by the local clinical team.

5.6.1.7 Surgery

Surgery and after care to follow treatment as usual, with no further study interventions until 6 weeks post-surgery. All POMs and length of hospital stay to be recorded in patient notes and ultimately captured in the eCRF.

5.6.1.8 Post-surgery discharge

POM Clavien-Dindo Classification to be recorded from surgery completion to point of discharge. Fitness for discharge to be assessed by clinical team blinded to treatment intervention.

5.6.1.9 30 day post-surgery visit

30 day post-operative morbidity (Clavien-Dindo Classification) to be recorded from review of patient notes, from the date of discharge to the 30 days post-surgery, SF-36 and EQ-5D-5L questionnaires to be completed and grip strength (measured using a standard digital grip strength dynamometer) recorded. This visit may take within -3 days and +7 days of the schedule.

Post-operative morbidities re-experienced or worsened from the post-surgery inpatient stay should be re-recorded at the 30 day time point. Otherwise the recording of post-operative complications should not be duplicated.

5.6.1.10 6 week post-surgery to 12 month post-randomisation treatment phase

If a patient's return to exercise/usual activities is delayed due to post-operative complications, they may continue in the study and re-commence the exercise intervention once they are able. The protocol treatment interruption should be noted in the eCRF.

Participants randomised to Arm A will receive:

Information on the location of local exercise facilities and physical activity schemes in their local communities. Patients will be encouraged to comply with current physical activity recommendations of completing 150 minutes of moderate intensity aerobic exercise per week (e.g. brisk walking, cycling etc.), measured at 13-15 on the Borg RPE Scale (Borg 1970), and two sessions of resistance exercise per week.

Patients will also be offered supervised "booster" exercise sessions, approximately monthly until 12 months post-randomisation.

Each session will comprise 6 x 5 minute repetitions at 60-80% of heart rate reserve (~60-80% peak VO_2; Borg RPE Scale 13-15 (Borg 1970) with 2.5 minute rest intervals. There will also be 2 home-based resistance exercise sessions per week.

These sessions will be delivered by a member of the Trial Intervention Team who has had trial specific training to deliver these interventions consistently to all Arm A participants.

Adherence to the exercise programme will be recorded in the eCRF from pedometer data, patient participation/attendance and patient completed exercise diaries. All exercise intervention AEs will continue to be recorded.

This intervention is in addition to all other treatment as usual, offered post-curative colorectal cancer surgery.

Participants randomised to Arm B will receive:

Information on local exercise facilities and will be encouraged to engage in weekly self-directed exercise of 150 minutes of moderate intensity aerobic exercise per week (e.g. brisk walking, cycling etc.), measured at 13-15 on the Borg RPE Scale (Borg 1970), and two sessions of resistance exercise.

Patients will receive a 15 minute telephone contact support session each month with a member of the Trial Intervention Team, until 12 months post-randomisation. During each telephone support session, exercise progress will be reviewed with an opportunity for participants to discuss any issues. The Intervention Team will reinforce cognitive–behavioural strategies and ensure exercise diaries are being kept up-to-date and properly completed. These telephone calls will be made by a member of the Trial Intervention Team who has had trial specific training to deliver these interventions consistently to all Arm B participants.

Adherence to the exercise programme will be recorded in the eCRF from pedometer data and patient completed exercise diaries. All exercise intervention AEs will continue to be recorded.

This intervention is in addition to all other treatment as usual, offered post-curative colorectal cancer surgery.

Participants randomised to Arm C will receive:

No other information relating to post-operative exercise will be offered outside of current practice for the site. All other treatment as usual will be offered post-curative colorectal cancer surgery.

5.6.1.11 6 and 12 month post-randomisation follow-ups

All participants will be asked to complete questionnaires, these may be sent by post or online ahead of routine clinic visits at 6 and 12 months post-randomisation (patients to bring completed postal questionnaires with them to their visit and may request assistance if required at the visit). The following questionnaires will be administered; Quality of Life Questionnaires SF36 and EQ-5D-5L, Hospital Anxiety and Depression Scale, Self -Efficacy for Exercise Scale (qualitative assessment at 6 months), Behavioural Regulation in Exercise Questionnaire (BREQ-3), Exercise Identity Scale (EIS), modified Godin Leisure Time Exercise Questionnaire and Health Resource Use. Grip Strength (measured using a standard digital grip strength dynamometer) will be recorded, this will need to be completed at a clinic visit and sites will aim to coincide this with a routine visit at 6 and 12 months post-randomisation (± 6 weeks of schedule).

5.6.2 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they're no longer participating in the exercise intervention. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn from the trial. NCTU should be informed of the withdrawal in writing via email and completing the relevant pages on the eCRF. Anonymised data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early. All identifiable data will be removed.

Participants who stop trial follow-up early will not be replaced.

5.6.3 Participant Transfers

If a participant moves from the area making continued follow up at their consenting site inappropriate, every effort should be made for them to be followed at another participating trial site. Written consent should be taken at the new site and then a copy of the participant's eCRF should be provided to the new centre. Responsibility for the participant remains with the original consenting site until the new consent process is complete.

5.6.4 Loss to Follow-up

Contact details will be stored in the patient records and usual hospital procedures will be used to contact the patient about follow up visits. If this is without success, the patient will be recorded as lost to follow up. Number of patients where this has occurred will be monitored by the TMG.

5.6.5 Trial Closure

The end of the trial is defined as 12 months after the last patient's randomisation to the trial.

5.7 Sample Size

An overall sample of 1146 patients (randomised 1:1:1) provides 90% power.

Post-operative complications are evident in 55% of patients by day 30 in patients receiving standard care. To detect a 25% reduction (relative risk 0.75) between standard care and each of the exercise groups (90% power, alpha 2.5%) 343 patients are required in each arm, giving 1029, 10% attrition rate - Total 1146. Average SF 36 score at 1 year is 52 SD 10.To detect a 3 unit difference between standard

care and each of the exercise groups (90% Power, alpha 2.5%) requires 276 in each arm, 3 arms 828, 20% attrition rate. Total 1035.

5.8 Recruitment and Retention

5.8.1 Recruitment

Recruitment will be organised on a regional basis with the support of NIHR LCRNs. It is anticipated the identified trial sites will between them recruit 1146 patients over the trial period agreed with the funder and all other relevant parties.

Clinicians working in the coloproctology units identified for the trial will be asked to identify potential patients. They will make an assessment of the patient's eligibility to join the trial before referring/providing patient information to prospective patients.

One of the stop/go criteria of the internal pilot study is to assess recruitment and retention after recruitment month 12 (trial month 18).

Following patient consent and recruitment, the Research Nurse will send the participant's GP a letter to inform him/her of their patient's participation in the study.

5.8.1.1 Recruitment to process evaluation

Pre-trial patients and staff: Patients and staff will be invited by a member of the research team to consent to allowing a researcher to observe pre- and post-operative consultations. Patients consenting to participate will not be randomised and will not be included in the main trial.

Main trial patients and staff: Patients and staff consenting to participate in the main trial will be given the additional option to participate in the process evaluation and offered this during recruitment to the main trial. Patients and staff will have the option of consenting to both the observations and interviews, or to only one or other of these components. Patients consenting to or interested in participating in the process evaluation will be approached by the local research team or research associate about being observed and/or for a future interview post-completion of the study.

5.8.2 Retention

Adherence to the treatment arms:

In order to be successful patients will need to adhere to the treatment arm. A pre-trial feasibility study confirmed that 90% of patients adhered to the prescribed pre-operative exercise training. An attrition rate of 10% has been included in the power calculation for the short-term primary outcome: 30-day complication. An attrition rate of 20% has been used for long-term primary outcome in keeping with other exercise intervention studies performed previously by members of the research team.

The pre-trial feasibility work included a patient perspective, which concluded that the intensity and duration of the aerobic exercise sessions were acceptable to the majority of patients. This is supported by the literature (Mazurek et al., 2014, Statts, 2002, Bartlett et al., 2011)

5.9 Assignment of Intervention

5.9.1 Allocation

Randomisation to treatment arm will take place after the baseline CPET (see Patient Assessments section 5.6.1) and all baseline assessments have been completed.

5.9.1.1 Sequence generation

Eligible, consented participants will be randomised on a 1:1:1 basis to one of three trial arms using a web based randomisation process. The randomisation scheme will be generated by the NCTU data manager and notified by email to the study team. Allocation will be stratified by centre using permuted block randomisation with randomly varying block sizes.

5.9.1.2 Allocation concealment mechanism

The allocation is computer generated so will not be known prior to the participant being randomised. The patient will be allocated a participant number at time of consent. When the results of the baseline CPET have been obtained, and all other pre-designated questions completed in the eCRF, the research staff will then have access to the randomisation process for that participant. (See also special circumstances for CPET collection in section 5.6.1.3). The treatment allocation will be revealed and linked to that participant number. Allocation is concealed prior to randomisation to prevent treatment bias.

