SupPoRtive Exercise Programs for Accelerating REcovery after major ABdominal Cancer surgery trial (PREPARE-ABC): pilot phase of a multi-centre randomised controlled trial

On behalf of the PREPARE-ABC Trial Collaborative*

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Originality Statement
Here we report on the pilot phase of the PREPARE-ABC RCT: confirming the feasibility of site set-up, patient recruitment, representativeness of the sample population and patient engagement with the exercise interventions.

SUMMARY

Background: PREPARE-ABC is a pragmatic multi-centre randomised controlled trial including an internal pilot designed to assess the clinical and cost-effectiveness of pre- and post-operative exercise in relation to short- and longer-term post-operative recovery outcomes in colorectal cancer patients undergoing surgical resection. Here, we report on internal pilot phase data for the first 200 patients randomised to the trial, which included pre-specified stop-go criteria used to inform the decision to progress to the fully powered trial by the funder.

Methods: Eligible and consenting patients are randomly assigned (1:1:1) to hospital-supervised exercise, home-supported exercise or treatment as usual (TAU). Randomisation is concealed but clinical teams providing treatment and participants are unmasked. Primary outcomes are 30-day morbidity (Clavien-Dindo) and 12-month health-related quality of life (Medical Outcomes Study Health Questionnaire). Here, we present findings from the pre-specified pilot phase which assessed feasibility of site set up, recruitment, adherence and acceptability of trial processes to patients and site staff. **Findings:** Between 9th November 2016 and 18th May 2018, 18 sites were set up, with 200 patients randomised to either hospital-supervised exercise (68), home-supported exercise (69) or Treatment as usual (TAU) (63). Across the groups, 19 patients did not proceed to surgery or withdrew

and 52% experienced a complication. Adherence to exercise was very good, with 57% patients in the hospital-supervised group attending ≥6 pre-operative sessions and 50% attending ≥5 monthly post-operative exercise "booster sessions". In the home-supported group, 70% patients engaged with ≥2 telephone support sessions in the pre-operative phase and 80% engaged in ≥5 monthly telephone support "booster sessions". Adverse events were reported by 22 patients and three patients reported a serious adverse event. The majority of complications were Clavien-Dindo grades 1-2, however, 16 patients experienced one or more Clavien-Dindo grade 3-4 complication(s). **Interpretation:** Results of the internal pilot phase confirm the feasibility of site set-up and patient recruitment, representativeness of the sample population and adequate adherence to hospital-supervised and home-supported exercise. On the basis of these positive results, progression to the fully-powered trial was authorised by the funder.

INTRODUCTION

The physiological stress of major surgery has been compared to that of an intense exercise challenge [1]. Patients with low cardiopulmonary fitness ('physiological reserve') may be unable to meet a substantial increase in oxygen demand resulting from systemic inflammation by increasing cardiac output and oxygen delivery to vital organs [2]. In combination with the catabolic stress response and loss of skeletal muscle mass induced by bed rest [3], this places inactive, deconditioned patients at increased risk of post-operative complications. Improvements in cardiopulmonary fitness and muscular strength, accompanied by amelioration of fatigue and other treatment-related side effects have been reported following structured exercise programs in people living with and beyond a broad range of cancer types [4]. Furthermore, a physically active lifestyle is associated with improved survival outcomes after curative-intent treatment for early-stage colorectal, breast and prostate cancer [5]. More recently, there has been increasing interest in the potential role of exercise as a treatment for optimising cardiometabolic fitness and maintaining skeletal muscle mass prior to major surgery ('prehabilitation'), with the aim of improving post-operative recovery outcomes.

Studies have reported an association between cardiopulmonary fitness and post-operative recovery outcomes in cancer patients, including those undergoing colorectal resection [6]. Furthermore, there is evidence that hospital-supervised exercise can lead to improvements in cardiopulmonary and functional fitness outcomes, maintenance of lean body mass and an augmentation of tumour regression grading in colorectal cancer patients prior to surgery [7, 8]. In addition, improved functional fitness and maintenance of lean body mass during the peri- and post-operative periods has been reported in colorectal cancer patients following home-based trimodal prehabilitation, incorporating exercise, nutritional and psychological support [9-11]. This raises the question of whether exercise prehabilitation could become an important adjunct to enhanced recovery after surgery (ERAS) programs for optimising peri- and post-operative recovery. However, most studies to date have been unable to show that exercise training alone or as part of multi-modal prehabilitation translates into reduced peri-operative risk or improved post-operative outcomes in colorectal cancer patients undergoing surgical resection [12-15].

PREPARE-ABC (SupPoRtive Exercise Programs for Accelerating REcovery after major ABdominal Cancer surgery) is a 3-arm, multi-centre randomised controlled trial designed to assess the effects of hospital-supervised and home-supported exercise on short- and longer-term post-operative recovery outcomes in colorectal cancer patients undergoing curative-intent major abdominal surgery. By addressing key limitations of previous research, the trial will generate robust research and cost-effectiveness data to underpin clinical guidance on how exercise should be implemented in the routine management of colorectal cancer patients awaiting surgical resection. The full trial protocol has been published (accepted, in press) [16]. The embedded internal pilot aimed to determine key uncertainties prior to the main study and to establish whether the components of the main study can all work together. The main objectives were to confirm feasibility of site set-up and patient recruitment, acceptability of the interventions and patient

adherence to hospital-supervised and home-supported exercise. Here, we report on these pilot phase outcomes in respect of the first 200 patients randomised to PREPARE-ABC. All data collected in the internal pilot phase are to be included in the main trial analyses.

