

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	3.0
Date	23 September 2016
Sponsor	Norfolk and Norwich University Hospital
Trial registration	ISRCTN82233115
CTA #	N/A
NRES #	16/EE/0190

Authorisation: Co-Chief Investigator

Name	Mr James Hernon
Role	Consultant General and Colorectal Surgeon
Signature	

Date

Authorisation: Co-Chief Investigator

Name	Professor John Saxton
Role	Professor in Clinical Exercise Physiology
Signature	

Date

Authorisation: Sponsor/NCTU Director Representative

Name	Ann Marie Swart
Role	NCTU Director
Signature	

Date

Authorisation: Senior Operations Staff

Name	Erika Sims
Role	Senior Clinical Trial Operations Manager
Signature	

Date

Authorisation: Trial Statistician

Name	Allan Clark
Role	Senior Statistician
Signature	

Date

Table of Contents

1	Administrative information.....	8
1.1	Compliance	8
1.2	Sponsor	8
1.3	Structured trial summary.....	9
1.4	Roles and responsibilities.....	14
1.4.1	Protocol contributors.....	14
1.4.2	Role of trial sponsor and funders.....	14
1.4.3	Trial Team.....	14
1.4.4	Trial Management Group.....	14
1.4.5	Trial Steering Committee	15
1.4.6	Data Monitoring Committee.....	15
2	Trial Diagram	15
3	Abbreviations	17
4	Introduction	18
4.1	Background and Rationale	18
4.1.1	Rationale for choice of interventions.....	19
4.1.2	Explanation for choice of comparator	20
4.2	Objectives.....	20
4.2.1	Primary objectives.....	21
4.3	Trial Design.....	21
4.3.1	Internal Pilot Phase	21
5	Methods.....	22
5.1	Site Selection.....	22
5.1.1	Study Setting	22
5.1.2	Site/Investigator Eligibility Criteria	22
5.1.2.1	Principal Investigator’s (PI) Qualifications and Agreements.....	23
5.1.2.2	Resourcing at site.....	23
5.2	Site approval and activation	23
5.3	Participants	23
5.3.1	Eligibility Criteria	23
5.3.1.1	Participant Inclusion Criteria.....	23
5.3.1.2	Participant Exclusion Criteria	24

5.3.1.3	Eligibility Criteria for Individuals Performing the Interventions	24
5.3.1.4	Co-enrolment Guidance.....	24
5.4	Interventions.....	25
5.4.1	Arm A – Hospital Based Supervised Exercise	25
5.4.1.1	Modifications, Interruptions and Discontinuations.....	25
5.4.2	Arm B – Supported Home Based Exercise	25
5.4.2.1	Modifications, Interruptions and Discontinuations.....	26
5.4.3	Arm C – Control, Current Practice.....	26
5.4.4	Compliance and Adherence	26
5.4.5	Concomitant Care	26
5.4.6	Cancer waiting times (CWT) for trial participants.....	26
5.4.7	Protocol Treatment Discontinuation	27
5.5	Outcomes.....	27
5.5.1	Primary Outcomes	27
5.5.2	Secondary Outcomes	27
5.6	Participant Timeline	30
5.6.1	Patient Assessments	31
5.6.1.1	Screening visit	31
5.6.1.2	Baseline visit.....	31
5.6.1.3	Randomisation	31
5.6.1.4	Pre-surgery treatment phase.....	31
5.6.1.5	Within ≤5 days pre -surgery	32
5.6.1.6	Surgery	33
5.6.1.7	Post surgery discharge	33
5.6.1.8	30 day post-surgery visit	33
5.6.1.9	6 Week post surgery to 12 month postrandomisation treatment phase.....	33
5.6.1.10	6 and 12 month post randomisation follow-ups	34
5.6.2	Early Stopping of Follow-up	34
5.6.3	Participant Transfers	34
5.6.4	Loss to Follow-up	34
5.6.5	Trial Closure	34
5.7	Sample Size	35
5.8	Recruitment and Retention	35