5.9.2 Blinding

Blinding is not applicable to the delivery of the intervention in this trial.

Post-operative morbidities are recorded in the patient notes as part of standard care procedures during the initial surgical admission and for any subsequent admissions experienced. CPETs will be performed by local Trust staff who conduct these assessments part of their standard care.

Both the clinical team(s) responsible for the initial surgical and any subsequent admissions and the CPET team are independent of the study and will therefore be blinded to treatment arm allocation. Local study staff will review patient notes and enter details of any post-operative complications, in accordance with the Clavien-Dindo classification method, and upload CPET results onto the eCRF.

5.10 Data Collection, Management and Analysis

5.10.1 Data Collection Methods

Data will be collected at the time-points indicated in the Participant Timeline (Section 5.6).

The research team will complete paper CRFs for questionnaires and assessments which take place during face to face visits. Standard care information should be recorded in patient notes. These data must then be entered onto a central database via an online system, access and training will be provided by NCTU. Identification logs, screening logs and enrolment logs will be kept locally, either in paper or electronic form. Patient questionnaires may be completed online if face-to-face or postal completion are unfeasible.

Source data worksheets will be drafted by the data manager with the CIs, trial statistician and PIs. These will be piloted and finalised. The database specification will be prepared by the NCTU data manager and approved by the CIs and trial statistician prior to the database being built. The database will be prepared by the NCTU Data Management Team and tested by the trial team and study site staff for user acceptability prior to the final system being launched.

Data collection, data entry and queries raised by a member of the PREPARE-ABC trial team will be conducted in line with NCTU and trial specific Data Management Standard Operating Procedures.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 1998 and GDPR (2018).

5.10.2 Data Management

Data will be entered in the approved PREPARE-ABC database by a member of the site staff identified on the delegation log.

Participants will be given a unique trial Participant Identification Number (PIN). Data will be entered under this identification number onto the central database stored on the servers based at NCTU. The database will be password protected and only accessible to members of the PREPARE-ABC trial team at NCTU. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

The database and coding frames have been developed by the Clinical Trial Manager in conjunction with NCTU. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data. Further details can be found in the PREPARE-ABC Data Management Plan.

After completion of the trial the database will be retained on the servers of NCTU for on-going analysis of secondary outcomes.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudo-anonymised Participant Identification Number, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 10 years unless otherwise advised by NCTU.

5.10.3 Non-Adherence and Non-Retention

The consent form will explain that if a participant wishes to withdraw from the study the data acquired prior to that point will be retained, unless the patient requests otherwise. Reason for withdrawal will be recorded, if given, as will loss to follow up.

Non-adherence to trial exercise procedures will be assessed by the Trial Intervention team and recorded in the eCRF.

5.10.4 Statistical Methods

5.10.4.1 Statistical Analysis Plan

A full Statistical Analysis Plan (SAP), and interim analysis plan(s) as required, will be developed between the trial statistician and Chief Investigators and agreed with the trial's governance committees.

5.10.4.2 Statistical Methods – Outcomes

Primary outcomes

- Total SF-36 score at 12 months post-randomisation; and
- The presence or absence of any morbidity at 30 days post-operation.

Secondary efficacy

- pre-operative outcomes: Cardiopulmonary exercise testing (CPET) variables; Grip strength
- post-operative outcomes: Length of hospital stay as measured from date of operation, time until fitness for discharge from date of operation, 90-day all cause re-admission rate from date of operation, 90 day post-operative mortality from date of operation, grip strength
- psychological health status: Hospital Anxiety and Depression Scale (HADS) at 6 and 12 months post-randomisation.
- Physical activity behaviour using the Godin Leisure time exercise questionnaire at 6 and 12 months
- EQ-5D-5L at 30 days post-operative, 6 and 12 months post-randomisation
- SF-36 at 30 days post-operative and 6 months post-randomisation
- SF-36 subscales, mental and physical health, at 6 and 12 months post-randomisation
- Self-efficacy and motivation for exercise using Self Efficacy for Exercise Scale, Behavioural Regulation in Exercise Questionnaire and Exercise Identity scale

5.10.4.3 Additional Analyses - Subgroup

No subgroup analyses are planned.

5.10.4.4 Additional Analyses

In addition to the efficacy analyses, analyses will be undertaken which will attempt to correlate the changes in outcomes with the changes in CPET and grip strength variables using multivariable regression models. Additionally, with the different exercise groups we will attempt to correlate the changes in outcomes with the adherence within the groups.

5.10.4.5 Analysis Population and Missing Data

The analyses population are defined as:

a) intention-to-treat: all randomised individuals regardless of adherence;

b) per-protocol: all randomised individuals who adhere to the study regime attending at least 50% of the hospital supervised exercise sessions or participate in at least 50% of scheduled phone calls with a member of the trial intervention team relative to the treatment arm they are allocated to.

c) safety population:

- Arm A – all randomised individuals who receive a manual and attended a minimum of one supervised exercise session
- Arm B – all randomised individuals who receive a manual
- Arm C - all randomised individuals

Missing data that occur in outcomes will be multiply imputed to increase precision of the treatment effect estimates. Sensitivity analyses will be conducted to assess the impact of the multiple imputations and a complete case analysis will also be conducted. All imputations will be examined to ensure sensible values are being generated. Imputation models will contain baseline measures, outcome measures and factors predictive of missing data.

5.10.4.6 Efficacy Analyses

The group comparisons which will be made are: a) TAU vs Hospital Based Supervised Exercise; b) TAU vs Home Based Supported Exercise; and c) Hospital Based Supervised Exercise vs Home Based Supported Exercise. The comparison a) and b) are the primary comparison and c) is an exploratory comparison as it is not possible to adequately power this comparison. No adjustment is made for multiple testing due to the number of groups as we are treating the comparisons a) and b) as separate research questions so we do not need to control the type 1 error/false positive rate.

For all 3 comparisons with the primary outcomes we will have a significance level of 2.5% to account for having two primary outcomes, this is based on the Bonferroni adjustment of dividing the significance level by the number of comparisons made for each research question. For all secondary outcomes the significance level will be 5%.

Within each group comparison for all continuous outcomes, a general linear model will be used to compare the average values between groups adjusted for the site as the randomisation is stratified by site. Depending on the number of individuals recruited at each site, site will be included as either a fixed or random effect. Assumptions will be checked graphically and if appropriate transformations will be used, if none are appropriate then a Bootstrap will be used. For binary outcomes a logistic regression model will be used adjusting for site.

In addition to the above analysis if any factor is imbalanced at baseline or is considered prognostic by discussion with the PI/TMG/DMC they will be included in an adjusted model. However, the primary analysis is the unadjusted analysis and the adjusted analysis exploratory.

If appropriate, that is to say that there is a large amount of non-adherers to the intervention, then a Complier Average Causal Effect (CACE) analysis will also be undertaken.

5.10.4.7 Safety Analyses

The safety analysis will be based on the pre-defined population (as above). Summary tables will be presented for incidence rates (number of patients with at least one incidence) of adverse events and SAEs coded according to the section 5.11.3.1 of the protocol.

5.10.5 Economic evaluation

An economic evaluation will be conducted alongside the randomised controlled trial. The form of this study will be a cost-utility analysis and the perspective will be societal, i.e. will include NHS and social services as well as costs incurred by participants. The comparisons evaluated in the economic evaluation will be the same groups as in the main trial, i.e., control (TAU), TAU plus hospital based exercise; and TAU plus home based exercise. The outcome measure used in the economic evaluation will be the quality adjusted life year (QALY). The QALY is calculated by multiplying duration of life by a measure of health related quality of life. HR-QoL will be estimated using two different instruments; the EQ-5D-5L (where 5L denotes five levels) and the SF-6D. The SF-6D will be obtained from SF-36, which is also being collected in this study. These instruments will be used to generate preference weightings for the calculations of QALYs using UK specific preference weights. Both the EQ-5D-5L and SF36 will be collected at 4 time points, baseline, 30 days post-operation and 6 and 12-months post-randomisation.

We will record all resources required to provide the two exercise interventions. Costs of the intervention will fall under a number of categories. Firstly, there will be any training required to ensure the intervention is provided in a consistent way. Staff time required to provide this training will be recorded, including appropriate preparation time as well as actual time of provision. Additionally, numbers of staff attending these sessions should be recorded by means of registers. Provision of the intervention will require staff time to supervise the group sessions. Time is also likely to be required in preparation for sessions and for administrative tasks. A sample of staff will be asked to complete a diary for a representative period of time to estimate time spent in providing contacts with participants and time spent on other tasks required. Each centre should record what facilities and equipment are required to provide the intervention and record any study expenditure on equipment. A similar process would be carried out for the home based exercise. A member of the Trial Intervention Team will record attendance at an initial 45 minute exercise counselling session. For the hospital based exercise group participant attendance at the group sessions should be recorded. These data will be entered directly onto the study eCRF. For the post-operative period attendance at the monthly booster sessions will be recorded on study eCRF. Details of exercise, both before and after surgery should be recorded on patient exercise diaries. These data on the resource required to provide the exercise interventions and the utilisation of exercise sessions in both groups will enable an estimate of the cost per person of the two exercise interventions.