METHODS

Study design and participants

This multi-centre, parallel group, randomised controlled trial included three arms: (1) hospital-based supervised exercise; (2) home-based supported exercise; (3) treatment as usual control group (Figure 1). Treatment as usual describes the current level of care delivered by the unit at the time the site opened to the study. Eligible patients were ≥ 18 years old; awaiting a curative elective colorectal resection for cancer (laparoscopic or open, with a treatment plan in place to manage the primary tumour and any metastatic disease [operative or radiological intervention] with the aim of cure); American Society of Anaesthesiologists physical status I-III; able and willing to provide informed consent; able to understand verbal and written instructions in English. The trial exclusion criteria are: presence of comorbid contra-indications to exercise such as 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; cardiovascular contra-indications, e.g. unstable angina, acute left ventricular failure, uncontrolled cardiac arrhythmias, uncontrolled hypertension; cardiac event in the previous 6 weeks or cerebral vascular disease resulting in transient ischaemic attacks. Written informed consent was obtained from patients following ethical approval being issued by the East of England – Essex Research Ethics Committee (Reference: 16/EE/0190). An independent trial Data Monitoring Committee was provided with safety data for each treatment arm, including frequency of adverse events (AEs) and serious adverse events (SAEs).

The internal pilot study was based on patients recruited during the first 18 months of the study, allowing an assessment of feasibility of site set up, patient recruitment, adherence and acceptability of the interventions.

Randomisation and masking

Eligible and consenting patients were randomly assigned (1:1:1) to hospital-supervised exercise, home-supported exercise or treatment as usual (TAU) after completion of baseline assessments. The study is single blind (assessors only). However, cardiopulmonary exercise test (CPET) assessors and clinicians recording post-operative morbidities are independent of the study team and blinded to treatment allocation.

Interventions

Full details of the interventions have been published elsewhere (accepted article, in press) ([16]). Briefly, in the pre-operative phase, both exercise interventions began with a 45-minute exercise counselling session in the hospital setting. Patients in the hospital-supervised exercise arm were then offered up to three vigorous intensity (60-80% heart rate reserve or 13-15 on the Borg Scale [17]) aerobic interval exercise sessions per week on a cycle ergometer prior to surgery. Commencement of the intervention (if applicable) was delayed for 6 weeks in patients with rectal cancer undergoing long course chemo-radiotherapy Patients in the home-supported exercise arm were encouraged to achieve a minimum of 150 minutes of moderate-vigorous intensity aerobic activity per week, and received weekly 15-minute telephone support to encourage adherence to the program. Patients in both arms were also instructed to undertake two home-based resistance exercise sessions per week using resistance bands (Theraband, Akron, OH, USA). Six weeks post-operatively, patients in both exercise arms were encouraged to achieve 150 minutes of moderate-vigorous intensity aerobic activity per week and two weekly sessions of resistance exercise. Encouragement and support was provided via a monthly supervised “booster” exercise session

(hospital-supervised group) or monthly telephone support sessions (home-supported group) until 12 months post-randomisation.

Control group

In the pre-operative period, participants randomised to the control arm receive TAU before and after curative colorectal cancer surgery, which does not include support for pre- or post-operative exercise.

Outcomes

Outcomes for the pilot were feasibility of site set up defined as 75% of originally planned 12 sites open by month 12; feasibility of recruitment with ≥30% of eligible patients from each site recruited to the study and 50% of 12 sites identified prior to study start-up achieving recruitment rates sufficient to sustain the fully powered randomised controlled trial (i.e. six sites accruing 4-5 patients per month during months 16-18); patients achieving meaningful adherence to the exercise arms, defined as ≥6 pre-operative supervised exercise or telephone support sessions in ≥70% of patients and ≥50% post-operative booster exercise or telephone sessions in ≥70% of patients. Acceptability and safety of the exercise interventions was assessed by review of serious and non-serious adverse events. Acceptability of trial processes was assessed by regular informal feedback from site staff to the trial team and by a review of patient and site staff experiences in a formal process evaluation (reported in detail elsewhere)

Statistical Analysis

The pilot phase analysis includes data on the first 200 patients randomised during the first 18 months of the study. Data are presented as mean (standard deviation) for continuous variables, median (interquartile range) for heavily skewed continuous variables and number (percentage) for categorical variables. AEs and SAEs are tabulated by category of AE using the MedDRA classification. The trial is listed in the ISRCTN registry (ISRCTN82233115).

RESULTS

Site recruitment and patient accrual

A total of 48 centres expressed an interest in participation during the first 12 months of the study, of which 30 did not proceed to set-up within this timeframe or withdrew before recruiting their first patient. Of 17 sites that were converted to recruiting centres during the first 12 months of the pilot phase, 12 (71%) opened within 9 months of expressing an interest (median of 8 months to opening for all 17 sites). As one additional site was recruited during the last 6 months of the pilot phase, data are reported from patients randomised at 18 sites.