5.8.1	Recruitment	35
5.8.1.1	Recruitment to process evaluation.....	35
5.8.2	Retention.....	35
5.9	Assignment of Intervention	36
5.9.1	Allocation	36
5.9.1.1	Sequence generation	36
5.9.1.2	Allocation concealment mechanism.....	36
5.9.2	Blinding	36
5.10	Data Collection, Management and Analysis	36
5.10.1	Data Collection Methods	36
5.10.2	Data Management	37
5.10.3	Non-Adherence and Non-Retention.....	37
5.10.4	Statistical Methods	37
5.10.4.1	Statistical Analysis Plan.....	37
5.10.4.2	Statistical Methods – Outcomes.....	37
5.10.4.3	Additional Analyses - Subgroup	38
5.10.4.4	Additional Analyses.....	38
5.10.4.5	Analysis Population and Missing Data	38
5.10.4.6	Efficacy Analyses	38
5.10.4.7	Safety Analyses	39
5.10.5	Economic evaluation.....	39
5.10.5.1	Health Economic Analysis Plan	40
5.10.5.2	Within-trial analysis	41
5.11	Data Monitoring.....	41
5.11.1	Data Monitoring Committee.....	41
5.11.2	Interim Analyses.....	42
5.11.3	Data Monitoring for Harm	42
5.11.3.1	Safety reporting	42
5.11.3.2	Clarifications and Exceptions	42
5.11.3.3	Exempted Adverse Events.....	43
5.11.3.4	Other Notifiable Adverse Events.....	43
5.11.3.5	Procedures to follow in the event of female participants becoming pregnant.....	43
5.11.3.6	Investigator responsibilities relating to safety reporting.....	43

5.11.3.6.1	Seriousness assessment.....	43
5.11.3.6.2	Causality.....	43
5.11.3.7	Notifications.....	44
5.11.3.7.1	Notifications by the Investigator to NCTU	44
5.11.3.7.2	NCTU responsibilities.....	45
5.11.4	Quality Assurance and Control	45
5.11.4.1	Risk Assessment	45
5.11.4.2	Central Monitoring at NCTU	46
5.11.4.3	On-site Monitoring.....	46
5.11.4.3.1	Direct access to participant records	46
5.11.4.4	Trial Oversight.....	46
5.11.4.4.1	Trial Management Team.....	46
5.11.4.4.2	Trial Management Group.....	46
5.11.4.4.3	Independent Trial Steering Committee	46
5.11.4.4.4	Independent Data Monitoring Committee	47
5.11.4.4.5	Trial Sponsor	47
6	Ethics and Dissemination.....	48
6.1	Research Ethics Approval.....	48
6.2	Competent Authority Approvals.....	48
6.3	Other Approvals.....	48
6.4	Protocol Amendments	48
6.5	Consent	48
6.5.1	Consent to Process Evaluation.....	49
6.5.2	Consent in Ancillary Studies.....	50
6.6	Confidentiality.....	50
6.7	Declaration of Interests	50
6.8	Indemnity	50
6.9	Finance	50
6.10	Archiving	50
6.11	Access to Data.....	50
6.12	Ancillary and Post-trial Care.....	50
6.13	Publication Policy	51
6.13.1	Trial Results	51

6.13.2	Authorship.....	51
6.13.3	Reproducible Research	51
7	Ancillary Studies.....	52
7.1	Process Evaluation	52
8	Protocol Amendments	55
9	References	57
10	Appendices.....	61

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 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
Contact for Public Queries	Prepare.ABC@uea.ac.uk
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
Health Condition(s) or Problem(s) Studied	Post-operative recovery in patients awaiting curative colorectal cancer surgery.
Intervention(s)	Intervention 1 Hospital-Based Supervised exercise programme consisting of: Pre-surgery: Initial 45 min 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

	<p>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.</p> <p>Plus: 6 weeks post-surgery to 12 months post randomisation: Patients will be encouraged to comply with current physical activity recommendations: 150 min 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.</p> <p>Intervention 2 Supported Home-Based exercise Pre-surgery: Initial 45 min 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 min 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 min telephone support from a Trial Physiotherapist to encourage compliance with the exercise programme.</p> <p>Plus: 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 min motivational telephone calls from a Trial Physiotherapist.</p> <p>Control 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.</p>
Key Inclusion and Exclusion Criteria	<p>Target population: NHS patients awaiting a curative elective colorectal resection for cancer.</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Male and female participants \geq 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

	<ol style="list-style-type: none"> 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 <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Contra-indications to exercise (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 (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.
Date of First Enrolment	1 November 2016
Target Sample Size	1146 patients
Primary Outcome(s)	<p>Two primary outcomes will be used:</p> <p>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</p> <p>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.</p>
Key Secondary Outcomes	<p>The following secondary outcomes will be assessed for standard care versus hospital based and standard care versus home based exercise interventions:</p> <p>Pre-operative outcomes</p>