For the home-based group in the pre-operative period we will record time required to provide telephone support by a member of the Trial Intervention Team as well as attendance at the 45 minute exercise counselling session. Post-operatively the home based group will receive a 15 minute motivational telephone call monthly from a member of the Trial Intervention Team, again this will be recorded on the eCRF. Finally, both groups will receive information on local exercise facilities.
In order to quantify any effects that the exercise interventions may have on health care received, we will estimate costs of providing healthcare in all participants. Secondary care costs are likely to be an important component of total costs so relevant resource use will be collected, including: operating time, time in ICU/ITU, length of stay, complications, re-operations, and need for re-admissions. These data will be recorded by study researchers from patient notes or hospital data at each site and recorded onto the eCRF. This will cover the duration of the 12 months follow up.

Other health care related resource use data will be collected via a patient-completed questionnaire, completed at baseline, and at 6 and 12 months post-randomisation. These data will be collected by means of a modified CSRI. Care will be taken to ensure that the forms are as simple as possible. It is anticipated that all care related to the secondary care received in the study hospital to which the patient is recruited will be collected directly from patient notes and hospital records. Therefore the modified CSRI will cover primary care services; prescribed medicines; social care; and own borne costs. Because of the requirement for attending hospital to receive exercise in the hospital exercise group these patients will be required to visit the hospital more often and hence may incur higher travel costs. Therefore it is important to quantify the costs borne by participants in attending hospital. Participants in the hospital exercise group are reimbursed travel expenses and these will be recorded in the eCRF to reflect extra costs incurred by this group. Relevant costs borne by participants would also include any out of pocket expenses. We will also collect data on time off work. Participants will self-complete these questionnaires. If a questionnaire is not returned then participants will be sent one reminder.

For all resource use data quantities will be multiplied by unit costs from standard NHS and other data sources (e.g. PSSRU and NHS Reference Costs) to estimate the cost per patient in each arm over one year. In the case of the costs of the intervention no representative cost will be available and a bespoke cost of the intervention will be calculated using resource use data collected as part of the study.

5.10.5.1 Health Economic Analysis Plan

A full health economics Analysis Plan (HEAP) will be developed between the trial health economist, Chief Investigators and trial statistician before any analysis is undertaken. The HEAP will be shared with the trial's governance committees.

5.10.5.2 Within-trial analysis

The health economic analysis will be carried out on an 'intention to treat' basis. For each of the 3 study groups we will estimate costs for the 12 months of the study follow-up. Total costs will include costs of providing the interventions, cost of secondary care, and costs incurred in primary care. We will also estimate costs borne by study participants as well as productivity costs incurred through time off work. We will estimate costs for each category of resource use for each participant, as well as an estimate of total cost for each participant. This will enable an estimate of total and average cost in each study group. We will estimate quality adjusted life years (QALYs) in all three groups for the 12 months of follow-up. This will be done through data collected at 4 time points, baseline; 30 day post-operation, 6-months of follow-up, and 12-months follow-up post-randomisation. As is recommended (Manca et al 2005) QALY gains from the two intervention groups will be estimated using regression based methods to allow for differences between groups in baseline HR-QoL and other relevant patient characteristics. Similar methods will be employed to estimate differences in total costs by groups. As recommended (Gold et al 1996), groups will be ranked in terms of increasing estimated QALYs and both incremental costs and QALYs will be calculated. The outcome measures of the economic evaluation will be estimated in incremental cost-effectiveness ratios. Uncertainty in the estimates of costs and QALYs will be incorporated in by the use of cost-effectiveness acceptability curves (CEACs). CEACS will be estimated by means of non-parametric bootstrapping.

We anticipate, a priori, that our base case analysis will use QALYs estimated by means of the EQ-5D-5L. However, we will also estimate QALYs by means of the SF-6D (derived from the SF-36 data). As part of the analysis, an assessment of the performance of both measures will be made against other data collected as part of PREPARE-ABC. Both instruments will be compared to other clinical and health related measures to compare their relative performance in this group of participants. There is a substantial literature that evaluates the performance of the EQ5D against disease based measures. Generally this is based on correlation and this method will be used for the current study group for both EQ5D and SF6D. For example, against physiological measures of fitness. If there is no compelling evidence that the SF-6D is performing better we will use QALYs estimated from this instrument in a sensitivity analysis.

Missing data can potentially bias results. One potential source of missing data could be non-completion of study eCRF. However, more likely is non completion of patient reported measures such as the EQ5D-5L and SF36, as well as resource use estimates obtained from the patient completed questionnaire. The amount of missing data in the health economic analysis will be scrutinised. Missing data and patterns of missing data will be analysed and discussed between study health economists, study CIs, and statistician. If deemed necessary we will use appropriate statistical techniques, such as

multiple imputation (Rubin et al 2004) to allow for missing data. Imputed data would be used in a sensitivity analysis.

5.11 Data Monitoring

5.11.1 Data Monitoring Committee

Further details of the roles and responsibilities of the Data Monitoring Committee (DMC), including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the PREPARE-ABC DMC Terms of Reference (ToR).

5.11.2 Interim Analyses

No efficacy interim analyses are planned. However, analysis of recruitment rates, withdrawal rates, etc. will be conducted as part of the internal pilot for subsequent publication as documented in the accompanying interim analysis plan.

5.11.3 Data Monitoring for Harm

The DMC will be provided with safety data for each treatment arm including frequency of exercise related adverse events. The committee will advise on the continuation or early stoppage of the trial in the unlikely event that there are concerns over harm to participants.

5.11.3.1 Safety reporting

The principles of ICH GCP require that investigators and sponsors follow specific procedures when notifying and reporting adverse events or adverse reactions in clinical trials. These procedures are described below.

Table 2: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant and which does not necessarily have a causal relationship with the trial exercise intervention.
Adverse Reaction (AR)	Any unintended or untoward response to an investigational intervention
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***
* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction) ** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-	

existing conditions (including the planned surgery/elective procedures that have not worsened as a result of exercise) do not constitute an SAE

*** Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

5.11.3.2 Clarifications and Exceptions

The intervention under investigation in Prepare ABC is pre- and post-operative exercise. Surgery is conducted in all patients on the trial as part of routine care. All post-operative morbidity up to 30 days post-operation and readmissions up to 90 days are collected as primary and secondary outcome measures in all patients and are not therefore subject to routine safety reporting.

Adverse events include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial exercise intervention. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after exercise intervention.)
- Continuous persistent disease or a symptom present at baseline that worsens

5.11.3.3 Exempted Adverse Events

Adverse events do NOT include

- Post-operative morbidity (within 30 days of surgery) – this should be graded according to the Clavien Dindo classification and reported on the appropriate eCRF
- Readmissions relating to post-operative morbidities within 90 days of surgery
- Recurrence of primary cancer- this should be reported on the appropriate eCRF
- Death due to primary cancer- this should be reported on the appropriate eCRF
- Medical or surgical procedures; the condition that led to the procedure is the adverse event
- Pre-existing disease or a condition present that was diagnosed before trial entry and does not worsen
- Hospitalisation where no untoward or unintended response has occurred e.g. elective surgery, social admissions

5.11.3.4 Other Notifiable Adverse Events

There are no further notifiable events in this trial.

5.11.3.5 Procedures to follow in the event of female participants becoming pregnant

In the event of a female participant becoming pregnant, trial intervention along with standard of care procedures should be discussed with the CIs. This should be reported on the eCRF. The pregnancy should be followed for outcome of mother and child.

5.11.3.6 Investigator responsibilities relating to safety reporting

All AEs and SAEs whether expected or not, should be recorded in the patient's medical notes and reported in the toxicity section of the relevant eCRF.

5.11.3.6.1 Seriousness assessment

When an AE occurs, the investigator responsible for the care of the participant must assess whether or not the event is serious using the definition given in Table 1.

5.11.3.6.2 Causality and Expectedness

The investigator must assess the causality of all serious adverse events in relation to the exercise intervention using the definitions in Table 2. There are 5 categories: unrelated, unlikely, possible, probably and definitely related. If the causality assessment is assessed as unrelated or unlikely to be related the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related then the event is classified as an SAR.

Expectedness is assessed by trained NCTU staff against a list of events produced by the co-CIs.

If the event is classified as 'serious' and assessed as being related to the exercise intervention then an SAE form must be completed and NCTU notified within 24 hours. If the event is classified as 'serious' and assessed as **not** being related to the exercise intervention or is thought to be related to a post-operative morbidity (POM) these should still be reported to NCTU via the relevant eCRF forms.

If an SAE is considered to be related to the exercise intervention then continuation of the exercise intervention should be discussed with the Chief Investigator

Table 3: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical	SAR

	condition or other concomitant treatment)	
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out	SAR

5.11.3.7 Notifications

5.11.3.7.1 Notifications by the Investigator to NCTU

NCTU must be notified of all SAEs related to the exercise intervention within 24 hours of the investigator becoming aware of the event.