Between 9th November 2016 and 18th May 2018, 200 patients from 18 sites across the UK were randomly assigned to receive either hospital-supervised exercise (68), home-supported exercise (69) or TAU (63). A total of 1309 patients were screened for participation of which 400 were eligible, giving an overall recruitment rate for the first 200 patients of 50% (Figure 2). Early scheduling of operation date (within 2 weeks), preconceptions amongst clinical teams about the inability of patients to engage in an intensive pre-operative exercise programme, the time commitment required for exercise and/or being reluctant (or unable) to travel were key reasons for non-participation amongst eligible patients. As a result of exceeding the site recruitment target, a modification of the target for patient accrual at each site was approved by the funder. Providing evidence that ≥50% of the 17 sites were accruing ≥2 patients per month (by months 16-18) was considered to be an adequate indicator of sustainable recruitment for the full trial. By month 16 of the study, 10 (59%)

of the 17 sites were recruiting ≥2 patients per month, showing that this revised target had been exceeded.

Patient baseline characteristics and surgical procedure

The three groups were generally well balanced for age, sex, smoking status ASA grade, tumour staging and comorbidities, although the home-supported exercise group had a slightly higher BMI and the hospital-supervised exercise group, a lower incidence of hypertension in comparison with the other groups (Table 1). Baseline (pre-randomisation) data also showed that self-efficacy for exercise, grip strength and self-reported weekly physical activity levels were similar across the three groups. The median time to surgery from randomisation was also comparable across the three groups (Table 2). Laparoscopic resection was the favoured surgical approach in the majority of cases, with 90% of the hospital-supervised exercise, 85% of the home-supported exercise and 77% of the TAU controls undergoing this procedure (Table 2).

Post-operative complications

To ensure that blinding to treatment arm is maintained until the full trial analysis, pooled post-operative complication data for the three groups are presented in Table 3. Following randomisation, 19 patients did not proceed to surgery or withdrew from the study before 30 days post-surgery. Of the 181 patients available for analysis of post-operative complications at day 30, 52% of the patients across the three groups experienced a complication at discharge or by 30 days, as assessed by the Clavien-Dindo classification, and a total of 229 complications were reported in 95 patients across the three groups (Table 3). The vast majority of reported complications were classified as Clavien-Dindo grades 1 and 2, however, 16 patients experienced one or more Clavien-Dindo grade 3 or 4 complication(s). Gastrointestinal complications were the most frequently reported, with post-

operative ileus predominating. None of the patients died within 30 days of their surgery but two patients died within 90 days of their operation.

Adherence to the exercise interventions

Adherence to the initial exercise counselling session was high (95%) amongst patients in the hospital-supervised and home-supported exercise groups. In the pre-operative period (excluding withdrawn patients), 57% of the patients in the hospital-supervised group attended at least six exercise sessions, 73% attended at least four sessions and 95% attended one or more sessions, with a median of 1.5 pre-operative sessions attended per patient per week. In the post-operative period (excluding withdrawn patients), 50% of the patients attended at least five (50%) of the monthly hospital-supervised "booster sessions" and 59% attended at least three sessions, with a median of 4.5 post-operative sessions attended per patient (Figure 3). Figure 3 shows a relatively even spread of patients who were able to achieve low, moderate and high levels of adherence. The proportion of non-compliant patients (attending none of the supervised exercise sessions was 5% and 22% in the pre- and post-operative periods, respectively.

Adherence to the home-supported exercise program was assessed in terms of patient engagement with the pre-operative weekly telephone support. Excluding withdrawn patients, 70% of the home-supported exercise group engaged with two or more telephone support sessions and 85% received at least one telephone support session prior to surgery, with a median of 0.6 telephone support sessions per patient. In the post-operative period, 80% of the patients engaged in at least five (50%) of the monthly telephone support "booster sessions" and 84% engaged in at least three sessions, with a median of 7.0 telephone support sessions per patient (Figure 4). Figure 4 shows a relatively even spread of patients who were able to achieve low, moderate and high levels of adherence. The percentage of non-compliant patients (engaging with none of the telephone support sessions) was 15% and 6% in the pre- and post-operative periods, respectively.

Adverse events and serious adverse Events

In the 181 patients available for review at 30 days post-surgery, 22 patients reported one or more AEs, including 11 (19%) patients in the hospital-supervised group, eight (12%) in the home-supported group and three (5%) in the TAU control group (Table 4). Musculoskeletal and connective tissue disorders were the most frequently reported AE. In addition, four SAEs were reported by three patients, including disorders of the immune, renal/urinary and reproductive system systems. There were no SAEs in the hospital-supervised group. As the intervention involves both pre and post-operative exercise, surgery is conducted in all patients within the trial as part of routine care. All post-operative morbidity up to 30 days post-surgery 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 (see appendices for further clarification).

Acceptability

Commonly identified themes preventing site recruitment were lack of capacity to deliver the interventions due to insufficient staff resource or equipment (e.g. exercise bikes), difficulties associated with the logistics of delivering pre-operative exercise and support sessions in the short-time window before surgery and loss of communication. The process evaluation found that travel to the hospital was an important barrier to supervised exercise and restricted the number of pre-operative exercise sessions patients were able to attend, consistent with previous research 21. In addition, clinical teams experienced logistical difficulties booking rooms for exercise sessions and telephone support and securing the use of exercise equipment. Involvement in the trial also inevitably meant an increased workload for clinical teams, which was compounded by inefficiencies associated with sporadic patient recruitment and concerns that trying to achieve a predefined number of pre-operative supervised exercise sessions could cause delays to surgery. Regarding the latter, it became clear that early expectations for patients to attend up to three pre-operative supervised exercise sessions per week would not be feasible for many study participants.