	<p>The following outcomes will evaluate response to the intervention in the pre-operative phase of the study only.</p> <p>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).</p> <p>Outcome: Pre-operative change in grip strength. Metric: Change in grip strength as measured using a standard digital grip strength dynamometer</p> <p>Post-operative outcomes: Outcome: Length of hospital stay Metric: Duration of stay from date of operation to discharge immediately following operation</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Outcome: 90-day post-operative mortality, Metric: Defined as percentage of patients who died on or up to 90 days following date of operation.</p> <p>Outcome: Post-operative change in grip strength. Metric: Change in grip strength as measured using a standard digital grip strength dynamometer</p> <p>The following outcomes will be evaluated at baseline, 6 months and 12 months post randomisation:</p> <p>Outcome: Physical activity behaviour</p>
--	--

	<p>Metric: Measured using modified Godin Leisure Time Exercise Questionnaire (modified)</p> <p>Outcome: Psychological health status, Metrics: Measured using Hospital Anxiety and Depression Scale (HADS)</p> <p>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)</p> <p>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</p>
--	---

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 Heron	NNUH	Co-Chief Investigator
John Saxton	Northumbria University	Co-Chief Investigator
Ann Marie Swart	NCTU	Norwich CTU Director, review and revision of protocol
Erika Sims	NCTU	Senior Clinical Trial Operations Manager
Juliet High	NCTU	Trial Manager
Allan Clark	NCTU	Statistician
David Turner	NCTU	Senior Health Economist
Lisa Irvine	NCTU	Health Economist

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Lisa Chalkley	NNUH	Sponsor's Representative
Marcus Flather	NNUH	R&D Director

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
James Heron	NNUH	Co-Chief Investigator
John Saxton	Northumbria University	Co-Chief Investigator
Jennifer Wilkinson	NCTU	Set-up and management of delivery of clinical trial
Erika Sims	NCTU	Senior Clinical Trial Operations Manager
Antony Colles	NCTU	Senior Data Programmer
Leodie Alibert	NCTU	Quality Assurance Lead
David Turner	NCTU	Senior Health Economist
Allan Clark	NCTU	Senior Statistician
Lisa Irvine	NCTU	Health Economist
Jamie Murdoch	NCTU	Process Evaluation Lead
Laura Thomas	Northumbria University	Exercise Psychologist

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
James Heron	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

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	UEA	Senior Clinical Trial 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		Patient Representative
Nicola Fearnhead	CUH	Principal Investigator and Co-Applicant
Simon Bach	QEHB	Principal Investigator and Co-Applicant
Jurgens Nortje	NNUH	Principal Investigator and Co-Applicant
Colin Rees	South Tyneside	Principal Investigator
Laura Thomas	Northumbria University	Exercise Psychologist