Investigators should record any SAEs related to the exercise intervention occurring from the time of randomisation until 12 months post-randomisation, when the exercise intervention stops.

The SAE form must be scanned and sent by email to the NCTU SAE reporting email address:

nctu.safety@uea.ac.uk

The SAE form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care). In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to NCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the PIN and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to NCTU as further information becomes available. Additional information and/or copies of test results etc. may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

5.11.3.7.2 NCTU responsibilities

Medically qualified staff at NCTU and/or the medical Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received.

NCTU is undertaking the duties of trial sponsor and is responsible for the reporting of intervention related SAEs to the REC as appropriate.

NCTU will keep investigators informed of any safety issues that arise during the course of the trial.

5.11.4 Quality Assurance and Control

5.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the PREPARE-ABC trial are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

5.11.4.2 Central Monitoring at NCTU

NCTU staff will review electronic Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the PREPARE-ABC Data Management Plan.

5.11.4.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the PREPARE-ABC Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports.

5.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits and REC review by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

5.11.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the NCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the PREPARE-ABC Quality Management and Monitoring Plan.

5.11.4.4.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management.

5.11.4.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

5.11.4.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

5.11.4.4.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) has access to accumulating comparative data between each arm of the study. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

5.11.4.4.5 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. When an institution is the trial sponsor and has delegated the duties as sponsor to NCTU, the delegation will be confirmed via a signed letter of delegation.

5.12 COVID-19 Impact and Adaptation

The emergence of the COVID-19 pandemic caused disruption to recruitment and greatly impacted the way in which cancer patients interact with the NHS along their care pathway. Recruitment was suspended at all sites by 23 March, 2020. In order to minimise face-to-face contact upon re-opening recruitment, Arm A (hospital supervised exercise) will be suspended until sites are able to offer this intervention.

During the suspension period, patients will be recruited into a 2-arm randomised control trial consisting of Arm B (home based intervention) and Arm C (treatment as usual) to 90% power with the two primary outcomes as originally planned: change in quality of life at 12 months and post-operative morbidities at 30 days.

6 Ethics and Dissemination

6.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

6.2 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required. A copy of the local R&D approval (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are randomised to the trial.

This trial also includes sites in devolved nations and Site Specific Information Forms will be submitted for all these sites in order to obtain approval.

The protocol has received formal methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

6.3 Protocol Amendments

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be decided by the Chief Investigators. Each site-PI will be informed of the potential changes. Such amendments will be submitted to NRES for approval. Once approved, the protocol amendments will be circulated to trial personnel.

6.4 Consent

Patients will be provided with a Patient Information Sheet (PIS) and given time to read it fully. Following a discussion with a medical qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant

will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

A copy of the approved consent form is available from the NCTU trial team.

6.4.1 Consent to Process Evaluation

As part of main trial recruitment, patients will also be asked to provide informed consent to be contacted by a member of the process evaluation team to discuss participation in an interview and/or allow a researcher to observe their care. If informed consent is provided, the researcher will arrange a suitable time and location for the interview. As part of patient's follow up within the main trial it will be noted on the eCRF if a patient is unsuitable or no longer wishes to be approached about being interviewed. Informed consent to the interview /observation will be taken by the researcher immediately prior to the interview/observation. Once informed consent has been obtained, the researcher will seek the participant's permission to audio record the interview, explaining the reasons for doing so. If a participant does not wish the interview to be recorded, the researcher will make written notes of the interview. Participants will be reassured that neither the transcription nor the handwritten notes will contain any personal identifying information and that nobody will listen to the tape or read the notes of the interview, except for members of the research team involved in transcribing and/or analysing the data.

The observational aspect of the process evaluation involves the researcher observing and taking brief field notes of pre- and post-surgery consultations, the 45 minute counselling session and supervised exercise sessions. In practice, this is likely to involve a researcher being present whilst the relevant member of staff undertakes the session/consultation. Participants receiving the 45 minute counselling session will also be asked to consent to the session being audio recorded. This will be done to understand communication patterns in how staff communicate the details of exercise interventions to patients. All patients, accompanying adults (observations only) and staff being observed/interviewed (including telephone interviewees) will be provided with details of interviews/observations within the process evaluation consent sheets. For both observations and interviews, a researcher will briefly introduce the study and will allow participants the opportunity to ask questions. Patients, accompanying adults and staff consenting to the process evaluation will be made aware of observations prior to consultations and offered the opportunity to participate.

Patients will be approached for observation of usual care at site before any recruitment and randomisation to the main study has commenced. Informed consent will also be sought from any adults who attend the consultations with the consented patient. Patients will be given information about the process evaluation of usual care before their appointment and will be asked to provide consent for a researcher to observe their consultation.

In the event that a patient is not approached for participation in the process evaluation at the time of approach for the main study, the local study team may contact the participant to discuss participation in the process evaluation by phone. The usual procedure for obtaining informed consent will be followed culminating in verbal consent being given by the patient if agreeable. Once verbal consent has been obtained, and documented in the patient notes, the local study team will send the relevant consent form to the participant to complete and return to site. The process evaluation team will then contact participants directly and arrange interviews as outlined above and in section 7.0.

Consent will be required from staff participating in telephone interviews about standard care. This is to allow permission for the researcher to record, analyse and publish any qualitative comments, quotes and researcher observations made during these calls. No patient data will be obtained. As we cannot easily anticipate which staff member will participate in the telephone interview, verbal consent will be obtained from the staff member at the time of interview. Information sheets and consent forms will then be sent to the staff member requesting they provide written consent. Qualitative data obtained during the telephone interviews will only be used for those providing written consent. Where written consent is not provided, the telephone interview data will be destroyed.

6.4.2 Consent in Ancillary Studies

There is no intention to collect any data for use in future studies. There is no current intention to perform any ancillary studies, other than that outlined in this protocol, should plans emerge for additional ancillary studies they will require additional funding and ethics applications to be made.

6.5 Confidentiality

Any paper copies of personal trial data will be kept at the participating site in a secure location with restricted access. Identifiable data (limited to consent forms for monitoring purposes), will be kept at the NCTU office with only authorised NCTU staff members having access. Only staff working on the trial will have password access to this information.

Confidentiality of patient's personal data is ensured by not collecting patient names on CRFs/eCRFs that will be sent to NCTU and storing the data in a pseudonymised fashion at NCTU. At trial enrolment the patient will be issued a participant identification number and this will be the primary identifier for the patient, with secondary identifiers of age (in years) at baseline and initials.

The patient's consent form will carry their name and signature. These will be kept at the trial site, and a copy sent to NCTU for monitoring purposes. They will not be kept with any additional patient data.

6.6 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

6.7 Indemnity

The NHS indemnity scheme will apply to the potential liability of the sponsor for harm to participants arising from the management and conduct of the research.

6.8 Finance

This project was funded by the National Institute for Health Research HTA Programme number 14/192/53. It is not expected that any further external funding will be sought.

6.9 Archiving

The investigators agree to archive and/or arrange for secure storage of PREPARE-ABC trial materials and records for a minimum of 5 years after the close of the trial unless otherwise advised by the NCTU.

6.10 Access to Data

Requests for access to trial data will be considered on a case by case basis, and approved in writing where appropriate, after formal application to the TMG and TSC. Data will not be released to the collaborating trial team until approval from the TMG and TSC has been received by co-CIs and/or NCTU trial team. Considerations for approving access are documented in the TMG and TSC Terms of Reference. The Co-CIs and trial statistician at NCTU will have access to the full trial dataset.

6.11 Ancillary and Post-trial Care

The sponsor does not intend to provide any interventions or other care to patients after trial completion.

6.12 Publication Policy

6.12.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect. Ownership of the data arising from the study resides with the trial team. The publication policy will be in line with rules of the International Committee of Medical Journal Editors. The TMG will decide on the dissemination strategy including presentations, publications and authorship with any difficulties being resolved by the TSC.

6.12.2 Authorship

For main publications, the TMG will nominate a writing group, which will consist of members of the TMG supplemented by site PIs and others who have made major contributions, who will be responsible for drafting the main manuscripts for publication. These individuals will be named on the final publication.

6.12.3 Reproducible Research

The PREPARE-ABC Trial Protocol will be published and made available for public access throughout the trial period.

7 Ancillary Studies

7.1 Process Evaluation – UK sites only

In order to assess fidelity of implementation, mechanisms of impact and any contextual factors associated with variation in outcomes a parallel process evaluation will be conducted in all colorectal units that recruit into the study. This will:
1) Evaluate usual care prior to implementing interventions, in order to accurately describe differences between the proposed interventions.
2) Describe how the supervised and home-based interventions are implemented and assess fidelity to the intervention protocol.
3) Assess patients' and staff expectations and experiences of the intervention arms, and their views of the acceptability of the interventions.
4) Describe the control arm and assess any variation in non-receipt of the interventions and any intervention contamination.
5) Develop possible explanations for why the supervised or home-based intervention did or did not work.