DISCUSSION

The main aim of this internal pilot study was to provide evidence that key objectives for successful delivery of the main trial could be achieved in the planned timescale. Twelve sites were initially identified as being potential recruitment sites, one of these sites, and further 29 sites that expressed an interest in participation did not set up. However, 18 sites (50% more than planned) were able to proceed to study set-up within the pilot phase, within a median timeframe of 8 months. As a result of exceeding the site recruitment target, a reduction of the target for patient accrual at each site to confirm feasibility was approved by the funder.

The recruitment rate for eligible patients was 50%, which exceeded our pre-specified target of 30%, and with >50% of sites recruiting an average of ≥2 patients per month by months 16-18. Previous studies have not reported recruitment rate [8, 18, 19], or have only expressed it in terms of the number of patients assessed for eligibility without reference to ineligible patients or the proportion declining to participate [9, 10, 13, 14]. However, a recent trial by Carli *et al*. (2020) comparing trimodal prehabilitation with rehabilitation in frail elderly colorectal cancer patients, reported a recruitment rate for eligible patients of 29% (dropping to 26% taking into consideration 10 patients who were excluded after randomisation) [12]. Other studies show that recruitment of eligible cancer patients to exercise trials is typically <40%, possibly because exercise is physically demanding and less attractive than other psychosocial/behavioural interventions [20]. A regular newsletter and monthly teleconferences supported recruitment endeavours by enabling healthcare teams to share experiences and best practice. Patient accrual at each site was also regularly communicated to all clinical teams via a monthly league table framed as the “pedal-push challenge”.

Targets set by NHS England dictate that following general practitioner referral for a suspected cancer, patients are to be investigated within 31 days and treated within 62 days, resulting in a time-window between decision to operate and surgery of 31 days. The early scheduling of operation date

(within 2 weeks) and preconceptions amongst clinical teams about the inability of patients to engage in an intensive pre-operative exercise programme, were key reasons for excluding patients from participation within the first few months of the pilot. These issues were addressed by improving awareness of the trial amongst patients before their operation date was set and providing reassurance to trial delivery teams of the capability of frail patients to engage in progressive, individualised, body weight-supported aerobic interval exercise. Nevertheless, the time commitment required for exercise and/or being reluctant (or unable) to travel to the hospital for supervised sessions were major reasons for declining participation amongst many other eligible patients, which is consistent with previously reported barriers to exercise in cancer patients [21].

The three groups were generally well balanced for key variables. The higher proportion of males to females reflects national averages and the age-range and disease stage are representative of national audit data, with the exceptions of a higher proportion of patients in whom metastasis could not be measured (Mx) and a lower proportion of ASA grade III colon cancer patients in our cohort [22]. The median time to surgery from decision to operate (24.5 – 26.5 days) was similar across the groups and the high proportion of patients undergoing laparoscopic resection reflects the increasing national trend for this procedure [22]. Gastrointestinal complications were most frequently reported, which is consistent with published data [23]. In addition, self-reported activity levels were comparable across the groups, with the data indicating patients were not achieving public health physical activity recommendations for moderate to vigorous aerobic activity and strength training [24], in accordance with participation rates amongst older people in the general population [25]. These baseline demographic data provide reassurance that the fully powered trial will be representative of the UK colorectal cancer population.

Adherence data show that this pragmatic approach to implementing exercise results in an adequate level of engagement amongst patients, whether support is provided via hospital-supervised sessions

or home-based telephone contacts. The process evaluation found that travel to the hospital was an important barrier to supervised exercise and restricted the number of pre-operative exercise sessions patients were able to attend, consistent with previous research [21]. In addition, clinical teams experienced logistical difficulties booking rooms for exercise sessions and telephone support and securing the use of exercise equipment. Involvement in the trial also inevitably meant an increased workload for clinical teams, which was compounded by inefficiencies associated with sporadic patient recruitment and concerns that trying to achieve a predefined number of pre-operative supervised exercise sessions could cause delays to surgery. Regarding the latter, it became clear that early expectations for patients to attend up to three pre-operative supervised exercise sessions per week would not be feasible for many study participants.

The quantity (volume and intensity) of pre- and post-operative exercise needed to positively impact short and longer-term post-surgical recovery outcomes is unknown. Data on adherence to pre- and post-operative exercise programs in patients undergoing major abdominal surgery (including rectal cancer) are available from smaller-scale, tightly controlled, single centre studies. These have reported high adherence to hospital-supervised programs in the range 89-97% [13, 18, 26]. Adherence to home-supported exercise programs [9, 10, 12, 27] has generally been higher in the pre-operative prehabilitation phase (range 43-80%) than in the post-operative rehabilitation phase (range 23-70%). However, the lack of large-scale, multi-centre effectiveness trials and need for adequately powered studies to assess determinants of exercise adherence amongst cancer patients in 'real-world' settings has been highlighted [28]. Although adherence to exercise programs is known to influence treatment outcomes in clinical populations [28], the positive psychological impact of exercise prehabilitation, in terms of helping patients to mentally prepare for surgery, should not be underestimated [29].