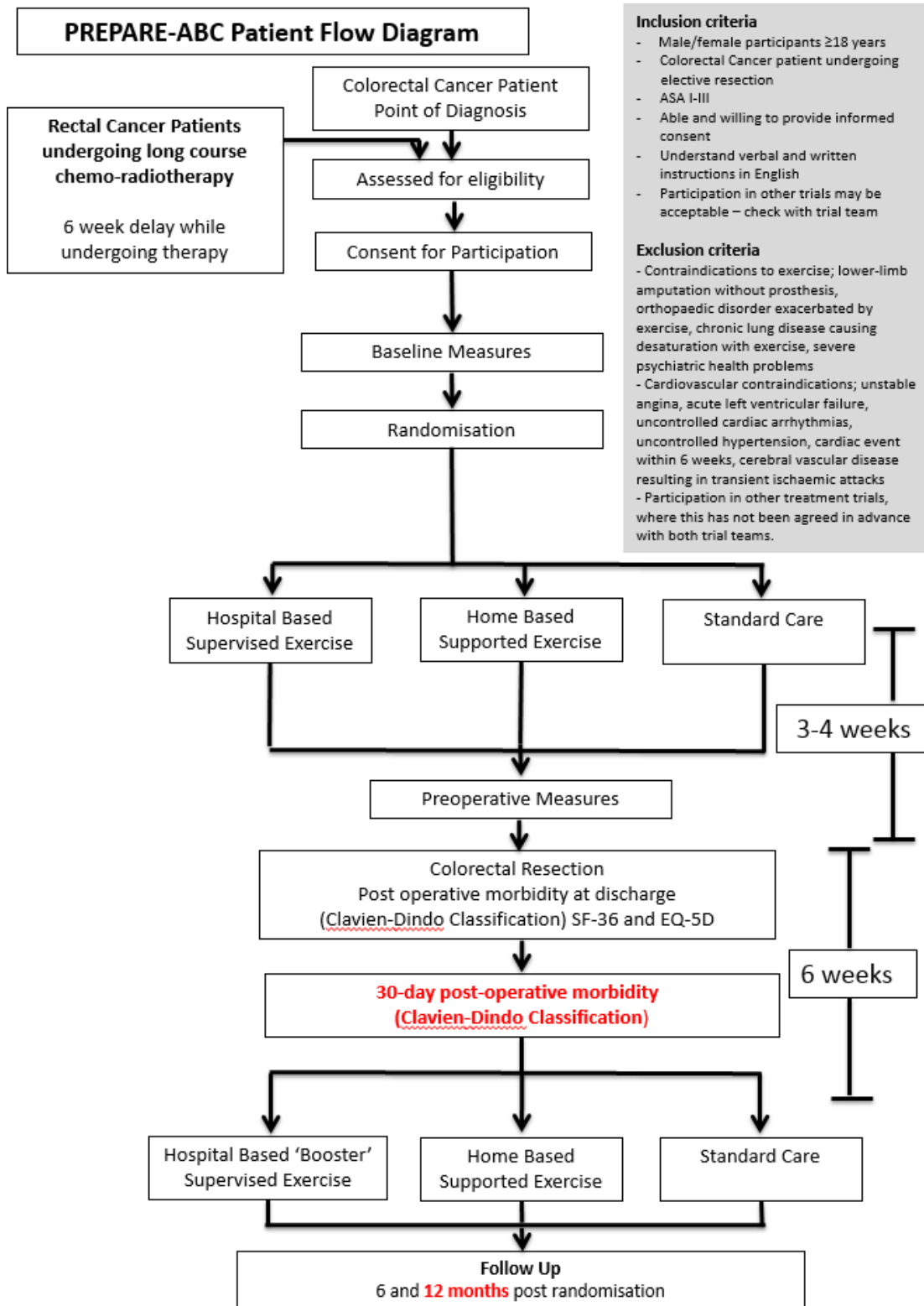
1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities

1.4.6 Data Monitoring Committee

Name	Affiliation	Role and responsibilities

2 Trial 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
CSRI	Client Service Receipt Inventory
CTA	Clinical Trial Authorisation
CUH	Cambridge University Hospitals NHS Foundation Trust
CWT	Cancer Waiting Times
DTH	Derby Teaching Hospitals
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
MHRA	Medicines and Healthcare products Regulatory Agency
NCRN	National Cancer Research Networks
NCTU	Norwich Clinical Trials Unit
NHC	Northumbria Healthcare NHS Foundation Trust
NIHR	National Institute for Health Research
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
SSA	Site Specific Approval
TAU	Treatment as usual
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TP	Trial Physiotherapist
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 postoperative 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 their trial physiotherapist, 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 programs 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 preoperative 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 treatment as usual. Patients are not routinely given advice on exercise pre or post-surgery.

4.2 Objectives

There are three trial arms:

- Arm A – Hospital based supervised exercise
- Arm B – Supported home based exercise
- Arm C – Control Arm, 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 single blind (assessors only), 3-arm, randomised controlled trial, to investigate the clinical and cost effectiveness of exercise interventions for cancer patients awaiting curative, elected colorectal cancer surgery in the UK.

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 Chief Investigators and NCTU.

5.1.1 Study Setting

Participants will be identified from colorectal units in the UK, at point of diagnosis. Initially the following centres will be opened, but with the intention to open further sites as the study progresses. The collaborating centres identified at study start-up are: Norfolk and Norwich University Hospital, Northumbria NHS Foundation Trust, Sheffield University Hospital, Cambridge University Hospital NHS Trust, Queen Elizabeth Hospital Birmingham, Derby Hospitals NHS Foundation Trust, Imperial College Healthcare NHS Trust, Royal Devon and Exeter NHS Foundation Trust, Western General Hospital Edinburgh, Central Manchester University Hospitals, Peterborough and Stamford Hospitals 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 physiotherapist 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 is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff are available to recruit participants, enter data and provide support
- A named lead physiotherapist available to fulfil the requirements of the trial
- A named lead to coordinate CPET testing
- The centre 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 NHS Trusts. Recruitment targets will be discussed with each centre.
- The centre 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 a NCTU Clinical Trial Agreement or 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 initiation. 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) 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

5.3.1.2 Participant Exclusion Criteria

1. Contra-indications to exercise (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 (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.