To achieve these objectives, we will adopt an ethnographic approach using qualitative methods employing interviews (Britten, 2006) with patients and hospital staff and non-participant observations (Green, Thorogood, & Ebrary, 2004) of usual care, the pre-op and post-op supervised sessions and the 45 minute counselling sessions. We will examine any leaflets and protocols followed by staff regarding exercise advice to establish usual care. We will also ask staff to complete a sub-sample of log sheets to confirm delivery of the supervised sessions and pre-counselling sessions. In the home-based intervention, patients will be given a pedometer to record number of steps taken on a daily basis and complete a log of exercise undertaken. The process evaluation data will be collected by a Research Associate from the NCTU primarily.

Baseline (prior to patient randomisation)
Objective 1 will be addressed using the following methods:
- Telephone interviews of standard care at each site, to obtain data including size of colorectal unit, details of Enhanced Recovery Programme or other policies, details of advice given to patients regarding exercise, policy or protocol documents relevant to understanding standard care, and any other comments or observations relevant to standard care prior to recruiting the first randomised patient in each site.
- Assessment of how leaflets offered by staff differ to advice delivered in 45 minute pre-surgery exercise counselling session.
- One 2-3 day period of non-participant direct observation per hospital of usual care. Observations will be undertaken of pre- and post-operative consultations to establish differences in practice between proposed interventions and usual care, and to establish change required to deliver interventions. This initial period of observation will take place prior to recruiting the first randomised patient in each site. Patients recruited for observations of usual care to address Objective 1 will therefore not be randomised and will not participate in the main study. Patients will be recruited by trained staff working in each centre.

During intervention delivery (7-18 months)
Objectives 2 and 3 will be addressed using the following methods:
- At two different time points per hospital, spread across the duration of patient recruitment in the pilot phase, a 2-3 day period of non-participant direct observation will be undertaken to understand how the intervention is delivered, including: 1) the 45 minute exercise counselling sessions in the hospital supervised and home-based interventions (these sessions will also be audio recorded by the researcher); 2) exercise sessions in the supervised intervention.

- Log sheets recording details of each exercise session in the supervision arm will be completed by session supervisors to help determine intervention fidelity. Supervisors will complete log sheets for all patients across the duration of patient recruitment in the pilot period. Log sheets will include the following checklist: confirmation of patient(s) completing supervised session; details of exercise completed – type, intensity (assessed by Borg scale) and duration. Fidelity to both exercise interventions will also be quantitatively assessed via adherence measurements (see 6.4.4).
- One interview (individual or group) per hospital with the Trial Intervention Team to identify challenges of intervention delivery. As the same team will deliver both the supervised and home-based interventions this interview will cover delivery of both interventions.
- Forty interviews (twenty per arm, 3-4 per hospital) with patients at 1-year post-randomisation to identify perceptions and responses to interventions.

Objective 4 will be addressed using the following methods:
For patients randomised to receive usual care:
- One period of direct observation per hospital during pilot patient recruitment to determine any variation in non-receipt of advice delivered in the exercise counselling sessions of the hospital and home-based interventions.
- Twenty interviews (1-2 per hospital) with patients at 1-year post-randomisation to understand their experience of their condition and identify type and level of exercise undertaken throughout the study period.

Objective 5 will be addressed by analysing all of the above data in an iterative process (see analysis section) to understand how the intervention arms differed from usual care at the point of introduction, how both intervention and control arms were delivered and differentiated in practice, and how patient and staff views of the interventions shaped their implementation. Additionally, analysis of exercise diaries and pedometers will provide a measurement of adherence to the intervention arms.

Patient Interviews:
Twenty interviews will be conducted with patients in each arm of the study, at 3 month follow-up to capture patient's perspectives following the primary endpoint. To achieve this number of interviews, it may be necessary to approach approximately 80 patients per arm. Researchers will select a sample of those agreeing to be interviewed to form a maximum diversity sample, on the basis of age, gender, and ethnicity. Participants who consent to be contacted by the process evaluation team will be contacted by a researcher to discuss the study with prior to agreeing to a date and time for an interview. Any participants who expressed an interested, but who were not selected to take part, will receive a letter thanking them for their interest and informing them that they will not be interviewed. As the analysis develops, theoretical sampling may also be used to investigate emerging theories. Written consent to participation will be obtained at interview. Patients will be interviewed at home or by telephone, according to their preference. Patients will be asked about their experiences of their condition, their care and, in the intervention arms, about their expectations, experiences and acceptability of the intervention. It is anticipated that the interviews will last between 30 and 60 minutes; they will be audio recorded with patients' permission.

Staff interviews:
Staff involved in the delivery of standard care will be interviewed on the telephone. Staff involved in the delivery of both interventions will be interviewed, one-to-one or in a group in their own hospital. Interviews will be undertaken while the intervention is being implemented to minimise recall bias. Staff involved will be asked about details of delivering the supervised sessions and the exercise counselling sessions in their hospital, the acceptability of the intervention, problems occurring and

how they were or were not solved, their general perceptions of the intervention. Interviews will be audio-recorded with participants' permission.

Direct observations:
Non-participant direct observations of the supervised exercise sessions, the 45 minute counselling session (home-based intervention only) and usual care will take place over the same 2-3 days in each hospital. It may be that the researcher will need to split the days depending on which patients are attending the hospital on what days. Non-participant observation involves the researcher observing and taking brief field notes of staff-patient interactions as they are implemented. In practice, this therefore involves a researcher being present whilst the relevant member of staff undertakes the consultation. Patients (and relatives if present) consenting to the process evaluation (and staff) will be made aware of observations prior to consultations and offered the opportunity to refuse consent.
The researcher will record contemporaneous written field notes and will be asked to note any activities which relate to the running of the study and the delivery of the intervention, or non-receipt on usual care in the control arm.

In addition the researcher will seek consent from staff and patients (and relatives if present) to audio record the 45 minute counselling session.

If for logistical reasons, the Research Associate is unable to personally observe the initial counselling session and the patient has provided written informed consent to participate in the process evaluation, the local study team will record the session and securely transfer the audio file to the research team.

Process data analysis
Telephone interview data: Quantitative data collected to evaluate standard care will be used to provide descriptive statistics of each colorectal unit prior to recruiting the first randomised patient in the trial. Any qualitative data collected during these interviews will be used to provide further insight into the specific circumstances of the participating unit.
***Interview data*:** Interview recordings will be transcribed and these will be analysed using a thematic analysis in the first instance, using some of the techniques of grounded theory such as constant comparison and theoretical sampling (Green, Thorogood, & Ebrary, 2004). The researcher will begin by coding transcripts using a coding scheme drawn up in collaboration with other team members. The specialist software programme NVIVO will be used to organise the qualitative analysis and ensure its systematic analysis.
Observational data: As with interview data, observational data will be analysed using a thematic analysis in the first instance, using some of the techniques of grounded theory such as constant comparison and theoretical sampling (Green, Thorogood, & Ebrary, 2004).
Audio data: Audio recordings will be transcribed using conversational analysis conventions and analysed to understand communication patterns between the Trial Intervention Team members and the patient. In particular we adopt principles of conversation analysis (Heritage & Maynard, 2006) to focus on question-response and advice giving sequences of interaction for how decisions about exercise are reached within the counselling session.

The analysis of interview and observational data will be iterative, moving between data collection and data analysis to test emerging theories. It may, for example, emerge that particular groups of patients have particular expectations about the interventions which shape their experiences of the interventions, and this may require deeper exploration. Care will be taken to identify and follow up deviant cases which do not fit into emerging theories. Preliminary findings will be sent to interviewees if desired for confirmation and correction. It will also involve analysis of any areas of emerging

agreement or disagreement about what worked or did not work, any observable conflicts and any differences of opinion between staff in the same hospital.

At least one of the co-applicants (JM) will contribute to the qualitative analysis and writing up of the qualitative data. The outputs of the qualitative analyses will include: descriptions of how the interventions were implemented and experienced by participants; assessments of the acceptability of each intervention; recommendations for optimising questioning and advice-giving within counselling sessions; and tentative explanations for the reasons underlying apparent successes or failures.

7.2 PREPARE-ABC Sub-Study – defining the relationship between body composition, cardiorespiratory fitness, systemic inflammatory response and post-operative outcome in patients with operable colorectal cancer participating in the PREPARE-ABC trial

The sub-study outlined below is the result of a collaboration of the co-CIs, trial team and overarching trial committees with the PREPARE-ABC teams at the LNWUH and NHS GGC sites. All PREPARE-ABC sites will participate in the PREPARE-ABC sub-study unless otherwise agreed with via the NCTU trial team and/or co-CIs. The PREPARE-ABC trial committees are also responsible for overseeing this sub-study; this includes an immediate trial management team, trial management group, trial steering committee and independent data monitoring committee.