Another key aspect of assessing acceptability in the PREPARE-ABC pilot phase was to consider the safety elements of the exercise programs. The results show that 22 patients in the exercise groups reported ≥1 AEs during the study, with musculoskeletal and connective tissue disorders predominating. Four SAEs were also reported by three patients, including disorders of the immune, renal/urinary and reproductive system systems. Data on adverse events encountered during exercise prehabilitation studies in cancer patients awaiting surgery have been poorly reported. However, on the basis of current evidence, exercise programs at all stages of the cancer treatment pathway are safe and feasible. For example, a systematic review of the safety and feasibility of exercise programs, which included data from over a thousand advanced cancer patients, reported an adverse event rate of 0.55%, all of which were musculoskeletal in nature [30]. Our data on AEs and SAEs are consistent with those reported in the literature and suggest that the PREPARE-ABC exercise interventions are safe and acceptable for cancer patients undergoing major colonic resection.

In conclusion, PREPARE-ABC is the first UK-based multi-centre randomised controlled trial designed to assess the effects of hospital-supervised and home-supported exercise pre- and post-operatively) on short- and longer-term post-operative recovery outcomes in colorectal cancer patients undergoing curative-intent major abdominal surgery. Data from the internal pilot phase presented herein confirm the feasibility of site set-up and patient recruitment, representativeness of the sample population and adequate adherence to hospital-supervised and home-supported exercise. On the basis of these positive results, recruitment to PREPARE-ABC continues. The full definitive pragmatic multi-centre trial will recruit 1146 participants with the aim of detecting a 25% reduction in post-operative complications and a difference of 3 units in SF-36 total score at 12 months between TAU and each exercise group. Findings will be reported in due course.

Ethics approval and consent to participate

The East of England – Essex Research Ethics Committee (Reference: 16/EE/0190) approved the trial at all participating centres. Participant consent is obtained prior to any trial-related procedure. During the consent process it is made clear that the participant can decline to participate in all or any aspect of the trial, at any time and for any reason, without affecting their future care or treatment. Patients unable to provide written informed consent are deemed ineligible for the trial.

Conflicts of interest

None.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report. The study sponsor delegated trial management to the Norwich Clinical Trials Unit and the authors held joint responsibility for the decision to submit for publication. The PREPARE-ABC trial is fully funded by National Institute for Health Research Health Technology Assessment Programme; Grant Number 14/192/53.

Trial sponsor

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Appendix

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PREPARE-ABC Patient Flow Diagram

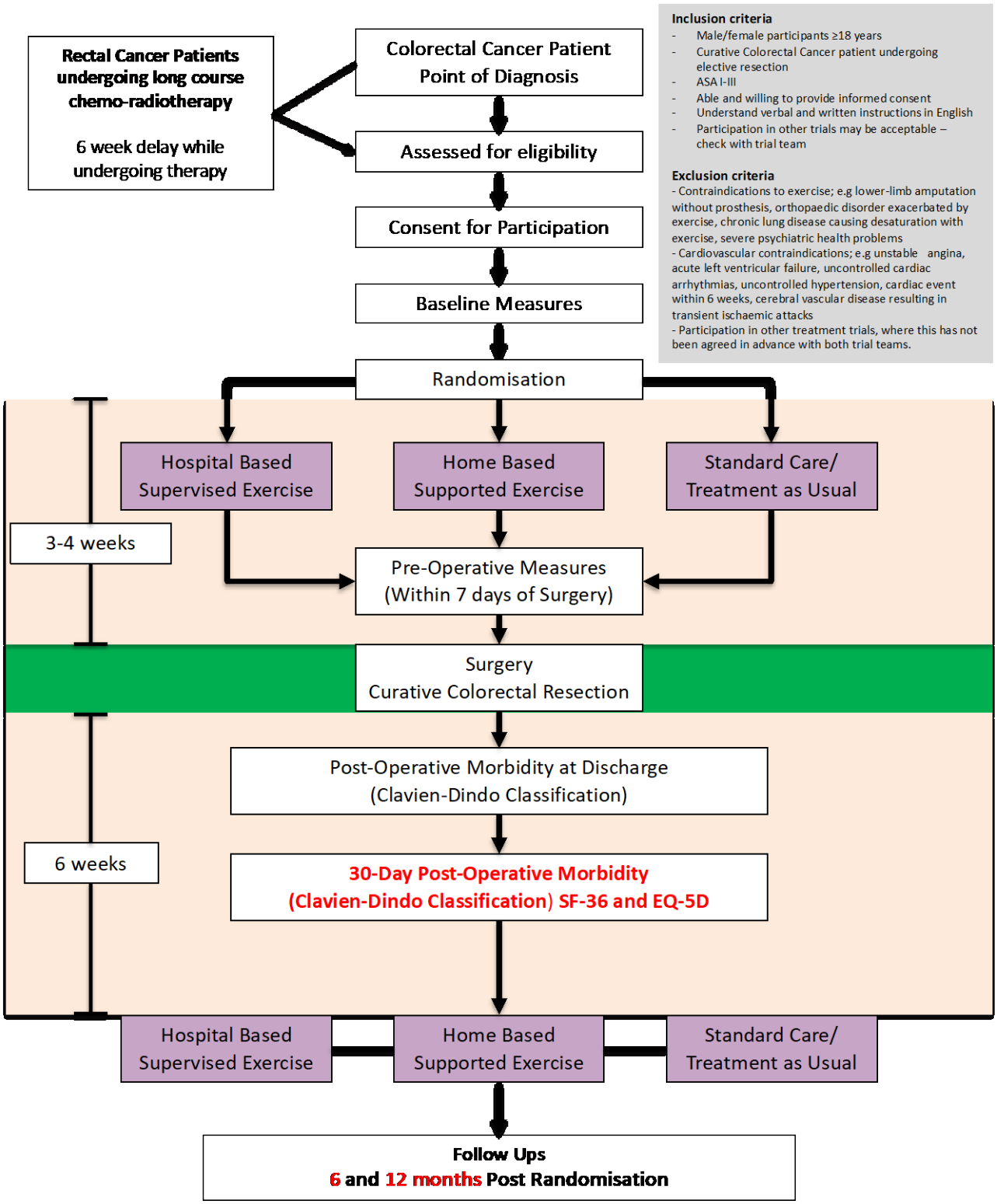
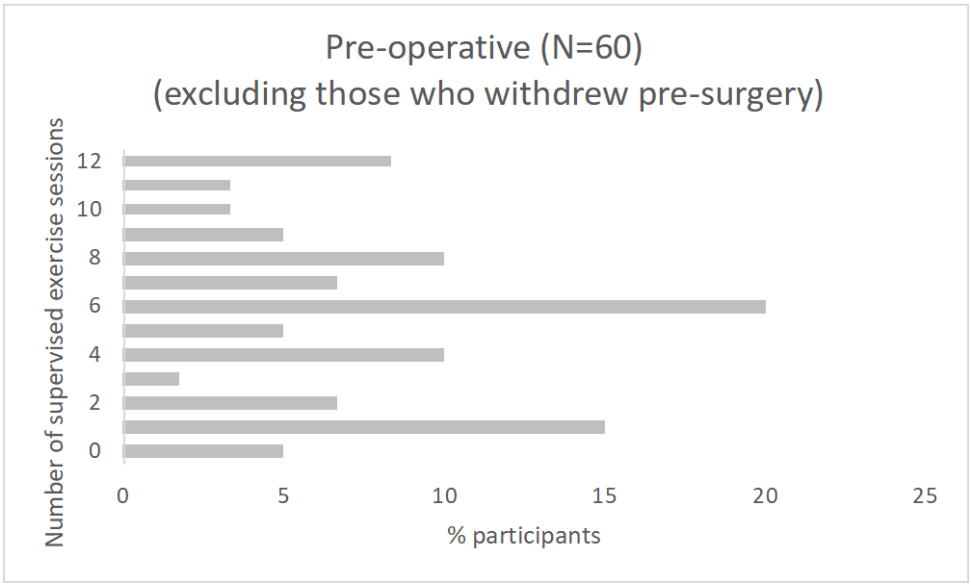