5.3.1.3 Eligibility Criteria for Individuals Performing the Interventions

Trial 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 an initial face to face session, refresher meetings and a physiotherapy manual.

For the purposes of the trial, a Trial physiotherapist is any member of the research team trained to deliver the trial intervention at site. These will include physiotherapists, registered nurses, exercise scientist, exercise trainer, exercise practitioner or health care assistant. This list is not exhaustive, and other appropriately trained members of the team can deliver the intervention at the agreement of the lead physiotherapist and PI of the site, and the co-CIs. A named physiotherapist 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 Norwich CTU to discuss this, prior to their recruitment.

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

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

5.4 Interventions

There are three trial arms:

- Arm A - Hospital based supervised exercise
- Arm B - Supported home based exercise
- Arm C - Control Arm, 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 5 days) of their planned colorectal surgery.

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 CPET 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

Baseline CPET will be performed.

Pre-surgery: Initial 45 min exercise counselling session, 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 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 or instructed to maintain their home exercise programme 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 min repetitions at 60-80% of heart rate reserve (~60-80% peak VO₂; Borg RPE Scale 13-15 (Borg 1970) with 2.5 min rest intervals. There will also be 2 home-based resistance exercise sessions per week.

Pre-surgery CPET to be completed not more than 5 days prior to 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 provided with a pedometer to record step counts throughout the study

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 CRF. Exercise intensity and duration will be closely controlled and will only be progressed through discussion with the physiotherapist.

5.4.2 Arm B – Supported Home Based Exercise

Baseline CPET will be performed.

Pre Surgery: Initial 45 min exercise counselling session, incorporating behaviour modification techniques, followed by a home exercise programme achieving a minimum of 150 min of moderate intensity aerobic

exercise per week (e.g. brisk walking/jogging/cycling/swimming, etc.) 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 min telephone support from the Trial Physiotherapist 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 5 days prior to 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 the Trial Physiotherapist.

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 CRF. Exercise intensity and duration will be closely controlled and will only be progressed through discussion with the physiotherapist.

5.4.3 Arm C – Control, Current Practice

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.

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 exercises. 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 log, with daily step counts also being recorded via the pedometer.

Compliance will be reviewed at the CPET 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.

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 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:

Preoperative 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 heart beat).

- 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 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

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

Visit	Pre-Surgery					Surgery	Post-Surgery			Post randomisation	
	Screening (Diagnosis)	Baseline	Randomisation - 4 weeks to surgery	Pre-surgery -4 to -3 weeks	Pre-surgery ≤ 5 days		Post surgery discharge ~ 5-7 days	Post surgery 30 days	Post surgery 6 weeks	6 month follow up visit	12 month follow up visit
Consent	X										
Eligibility	X										
Demographics		X									
Medical history		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	
Grip Strength		X			X		X		X	X	
Randomise to Intervention			X								
Exercise Intervention (or TAU Arm C)				←————→				←————→			
Record exercise related AEs where applicable				←————→				←————→			
Record POMs in CRF						←————→					
POM Clavien–Dindo Classification						X	X				
Blinded assessment of fitness for discharge						X					
Resource Use questionnaire		X							X	X	
Review of adherence to exercise interventions (if applicable)					X				X	X	

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 the 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 CPET.

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 in the eCRF 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.

5.6.1.4 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 12 sessions. Each session will comprise

6 x 5 min repetitions at 60-80% of heart rate reserve (~60-80% peak VO₂; Borg RPE Scale 13-15 (Borg 1970), with 2.5 min 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 log 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 Trial Physiotherapist 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 logs. 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.) 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 log 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 the Trial Physiotherapist to encourage compliance with the exercise programme.

These telephone calls will be made by a Trial Physiotherapist 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 logs. 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 (current practice). They will receive all other treatment as usual, offered prior to curative colorectal cancer surgery.

5.6.1.5 Within ≤5 days pre -surgery

All participants (all arms) must have their second CPET within 5 days prior to their curative surgery taking place, grip strength should be measured at the same time.

5.6.1.6 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.

5.6.1.7 Post surgery discharge

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

5.6.1.8 30 day post-surgery visit

30 day post-operative morbidity (Clavien-Dindo Classification) to be recorded and SF-36 and EQ-5D-5L questionnaires to be completed.

5.6.1.9 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 date of return to usual activities 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 and will be encouraged to engage in weekly self-directed exercise.