The data collected for the sub-study is either already collected through participation in PREPARE-ABC or routinely as part of standard care for patients with colorectal cancer and will be entered into the main study eCRF. Therefore no additional funding or safety reporting is required for the sub-study and data collected will be subject to standard monitoring procedures in accordance with PREPARE-ABC quality management and monitoring plan.

Site staff and all trial team members will receive sub-study training.

7.2.1 Sub-study summary

Details specific to PREPARE-ABC are described in sections 1-7.1 of the PREPARE-ABC Protocol, the table below refers to details specific to the PREPARE-ABC sub-study only.

Table 4: Sub-study summary.

Source of Monetary or Material Support	Not applicable
Contact for Public Queries	prepare.abc@uea.ac.uk
Contact for Scientific Queries on sub-study	Dr Campbell Roxburgh PhD Campbell.Roxburgh@glasgow.ac.uk Senior Clinical Lecturer and Honorary Consultant Colorectal Surgeon Academic Unit of Surgery 2nd Floor, New Lister Building Glasgow Royal Infirmary G31 2ER Mr Ian Jenkins MD mrianjenkins@me.com Consultant Colorectal Surgeon and Honorary Senior Clinical Lecturer St Marks Hospital and Academic Institute Northwick Park Harrow HA1 3UJ

Sub-study Scientific Title	Defining the relationship between body composition, cardiorespiratory fitness and systemic inflammation in patients with operable colorectal cancer participating in the PREPARE-ABC trial.
Key Inclusion and Exclusion Criteria	In addition to the eligibility criteria for participation in the PREPARE-ABC study, the following sub-study eligibility criteria apply: • Have a pre-operative staging CT scan suitable for body composition (muscle and fat) analysis within the 6 months preceding enrolment in PREPARE-ABC • Have height and weight recorded at baseline • Have results available for full blood count and liver function tests (with or without CRP) taken within the 3 months preceding enrolment in the main trial
Sub-Study Type	This sub-study is performed in conjunction with PREPARE-ABC analysing routine clinical and study-specific data.
Date of First Enrolment	Enrolment into PREPARE-ABC began in November 2016. This sub-study analysis uses routine and study-specific data collected from this point onwards.
Target Sample Size	285 participants (95 per group)
Primary Outcome(s) of sub-study	The following primary outcome will be assessed for standard care versus hospital-based and standard care versus home-based exercise intervention groups: **Outcome:** Change in muscle mass attenuation on the pre-operative and first surveillance CT scans obtained as part of routine care. **Metric:** Assessed in Hounsfield units using slice-O-matic software.
Key Secondary Outcomes of sub-study	The following secondary outcomes will be assessed for standard care versus hospital-based and standard care versus home-based exercise interventions: **Outcome:** Pre-operative change in cardiopulmonary exercise test (CPET). **Metric:** Change in cardiopulmonary fitness variables, as measured using an incremental CPET between 4 weeks prior to surgery and the pre-surgery visit (e.g. peak VO_2; anaerobic/ventilatory threshold; VE/VCO_2; oxygen pulse). **Outcome:** Change in systemic inflammatory response measured using serum inflammatory markers from blood samples obtained as part of routine care in the pre-operative period (two timepoints: at diagnosis and pre-surgery. **Metric:** The results will be used to assess the neutrophil:lymphocyte ratio (NLR) and modified Glasgow Prognostic Score (mGPS).

	Outcome: Pre-operative change in grip strength. **Metric:** Change in grip strength as measured using a standard digital grip strength dynamometer between baseline and pre-surgery.

7.2.2 Sub-study background and rationale

Colorectal cancer is the fourth most common cancer type in the UK with over 40, 000 cases diagnosed annually (CRUK, 2015).

While features such as advanced disease stage at presentation can be used to identify patients at risk of poor long-term outcomes, a number of more subtle markers exist which can predict adverse outcome in both the short- and long-term. Body composition techniques assess the distribution of adipose tissue relative to lean muscle mass on CT and can be used to predict post-operative complications and survival in patients undergoing colorectal cancer resection. Depleted skeletal muscle mass, also known as myopenia, confers an unfavourable prognosis, with negative effects on short-term surgical outcomes including higher rates of infective complications (Huang et al., 2015, Joglekar et al., 2015) and prolonged length of stay (Joglekar et al., 2015, Reisinger et al., 2015) as well as poorer long-term survival (Malietzis et al., 2016a, Feliciano et al., 2017). A recent meta-analysis examining the prognostic role of myopenia in patients undergoing gastrointestinal cancer resection reported a prevalence of between 12 to 60% in colorectal populations (Simonsen et al., 2018). The underlying aetiology is multifactorial and poorly understood but includes systemic inflammation, endocrine imbalance and negative energy balance, with impairment manifesting as loss of function and fatigue (Pring et al. 2018). Myopenia can be readily measured on pre-operative CT imaging, providing a quantifiable measure of those at risk of poor outcome following colorectal cancer resection.

The systemic inflammatory response (SIR) represents a further established indicator of adverse post-operative outcome. The presence of an elevated SIR prior to elective colorectal cancer resection is associated with higher rates of infective complications (Moyes et al., 2009) and poorer cancer-specific survival (Crozier et al., 2007), independent of comorbidity (Roxburgh et al., 2011). Its association with myopenia has been explored in colorectal cancer populations previously: Richards and colleagues reported a relationship between elevated SIR markers and reduced skeletal muscle index (Richards et al., 2012), while Malietzis found patients with an elevated neutrophil: lymphocyte ratio (NLR) had significantly lower skeletal muscle mass when compared with their non-inflamed counterparts (Malietzis et al., 2016b). More recently, Feliciano and co-workers confirmed a dose-response relationship between the NLR and degree of myopenia, which translated to reduced overall and cancer-specific survival (Feliciano et al., 2017).

The independent prognostic value of metrics derived from muscle and fat CT analysis and the inflammatory response presents a context in which to risk-stratify patients pre-operatively. Patients who are identified as high risk for adverse outcome through these features may require more intensive or targeted interventions to address their adverse risk profile. In healthy subjects, exercise by repetitive muscle use physiologically leads to an increase in muscle mass and also imparts anti-inflammatory effects by attenuating the cellular response to pro-inflammatory cytokines whilst

increasing circulating levels of anti-inflammatory cytokines (Keller et al, 2004, Starkie et al., 2003, Gould et al., 2013, Steensburg et al., 2002, Petersen and Pedersen, 2005, Steensburg et al., 2003).

While several studies have explored prehabilitation in patients with cancer with the aim of improving fitness, the effect of exercise on preservation of lean muscle mass or attenuation of muscle wasting has not yet been examined (Bruns et al., 2016). Similarly, the influence of SIR status on response to prehabilitation as measured by change in cardiorespiratory fitness remains unexplored. By assessing the presence and degree of myopenia on the staging and first surveillance CT scans in the 12 months following surgery carried out as part of standard care in patients participating in the PREPARE-ABC trial, it may be possible to address whether prehabilitation can be used to improve muscle quality and prevent muscle wasting in response to the acute insult of surgery. Furthermore, combining assessment of myopenia with the pre-operative systemic inflammatory response may enable patients to be risk-stratified in order to interpret their subsequent response to prehabilitation.

7.2.3 Sub-study objectives

As in the main study, there will be three trial arms:

- Arm A – Hospital based supervised exercise
- Arm B – Home based supported exercise
- Arm C – Standard care, treatment as usual

There are two primary research hypotheses:

- hospital-supervised exercise training in the pre- and post-operative period, in addition to standard care, leads to a change in muscle attenuation at 12 months versus standard care alone.

- home-supported exercise training in the pre- and post-operative period, in addition to standard care, leads to a change in muscle attenuation at 12 months versus standard care alone.

An exploratory hypothesis that hospital-supervised exercise training in the pre- and post-operative period, in addition to standard care, leads to a change in muscle attenuation at 12 months versus home-supported exercise will also be examined.

7.2.3.1 Sub-study primary objectives

- To assess the effect of a formal pre- and post-operative exercise programme on muscle and visceral adiposity (including the reversal/arrest of myopenia) and the systemic inflammatory response in the PREPARE-ABC trial.

7.2.3.2 Sub-study secondary objectives

- To assess the dose-response associations between the amount and type of exercise that is undertaken by participants in the PREPARE-ABC trial and preservation of skeletal muscle on CT in the PREPARE-ABC trial
- To examine the association between myopenia at baseline and subsequent change in pre-operative cardiopulmonary fitness variables in participants in the PREPARE-ABC trial
- To examine the association between systemic inflammation at baseline and subsequent change in pre-operative cardiopulmonary fitness variables in participants in the PREPARE-ABC trial

- To assess the effect of myopenia and/or systemic inflammation at baseline on complications in the post-operative period in the PREPARE-ABC trial
- To determine the relationship between the presence of myopenia on CT and grip strength in the PREPARE-ABC trial

7.2.4 Methods

7.2.4.1 Sub-study participant eligibility criteria

In addition to the eligibility criteria for participation in the PREPARE-ABC study, patients will be eligible for inclusion in the sub-study if:

- a pre-operative staging CT scan suitable for body composition (muscle and fat) analysis within the 6 months preceding enrolment in PREPARE-ABC is available
- height and weight were recorded at baseline
- results are available for full blood count and liver function tests (with or without CRP) taken within the 3 months preceding enrolment in the main trial

7.2.4.2 Sub-study consent procedures

We shall be collecting fully anonymised routine clinical data as part of this study. In accordance with section 4 of the existing consent form and in view of the fact that no further intervention or investigation of patients is required no further specific consent shall be sort for this sub-study analysis.