Figure 2. Flow of patients through the pilot phase of PREPARE-ABC

Figure 3 Number of supervised exercise sessions attended in the pre-operative and post-operative phases (supervised exercise group)



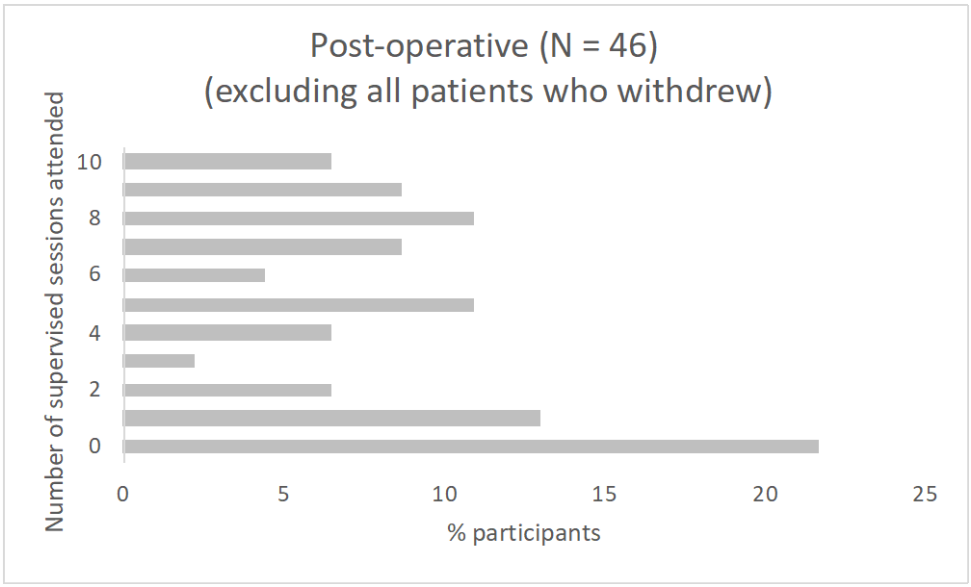
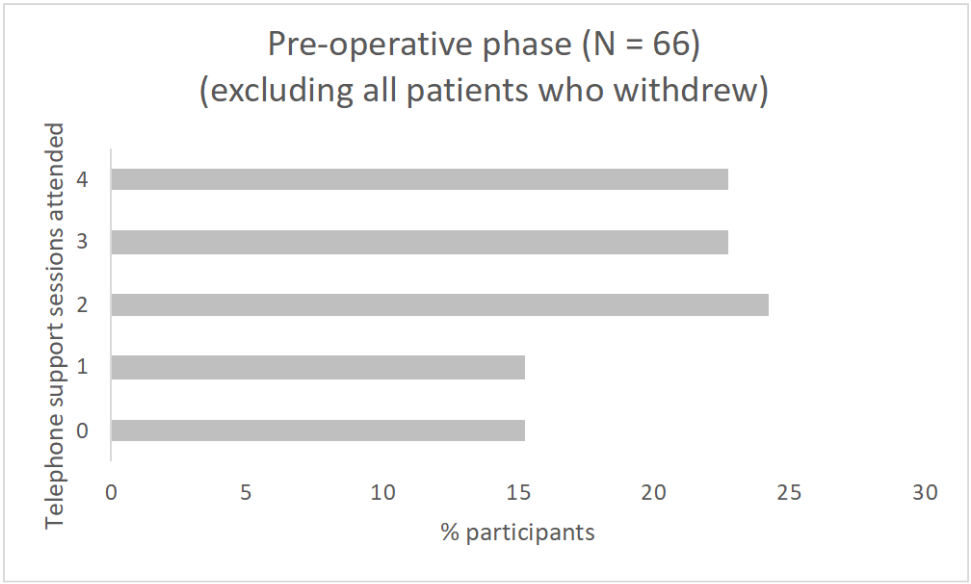