Patients will also be offered supervised "booster" exercise sessions, approximately monthly until 12 months post randomisation. These exercise sessions will last for around 1 hour and the same exercise choices will be offered as before e.g. cycle-ergometer, Thera-bands and free weights (if available). Participants will be encouraged to exercise at moderate intensity activity (50-69% of predicted maximum heart rate [220-age] or 12-14 on the Borg Ratings of Perceived Exertion Scale). These sessions will be delivered by a Trial Physiotherapist 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 logs. 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.

Patients will receive a 15 minute telephone contact support session each month with the Trial Physiotherapist, 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 physiotherapist will reinforce cognitive-behavioural strategies and ensure exercise logs are being kept up-to-date and properly completed. These telephone calls will be made by a Trial Physiotherapist 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 logs. 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 (current practice). All other treatment as usual will be offered post curative colorectal cancer surgery.

5.6.1.10 6 and 12 month post randomisation follow-ups

All participants will be asked to complete questionnaires, these will be sent by post ahead of routine clinic visits at 6 and 12 months post randomisation (patients to bring completed 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.

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 using the appropriate PREPARE-ABC trial documentation. 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 moved.

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 centre inappropriate, every effort should be made for them to be followed at another participating trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre 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 centres will between them recruit 1146 patients over the 2.5 year trial period.

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 participate in the process evaluation will be approached by the local research team 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 entered, and all other pre-designated questions completed in the CRF, 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.

Outcomes will be assessed by an independent assessor, blinded to treatment allocation. CPET tests will be performed by blinded hospital CPET technicians. There will be no contact between the independent assessors/CPET technicians and physiotherapists delivering the intervention.

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 of 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 Norwich CTU. Identification logs, screening logs and enrolment logs will be kept locally, either in paper or electronic form.

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 CTU data programmer and tested by the trial statistician 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.

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 trained site team and recorded in the CRF.

5.10.4 Statistical Methods

5.10.4.1 Statistical Analysis Plan

A full Statistical Analysis Plan (SAP) 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 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 50% of the hospital based sessions or home-based if they are allocated an exercise-based group;
- c) safety population: all randomised individuals who start at least one exercise session if they are allocated an exercise-based group.

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. The Trial Physiotherapist 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 logs. 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 physiotherapists as well as attendance at the 45 minute exercise counselling session. Post-operatively the home base group will receive a 15 minute motivational telephone call monthly from the Trial Physiotherapist, 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, withdraw rates, etc. will be conducted as part of the internal pilot.

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 1: 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: <ul style="list-style-type: none"> • 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***
<p>* 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)</p> <p>** 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</p> <p>*** 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).</p>	

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 CRF. 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

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.

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 exercise or reported as a post-operative morbidity (POM) these should still be reported to NCTU.

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 2: 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 condition or other concomitant treatment)	SAR
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 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.

The SAE form must be scanned and sent by email to the trial team at NCTU if assessed as related to the intervention.

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 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 trial 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. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

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.

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 Competent Authority Approvals

This is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is not required in the UK.

6.3 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 in each country. 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.

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

6.4 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.

6.5 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.

6.5.1 Consent to Process Evaluation

As part of main trial recruitment, patients will also be offered the option to provide informed consent to be interviewed and/or allow a researcher to observe their care. As patient interviews will take place 12 months after randomisation, we will ask patients to provide permission to contact them and/or a carer within 1 month prior to completion of the study to request informed consent to be interviewed. If informed consent is provided, we will then 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. 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. All patients, accompanying adults (observations only) and NHS 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.

Consent will be required from NHS 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 NHS 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.

6.5.2 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 but should plans emerge they will require additional funding and ethics applications to be made.

6.6 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 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 month and year of birth 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.

6.7 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.

6.8 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.

6.9 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.

6.10 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.

6.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG and TSC. 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.

6.12 Ancillary and Post-trial Care

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

6.13 Publication Policy

6.13.1 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.

6.13.2 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.

6.13.3 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

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 CTU.

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 min exercise counselling sessions in the hospital supervised and home-based interventions; 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 Physiotherapists to identify challenges of intervention delivery. As the same Physiotherapist 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 log sheets 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 1-year follow-up and completion of the study, in order to not bias the effect of the intervention and 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. Potential participants will be telephoned, and given the opportunity to discuss the study with a researcher prior to agreeing to a date and time for an interview. Any participants who expressed an interest, 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.

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).

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; and tentative explanations for the reasons underlying apparent successes or failures.

8 Protocol Amendments

Document Name	Version No.	Effective Date	Reason for Change
Prepare-ABC Protocol	1.0		New protocol
Prepare-ABC Protocol	2.0		Response to provisional opinion from Ethics committee
Prepare-ABC Protocol	3.0		<ul style="list-style-type: none"> • 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.