Inclusion in the sub-study will be independent of adherence to treatment arm within the main study. Patients who discontinue the main trial treatment but remain in the trial for follow-up will be included in data analysis of both the main trial and sub-study (where applicable).

Withdrawal from the main trial includes a withdrawal from the sub-study. Data already collected will be kept and included in sub-study analyses for all participants who stop follow up early.

7.2.4.3 Outcomes

7.2.4.3.1 Primary Outcomes

Outcome: Change in muscle mass

Change in muscle mass will be assessed using image analysis of the pre-operative and first surveillance CT scans obtained as part of routine care for standard care versus hospital-based and standard care versus home-based intervention groups.

7.2.4.3.2 Secondary Outcomes

The following secondary outcomes will be assessed for standard care versus hospital-based and standard care versus home-based exercise interventions:

Outcome: Change in systemic inflammatory response

Change in systemic inflammatory response will be assessed using the neutrophil:lymphocyte ratio (NLR) and modified Glasgow Prognostic Score (mGPS) measured on serum blood tests obtained as part of routine care (at diagnosis and prior to surgery).

Outcome: Pre-operative change in cardiopulmonary fitness

Change in cardiopulmonary fitness will be measured using CPET variables, as measured using an incremental CPET between 4 weeks prior to surgery and shortly before surgery obtained as part of the main trial. Variables assessed will include but not be limited to peak VO_2, anaerobic/ventilatory threshold, VE/VCO_2 and oxygen pulse.

Outcome: Pre-operative change in grip strength

Metric: Change in grip strength as measured using a standard digital grip strength dynamometer.

7.2.4.3.3 Sample size

The primary outcome is the change in mean muscle attenuation on CT at 6 months. For a comparison between two groups (standard care versus hospital-based and standard care versus home-based exercise interventions), a total of 95 participants per group (285 in total) will be required. This will have 90% power to detect a difference of 5 HU in mean muscle attenuation between any two treatment groups, assuming a standard deviation of 9.4 HU and a significance level of 5%, using a t-test. This will account for a drop-out rate of 20%.

7.2.5 Sub-study data collection

This sub-study does not require any visits or assessment outside of those required as part of standard care and/or participation in the PREPARE-ABC study.

The collaborating teams will be given access to the PREPARE-ABC database as appropriate; access will be managed by the NCTU trial and data management teams.

Each participant will be given a unique trial Participant IDentification Number (PID) following enrolment into PREPARE-ABC. This PID will be used to identify patients in the sub-study also. Data will be collected at the time-points indicated in the participant timeline.

All data will be handled in accordance with the Data Protection Act 1998 and GDPR (EU) 2016/679.

Basic demographic and clinicopathologic data is routinely collected as part of PREPARE-ABC. A number of these data will be required for sub-study analyses including but not limited to patient demographics, randomisation status, grip strength, CPET results, baseline height and weight and pre- and post-operative chemoradiotherapy details. In addition, for patients randomised to hospital-based or home-based exercise interventions, data from the supervised exercise sessions, motivational phone calls and exercise diary will also be included in the sub-study analyses.

Assessment of body composition

CT scans obtained as part of routine care at diagnosis and for cancer surveillance in the 12 months following surgery will be assessed for body composition analysis. DICOM images of the axial L3 vertebral level will be extracted by teams at each site. These data will be sent for analysis at St Mark's Hospital using SliceOmatic V5.0 software with the ABACS L3 Plug in.

The CT data will be analysed by automatic validated software which measures total fat, subcutaneous fat, visceral fat and skeletal muscle cross-sectional areas (cm^2) using standard Hounsfield unit ranges (adipose tissue: −190 to −30; skeletal muscle: −29 to +150, HU). Measurements will be standardised

for height to enable an index to be generated for each component, measured in cm^2/m^2 (total fat index (TFI), subcutaneous fat index (SFI), visceral fat index (VFI) and skeletal muscle index (SMI)). Sex-specific cut-offs as defined by Prado and colleagues will be applied to the skeletal muscle index to categorise patients by presence of myopenia (SMI <52.4 cm^2/m^2 for males and <38.5 cm^2/m^2 for females).

Assessment of systemic inflammatory response

Serum blood samples obtained as part of routine care at the time of diagnosis and at the pre-surgery visit prior to surgery will be used to assess the systemic inflammatory response. This will include full blood count, liver function tests and, where available, C-reactive protein (CRP).

Baseline serum CRP (mg/L) and albumin (g/L) concentrations where available will be used to calculate the modified Glasgow Prognostic score as detailed in Table 1. Neutrophil: lymphocyte ratio will be calculated from the differential white cell count and values of greater than three considered as elevated. In patients who do not have a recorded pre-operative CRP, NLR alone will be used for assessment of SIR status.

The modified Glasgow Prognostic Score (mGPS)	
C-Reactive protein ⩽ 10 mg/l and albumin ⩾35 g/l	0
C-Reactive protein >10 mg/l	1
C-Reactive protein >10 mg/l and albumin <35 g/l	2

Table 5: The modified Glasgow Prognostic Score

7.2.6 Sub-study blinding status

As this study has been proposed by collaborators at two PREPARE-ABC recruiting centres, it is possible that members of the sub-study team could be unblinded to treatment arm allocation of patients at their respective centres. They will remain blinded to the treatment arm allocation of patients at other centres. As this will only constitute a small overall proportion of patients for inclusion in the sub-study and a risk to the integrity of the sub-study analyses has not been identified, no further blinding procedures will be implemented for the sub-study teams.

Radiologists involved in carrying out CT scans as part of standard care as well as those involved in the analysis are independent of the study teams and thus will be blinded to intervention arm allocation. The CT analysis is automated and therefore further measurement bias is minimal. Any incidences of unblinding will be recorded on the eCRF.

7.2.7 Sub-study statistical methods

Statistical analysis will be performed using SPSS software (Version 24.0. SPSS Inc., Chicago, IL, USA).

Descriptive statistics will be used to analyse the baseline characteristics of the study population. For the primary outcome of muscle attenuation at 6-12 months post-procedure, the two groups (standard

care versus hospital-based and standard care versus home-based exercise interventions) will be compared using chi-squared test. Similar methods will be used to assess the change in muscle mass between each group, from baseline to their post-operative CT. Previous research (Martin et al) has suggested a standard deviation for this outcome of 9.4 HU. A difference in outcome between groups of 5 HU would be regarded as clinically important.

Dose Response Relationships

Using the self-reported physical activity data recorded in the patient exercise diaries, the sub-study team will correlate type and amount of exercise against changes in muscle mass. The muscle mass will be calculated as described above making particular note of mean muscle attenuation and L3 muscle area.

7.2.7.2 Sub-study statistical analysis plan

A sub-study statistical analysis plan (SAP) will be produced separately detailing all statistical aspects of this sub-study. The collaborating study teams will work to develop this plan with the trial statisticians and co-chief investigators. This SAP will be agreed by the PREPARE-ABC oversight committees as appropriate.

7.2.8 Sub-study publication policy

The results of the sub-study will be disseminated regardless of the direction of effect. Ownership of the data arising from this sub-study resides with the trial team and collaborating study teams. The publication(s) produced from this sub-study will be included in the publication policy of the main trial with the aim to publish in a peer-reviewed journal. The results of this sub-study will not be published prior to the publication of the results of the main trial.