Figure 4 Number of telephone support sessions attended in the pre-operative and post-operative phases (home-supported exercise group)



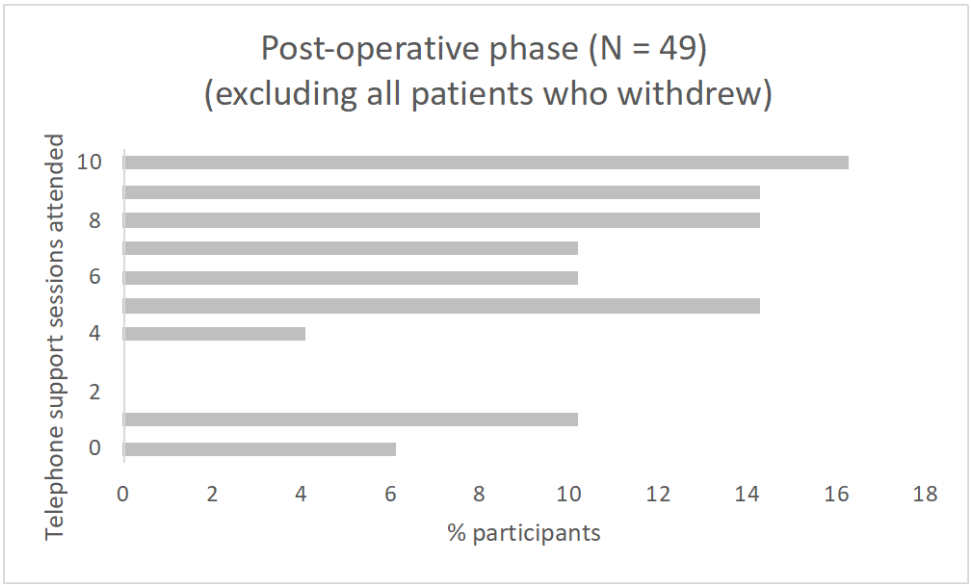


Table 1. Baseline characteristics of the three groups. Abbreviations are as follows: Treatment as usual: TAU. BMI: Body Mass Index. COPD: Chronic Obstructive Pulmonary Disease. T1DM: Type 1 Diabetes Mellitus. T2DM: Type 2 Diabetes Mellitus. ASA Grade: American Society of Anaesthesiologists. IQR: interquartile range.

	Hospital-supervised exercise (N=68)	Home-supported exercise (N=69)	TAU Control (N=63)
Males, n (%)	47 (69%)	46 (67%)	43 (68%)
Age, y (range)	67.6 (35–86)	66.7 (39-84)	69.1 (53-85)
BMI[1], mean (SD)	26.5 (5.2)	29.1 (4.9)	27.6 (4.4)
Smoking status, n (%)[2]			
Never	35 (51%)	37 (54%)	28 (44%)
Ex-smoker	31 (46%)	28 (41%)	33 (52%)
Current smoker	1 (1%)	4 (6%)	1 (2%)
Medical history, n (%)			
Hypertension	23 (34%)	31 (45%)	30 (48%)
Heart failure	2 (3%)	1 (1%)	0
Asthma	10 (15%)	5 (7%)	5 (8%)
COPD	2 (3%)	3 (4%)	3 (5%)
T1DM	0	0	2 (3%)
T2DM	5 (7%)	12 (17%)	9 (14%)
Orthopedic condition	6 (9%)	4 (6%)	7 (11%)
Parkinson's Disease	0	0	0
Previous malignancy	15 (22%)	10 (14%)	7 (11%)
ASA Grade, n (%)			
I	22 (32%)	17 (25%)	21 (33%)
II	37 (54%)	40 (58%)	33 (52%)
III	9 (13%)	12 (17%)	9 (14%)
Staging (from histology at 30 days post-surgery) , n (%)			
T stage			
Tx	0	1 (1%)	0
T0	1 (1%)	1 (1%)	3 (5%)
T1	7 (10%)	8 (12%)	5 (8%)
T2	10 (15%)	9 (13%)	6 (10%)
T3	38 (56%)	37 (54%)	35 (56%)
T4a	1 (1%)	0	3 (5%)
T4b	3 (4%)	5 (7%)	3 (5%)
T4 (unable to confirm)	1 (1%)	1 (1%)	1 (2%)
T stage info missing	7 (10%	7 (10%)	7 (11%)
N stage, n (%)			
Nx	0	2 (1%)	0
N0	40 (59%)	39 (57%)	36 (57%)
N1a	7 (10%)	9 (13%)	6 (10%)
N1b	2 (3%)	0	2 (3%)
N1c	0	1 (1%)	0
N2a	3 (4%)	3 (4%)	2 (3%)
N2b	0	2 (3%)	2 (3%)
N1 (unable to confirm)	5 (7%)	5 (7%)	6 (10%)
N2 (unable to confirm)	4 (6%)	1 (1%)	2 (3%)
N stage info missing	7 (10%)	7 (10%)	7 (11%)
M stage, n (%)			

Table 2. Surgical data for the three groups. Abbreviations as follows: TAU: Treatment as usual.