9 References

ACPGBI 2015 <http://www.acpgbi.org.uk/surgeon-outcomes/>

ASA 2014, <https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system> Last approved by the ASA House of Delegates on October 15, 2014

Bartlett JD, Close GL, MacLaren DP, Gregson W, Drust B and Morton JP. (2011) High-intensity interval running is perceived to be more enjoyable than moderate-intensity continuous exercise: implications for exercise adherence. *Journal of Sports Science*. 29(6), 547-53

Benzo R, Kelley GA, Recchi L, Hofman A and Sciruba F. (2007) Complications of lung resection and exercise capacity: a meta-analysis. *Respiratory Medicine*. 101, 1790-1797.

Borg G. (1970) Perceived exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitation Medicine*. 2, 92-98

Britten N. (2006) Qualitative interviews in medical research. In Pope C., Mays N., eds. *Qualitative research in health care*, Oxford: Blackwell Publishing Ltd.

Carli F, Charlebois P, Stein B., Feldman L, Zavorsky D, Kim J, Scott S. and Mayo NE (2010) Randomized clinical trial of prehabilitation in colorectal surgery. *British Journal of Surgery*. 97: 1187-1197

Chan A.W., Tetzlaff J.M., Altman D.G. et al. SPIRIT 2013 Statement: Defining Protocol Items for Clinical Trials. *Ann Intern Med* 2013; 158:200-207.

Chan A.W. , Tetzlaff, Gotzsche et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346: e7586.

Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, et al. (2009) The Clavien- Dindo classification of surgical complications: five-year experience. *Annals of Surgery*. 250(2), 187-96

CRUK, 2015 <http://www.cancerresearchuk.org/content/cancer-incidence-for-common-cancers#heading-Zero>

DOH 2011, Department of Health. Enhanced recovery partnership programme 2011

Department of Health. UK Physical activity guidelines. 2011. Crown.
<https://www.gov.uk/government/publications/uk-physical-activity-guidelines>

Fazio VW, Zutshi M, Feza H, Remzi FH, et al. (2006) A Randomized Multicenter Trial to Compare Long-Term Functional Outcome, Quality of Life, and Complications of Surgical Procedures for Low Rectal Cancers. *Annals of Surgery*. 246, 481–490

Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, Sender Liberman A, Stein B, Charlebois P, Feldman LS and Francesco Carli. (2012) Prehabilitation versus Rehabilitation: A Randomized Control Trial in Patients Undergoing Colorectal Resection for Cancer. *Anesthesiology*. 121, 937-47

Godin G, and Shepard RJ. (1985) A simple method to assess exercise behaviour in the community. *Canadian Journal of Applied Sport Science*. 10, 141-146.

- Gold M.R., Siegel J.E., Russell L.B., Weinstein M.C. Cost-effectiveness in health and medicine. (ed.) 1996. Oxford University Press, New York.
- Gouvas N, Tan E, Windsor A, Xynos E and Tekkis PP. (2009) Fast-track vs standard care in colorectal surgery: a meta-analysis update. *International Journal of Colorectal Disease*. 24, 1119-1131.
- Green J, Thorogood N, and Ebrary I. (2004) *Qualitative methods for health research*. London: SAGE
- Grocott MPW, Browne JP, Van der Meulen J et al. (2006) The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *Journal of Clinical Epidemiology* 60, 919-928.
- Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, and Badia X. (2011) Development and preliminary testing of the new five level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*. 20(10): 1727–1736.
- Huang G, Wang R, Chen P, Huang SC, Donnelly JE, and Mehifeber JP. (2015) Dose-Response relationship of cardiorespiratory fitness adaptation to controlled endurance training in sedentary older adults. *European Journal of Preventative Cardiology*, (Epub ahead of print) PMID: 2590100
- Improving Surgical Outcomes Group (ISOG). *Modernising care for patients undergoing major surgery: improving patient outcomes & increasing clinical efficiency. A report by the Improving Surgical Outcomes Group*. 2005.
- Kehlet H and Wilmore DW. (2008) Evidence-based surgical care and the evolution of fast-track surgery. *Annals of Surgery*. 248, 189-198.
- Kennedy RH, Francis EA, Wharton R, Blazeby JM, Quirke P, West NP, and Dutton SJ. Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL. *Journal of Clinical Oncology*. 2014 32(17):1804-1811
- Li C, Francesco Carli F, Lee L, Charlebois P, Stein B, Liberman AS, Kaneva P, Augustin B, Wongyingsinn M, Gamsa A, Kim DJ, Vassiliou MC, Feldman LS. (2013) Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surgical Endoscopy*. 27, 1072–1082
- Manca A, Hawkins N, and Sculpher MJ. "Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility." *Health economics* 14.5 (2005): 487-496.
- Mazurek K, Krawczyk K, Zmijewski P, Norkowski H, and Czajkowska A. (2014) Effects of aerobic interval training versus continuous moderate exercise programme on aerobic and anaerobic capacity, somatic features and blood lipid profile in collegiate females. *Annual Agricultural and Environmental Medicine*, 21(4), 844-849.
- Meyerhardt JA, Heseltine D, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Schilsky RL, and Fuchs, CS. (2006) Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *Journal of Clinical Oncology* 24(22), 3535-3541
- Miles A, Simon A, Wardle J (2010) Answering patient questions about the role lifestyle factors play in cancer onset and recurrences. *Journal of Health Psychology*, 15, 291-298.
- NBOCA (National Bowel Cancer Audit) 2014, <http://www.hscic.gov.uk/catalogue/PUB16021>