8 Protocol Amendments

Document Name	Version No.	Effective Date	Reason for Change
Prepare-ABC Protocol	1.0		New protocol
Prepare-ABC Protocol	2.0	14.06.2016	Response to provisional opinion from Ethics committee
Prepare-ABC Protocol	3.0	23.09.2016	• Addition of trial identifying numbers in section 1.3 • Update of questionnaire from BREQ-2 to BREQ-3 in sections 1.3, 5.5.2, 5.6, 5.6.1.2, 5.6.1. 10 • Trial diagram updated in section 2 to reflect when patients receiving pre-operative chemotherapy will be recruited • Stop/Go criteria in section 4.3.1 for the internal pilot stage updated to reflect strengthened criteria provided to HTA in response to full application. • Confirmation on who can undertake the "Trial Physiotherapist" role for delivering the intervention at site • Addition of grip-strength measurement at 30 days following surgery in sections 5.5.2 and 5.6 • Change to section 5.4, 5.6.1.1 to when patients who are receiving pre-operative chemotherapy will be recruited to the study • Removal of collection of expenses on patient questionnaire in 5.10.5 • Addition of details of consent process for NHS staff providing information on standard care through telephone interviews with researcher in section 6.5.1 • Addition of details of consent process for people attending appointments with patients (accompanying adult) • Addition of analysis of data collected on standard care at each trust through telephone interviews with staff

			In addition to the above, minor administrative, typographical and formatting changes have been made throughout the protocol.
Prepare- ABC Protocol	4.0	16.05.2017	• Update of Protocol Authorisation signatories • Sections 1.42 -1.4.6 updated to following personnel changes and confirmation of committee members • Clarification of who an act as local Principal Investigator (Section 5.1.2) • List of studies approved for co-enrolment updated (Section 5.3.1.4) • Timeframe for pre-operative CPET amended to not more than 7 days pre-surgery (throughout Section 5.4 and 5.6.1.5) • Amendment of post-operative hospital based exercise sessions specifications to match pre-operative exercise sessions (Section 5.6.1.9) • Clarification that home-supported patients should be exercising at 13-15 on the Borg RPE Scale in-keeping with the specifications for the hospital supervised exercise sessions (Sections 5.4.2, 5.6.1.4 and 5.6.1.9) • Clarification of post-operative exercise plans for hospital supervised patients (Sections 5.4.1 and 5.6.1.9) and home supported patients (Sections 5.4.2 and 5.6.1.9) • Addition of the option for patients to subscribe to a patient newsletter and

			update email service prior to discharge following surgery (Section 5.4.4) • Addition to collect planned type of surgery (laparoscopic or data) (section 5.4) • Addition to collect tumour histological stage data at 30 days post-surgery (section 5.4). • Addition of information for sites regarding patients presenting with anaemia (Section 5.4.7) • Participant Timeline table (Section 5.6) updated to allow flexibility around 30 Day post-surgery and 6 and 12 Month follow up visits. • Addition of SAE reporting method for sites (Section 5.11.3.7.1) • Clarification of safety and per protocol definitions for patients randomised to all three treatment arms (Section 5.10.4.5) • Removal of Section 6.2 (from v3.0, 23/09/2016) as Competent Authority Approvals are not applicable to this study • Addition to permit the audio recording of intervention counselling sessions observed as part of the Process Evaluation and description of transcription analysis arrangements for the recordings (Section 7.1) • Follow-up period following patient interviews carried out as part of the Process Evaluation reduced to 3 Months (Section 7.1)

			• Addition of recommendations for optimising questioning and advice giving within counselling sessions as a component of the qualitative data analysis (Section 7.1) • Section 7.1 new reference added In addition to the above, minor administrative, typographical and formatting changes have been made throughout the protocol.
Prepare- ABC Protocol	5.0	01.03.2018	• Section 1.3 – Addition of Ireland to recruiting countries • Section 1.4 – Protocol contributors, trial management group and trial team lists updated. • Section 5.3.1.1 – Additional clarification on approaching patients with metastasis • Section 5.3.1.2 – Clarification on intention of exclusion criteria to exclude patients for whom exercise in unsafe. • Section 5.3.1.4 - Updated list of studies/projects where co-enrolment with PREPARE-ABC is and is not permitted • Section 5.4 – Clarification that patients found to have benign tumours post-operatively can remain in the study as per protocol. • Section 5.6.1.4 – section on CPET guidance added. • Section 5.6.1.5 - Clarification that patients should be encouraged to attend as many pre-operative supervised sessions as possible as opposed to a set minimum number of sessions.

			• Section 5.6.1.6 – Clarification that in the event where a patients surgery is delayed and the patient is randomised to an intervention arm, they should continue to exercise up until their surgery has taken place. • Section 5.6.1.11 – Addition of option for patients to consent to receive newsletters/trial updates during their participation. • Section 5.9.2 – Clarification on the blinding status of local study teams and independent assessors. • Section 6.4.1 – option for patients to express interest to be contacted for participation in Process Evaluation during consent process for main trial. • Section 6.4.1 – addition for patients already enrolled in the study who were not approached for participation in the PE, at the time of consent to the main trial, to express verbal consent to the local study team prior to sending relevant consent form for completion via post. • Section 7.1 – addition to allow site study staff to audio record counselling sessions if UEA research associate is unable to attend session and patient has provided written consent. • Section 7.1 – Clarification that the Process Evaluation will be conducted at UK sites only.

			In addition to the above, minor administrative, typographical and formatting changes have been made throughout the protocol.
PREPARE-ABC Protocol	6.0	05/09/2019	• Sections 1.1, 5.10.1 and 7.2.5 - Inclusion of General Data Protection Regulation (2018) adherence following implementation of legislation • Sections 1- 7 - Amendments to ensure study specific terminology is consistent • Section 1.4 - Update of study personnel and their affiliated institutions including removal of individuals no longer associated with the trial • Sections 2, 4 – 5 - Update of pre-operative exercise period to 2-4 weeks (including on trial diagram) • Sections 4.1.2, 5.4.3, 5.6.1.5, 5.6.1.10 - Confirmation that exercise advice offered as part of standard care will remain for all patients recruited into the trial and no advice regarding exercise (outside of this) will be offered to patients randomised to the control/treatment as usual arm • Section 5.1.2 - Clarification that a CPET lead only need be named for sites where available • Sections 5.3.1.1 and 5.3.1.4 - Clarification regarding the timeframe for co-enrolment assessments • Section 5.3.1.4 - Clarification that co-enrolment assessments are still required where patients remain in follow-up

			and/or have discontinued trial treatment in the opposite trial • Section 5.3.1.4 - Update to list of studies where co-enrolment has and/or has not been agreed • Section 5.3.1.3 - Confirmation of and details of remote exercise intervention training • Section 5.4.1 and 5.6.1.5 - Clarification that up to 3 sessions per week are offered in the pre-operative phase for hospital supervised patients • Section 5.4.1.1 - Addition of modified recruitment pathway for patients expressing concerns around randomisation to the hospital-supervised exercise arm • Section 5.4.4 - Clarification of timing of consent for and arrangement regarding the patient newsletter (removed duplicated information from section 5.6.1.11) • Section 5.6, 5.6.1.11 - Increased flexibility for the scheduling of the 6 and 12M follow-up visits to +/-6 weeks • Section 5.6.1.4 - Clarification of the preferred format for CPET results • Section 5.6.1.9 - Addition to text that grip strength should be measured at the 30days post-surgery visit • Section 5.6.1.8 and 5.6.1.9 - Clarification of timelines for recording post-operative complications

			• Section 5.8.1 - Update of the trial recruitment period • Section 5.8.1.1 - Confirmation that research associates can approach patients who have consented to or are interested in the process evaluation assessments • Section 5.10.4.1 - Confirmation that an interim statistical analysis plan will be produced for all planned interim analyses • Section 5.11.3.6.2 - Confirmation of expectedness assessments for serious adverse events • Section 5.11.3.6.2 - Clarification of recording requirements for serious but unrelated adverse events • Section 6.2 - Confirmation that site specific information forms will be completed for sites in devolved nations • Section 6.5 - Confirmation that only patient age in years will be recorded as opposed to month and year as previously listed • Section 6.10 - Confirmation that trial data will not be shared with collaborators without TMG and TSC approval on an individual basis • Section 7.2 – 7.2.8 - Addition of the PREPARE-ABC sub-study: defining the relationship between body composition, cardiorespiratory fitness, systemic inflammatory response and post-operative outcomes in patients with

			operable colorectal cancer participating in the PREPARE-ABC trial • Section 9 – References updated as in text citations require. In addition to the above, minor administrative, typographical and formatting changes have been made throughout the protocol.
PREPARE-ABC Protocol	7.0	11/02/2020	• Sections 2, 4 – 5 - Update of pre-operative exercise period to 3-4 weeks (including trial diagram) • Section 5.3.1.4 - Update to list of studies where co-enrolment has and/or has not been agreed • Section 5.4.1 and 5.6.1.5 – Removal of clarification that up to 3 sessions per week are offered in the pre-operative phase for hospital supervised patients • Section 5.4.1.1 – Removal of the addition of modified recruitment pathway for patients expressing concerns around randomisation to the hospital-supervised exercise arm • In addition to the above, minor administrative, typographical and formatting changes have been made throughout the protocol.
PREPARE-ABC Protocol	8.0	23/06/2020	• Section 5.4.1 – added a note referencing the updates regarding the temporary suspension of Arm A due to COVID-19 in section 5.12. • Sections 5.6.1.11 and 5.10.1 adding clarification for postal or online completion of the questionnaires as

			face-to-face visits will be reduced due to COVID-19 • Addition of Section 5.12 to outline the impact and adaptations as a result of COVID-19 including the temporary suspension of Arm A (hospital supervised exercise) • In addition to the above, minor administrative, typographical and formatting changes have been made throughout the protocol.

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10 Appendices

Appendix 1: Clavien Dindo classification of Post-Operative Morbidities (POM)

Full Scale	
Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.