	Hospital-supervised exercise (N=60)	Home-supported exercise (N=66)	TAU Control (N=60)
Days between randomisation and surgery			
Mean (SD)	27.1 (10.4)	27.2 (12.2)	26.9 (15.0)
Median (IQR)	26.5 (20 – 33)	24.5 (19 – 33)	26 (17.5 – 34)
Surgery characteristics			
Initial operation approach			
Laparoscopic	54 (90%)	56 (85%)	46 (77%)
Open	6 (10%)	10 (15%)	14 (23%)
Operation type			
Right hemicolectomy	12 (20%)	15 (23%)	15 (25%)
Extended right hemi	1 (2%)	1 (2%)	1 (2%)
Sigmoid colectomy	0	1 (2%)	0
Anterior resection	16 (27%)	23 (35%)	25 (42%)
Anterior resection with ileostomy	14 (23%)	14 (21%)	6 (10%)
Abdominal perineal excision	8 (13%)	2 (3%)	4 (7%)
Hartmann's	0	2 (3%)	0
Other	9 (15%)	8 (12%)	9 (15%)

Table 3. Complications experienced up to 30 days post-operatively (excluding 19 participants who withdrew either prior to surgery, or up to 30 days after surgery). Abbreviations as follows: AF: Atrial Fibrillation. DVT: Deep Vein Thrombosis. PE: Pulmonary Embolism. TIA: Transient Ischemic Attack.

Complications	**All groups combined (N=181)**	**Complications reported (N)**
	Patients N (%)	Events N
All complications (at discharge & 30 days post-operative)	95 (52%)	229
At discharge	69 (38%)	156
At 30 days post-operative	46 (25%)	73
Grade (at discharge & 30 days post-operative)		
I	57	108
II	62	98
IIIa	7	9
IIIb	7	8
IVa	2	2
IVb	0	0
V	0	0
Highest grade of complication reported		
No complications	105 (52.5%)	
I	30 (15.0%)	
II	49 (24.5%)	
IIIa	7 (3.5%)	
IIIb	7 (3.5%)	
IVa	2 (1%)	
IVb	0	
V	0	
Type (at discharge and 30 days post-operative)		
Cardiac	12 (7%)	13
AF	3 (2%)	3
Arrhythmia	1 (1%)	1
Myocardial infarction	1 (1%)	1
Heart failure	0	0
DVT	0	0
PE	1 (1%)	1
Other	6 (3%)	7
Respiratory	13 (7%)	17
Post-operative atelectasis	3 (2%)	3
Respiratory tract infection	8 (4%)	8

Table 4. Adverse Events (AEs) and Serious Adverse Events (SAEs) up to 30 days post-surgery (excludin participants who withdrew either prior to surgery or up to 30 days after surgery).

	Hospital-supervised exercise (N=59)		Home-supported exercise (N=65)		Control (N=57)	
	Patients N (%)	Events N	Patients N (%)	Events N	Patients N (%)	Ev
All AEs (up to 30 days post-surgery)	11 (19%)	15	8 (12%)	12	3 (5%)	
Blood and lymphatic disorders	0		0		0	
Cardiac disorders	0		0		0	
Gastrointestinal disorders	1 (2%)	1	2 (3%)	2	1 (2%)	
General disorders & administration site conditions	0		0		0	
Immune system disorders	0		0		1 (2%)	
Infections and infestations	0		1 (2%)	1	0	
Injury, poisoning & procedural complications	1 (2%)	1	2 (3%)	2	0	
Investigations	2 (3%)	2	0		0	
Metabolism & nutrition disorders	0		0		0	
Musculoskeletal & connective tissue disorders	7 (12%)	8	3 (5%)	4	0	
Neoplasms (benign malignant & unspecified)	0		1 (2%)	1	0	
Nervous system disorders	2 (3%)	2	0		0	
Renal & urinary disorders	0		0		1 (2%)	
Reproductive system & breast disorders	0		1 (2%)	1	0	
Respiratory, thoracic & mediastinal disorders	0		0		0	
Skin & subcutaneous tissue disorders	0		1 (2%)	1	0	
Surgical and medical procedures	0		0		0	
Vascular disorders	1 (2%)	1	0		0	
All SAEs (up to 30 days post-surgery)	0	0	1 (2%)	1	2 (3%)	
Cardiac disorders	0		0		0	
Gastrointestinal disorders	0		0		0	
General disorders & administration site conditions	0		0		0	
Immune system disorders	0		0		1 (2%)	
Infections and infestations	0		0		0	
Injury, poisoning & procedural complications	0		0		0	
Investigations	0		0		0	
Musculoskeletal & connective tissue disorders	0		0		0	
Neoplasms (benign, malignant & unspecified)	0		0		0	
Nervous system disorders	0		0		0	
Renal & urinary disorders	0		0		1 (2%)	

Adverse Events and Post-Operative Morbidities (Clavien Dindo Classification).

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

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

Other Notifiable Adverse Events

There are no further notifiable events in this trial.

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.