NCSI, (National Cancer Survivorship Initiative) 2014 <http://www.ncsi.org.uk>

NIAA (National Institute of Academic Anaesthesia) 2015, <http://www.niaa.org.uk/JLA-NIAA-Priority-Setting-Partnership-Final-Results> (May 2015)

Phypers BJ, Robiony-Rogers D, Pickering RM and Garden AL. (2011) Test-retest reliability of the oxygen uptake efficiency slope in surgical patients. *Anaesthesia*. 66, 659-666.

Resnick B and Jenkins LS. (2000) Testing the reliability and validity of the Self-Efficacy for Exercise scale. *Nursing Research*. 49, 154-159.

Resnick B, Luisi D, Vogel A and Junaleepa P. (2004) Reliability and validity of the self-efficacy for exercise and outcome expectations for exercise scales with minority older adults. *Journal of Nursing Measurement*. 12, 235-247.

Rubin, Donald B. *Multiple imputation for nonresponse in surveys*. Vol. 81. John Wiley & Sons, 2004

Santa Mina D, Clarke H, Ritvo P, Leung YW, et al. (2014). Effect of total body prehabilitation on postoperative outcomes: a systematic review and meta analysis. *Physiotherapy*. 100(3), 196-207

Singh F, Newton RU, Galvão DA, Spry N., Baker MA. A systematic review of pre-surgical exercise intervention studies with cancer patients. (2013). *Surgical Oncology*. 22, 92-104

Smith TB, Stonell C, Purkayastha S and Paraskevas P. (2009) Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. *Anaesthesia* 64, 883-893.

Statts WC. (2002) Physical activity determinants in adults. Perceived benefits, barriers and self-efficacy. *AAOHN Journal* 50, 499-507.

Thompson AR, Peters N, Lovegrove RE. et al. (2011) Cardiopulmonary exercise testing provides a predictive tool for early and late outcomes in abdominal aortic aneurysm patients. *Annual of the Royal College of Surgeons of England*. 93, 474-481.

Thorpe G and HERNON J. (2015) Hidden morbidity following colorectal resection: Postoperative evaluation. *Digestive Disorders Federation* June 2015, Abstract PTU-271

Timmerman H, de Groot JF, Hulzebos HJ, de Knikker R, et al. (2011). Feasibility and preliminary effectiveness of preoperative therapeutic exercise in patients with cancer: a pragmatic study. *Physiotherapy Theory and Practice*. 27(2), 117-24.

Valkenet K, van de Port I, Dronkers JJ, de Vries WR, Lindeman E and Backx FJ. (2011) The effects of preoperative exercise therapy on postoperative outcome: a systematic review. *Clinical Rehabilitation* 25, 99-111.

Vonlanthen R, Slankamenac K, Breitenstein S, Puhan MA, Muller MK, Hahnloser D, Hauri D, Graf R, and Clavien PA. (2011) The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. *Annals of Surgery*. 2011 254(6) 907-13

Ware JE Jr. and Sherbourne CD. (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 30, 473-483.

West MA, Lythgoe D, Barben CP, et al. (2013) Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. *British Journal of Anaesthesia*. 112, 665-71.

West MA, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, Grocott MP, and Jack S. (2015) Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Br J Anaesth*. 114(2):244-251

Zigmond AS and Snaith RP. (1983) The hospital anxiety and depression scale. *Acta Psychiatr.Scand*. 67, 361-370.

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.