SupPoRtive Exercise Programmes for Accelerating REcovery after major ABdominal Cancer surgery trial (PREPARE-ABC): study protocol for a multi-centre randomised controlled trial

On behalf of the PREPARE-ABC Trial Collaborative*

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ABSTRACT

Background: Exercise programmes can increase cardiopulmonary reserve and functional capacity prior to surgery and can improve clinical, functional and survival outcomes after a colorectal cancer diagnosis. However, the impact of pre- and post-operative exercise on post-operative recovery outcomes and longer-term health-related quality of life are unknown, thus there is a need for high quality randomised controlled trials.

Method: SupPoRtive Exercise Programmes for Accelerating REcovery after major Abdominal Cancer surgery (PREPARE-ABC) is a 3-arm multi-centre randomised controlled trial with internal pilot. The primary objective is to assess the effects of pre- and post-operative exercise on surgical outcomes and longer-term health-related quality of life in cancer patients undergoing colorectal resection. PREPARE-ABC aims to randomise 1146 patients at the individual level (1:1:1) to either hospital-supervised exercise, home-supported exercise or treatment as usual. The primary outcomes are short-term (30-day) morbidity using the Clavien-Dindo classification and longer-term health-related quality of life using the Medical Outcomes Study Health Questionnaire (SF-36). Secondary outcomes include cardiopulmonary fitness, physical activity behaviour change, psychological health status and cost-effectiveness. A process evaluation of intervention delivery and usual care will also be undertaken.

Discussion: This is the first UK-based definitive randomised controlled trial to investigate the effects of pre- and post-operative exercise on short-term post-operative health outcomes and longer-term health-related quality of life in colorectal cancer patients. The trial will yield robust clinical and cost-effectiveness data to underpin clinical guidance on how exercise programmes should be implemented in the routine management of patients undergoing major colorectal cancer surgery.

Keywords: colorectal cancer, exercise prehabilitation, post-operative recovery, health-related quality of life.

BACKGROUND

Colorectal cancer is the fourth most common cancer in the UK with more than 40,000 patients diagnosed every year [1]. The current standard and best-proven treatment for this patient group is a surgical resection, with approximately 25,000 abdominal resections completed annually in the UK. Colorectal resection offers the best chance of cancer survival, with a 90-day post-operative mortality of 3% [2]. However, post–operative complications occur frequently and are associated with poor short- and long-term health outcomes [3, 4], placing a significant burden on patients and impacting greatly on healthcare costs [5].

The health benefits of maintaining a physically active lifestyle after curative colorectal cancer treatment is evidenced by epidemiological data suggesting an association between physical activity and survival outcomes [6, 7]. In addition, improvements in physical function and fatigue have been reported in colorectal cancer patients following post-treatment programmes of structured exercise or physical activity [8-13] and there is observational evidence of an association between a physically active lifestyle and quality of life in long-term colorectal cancer survivors [14]. However, the importance of establishing the causative effects of physically active lifestyles on health-related quality of life (HR-QoL) after colorectal cancer treatment [14], of including comparisons of different types of exercise versus controls in studies of colorectal cancer survivors [15], and of integrating trials within colorectal cancer treatment pathways, has been highlighted [8].

In recent years, there has been growing interest in the role of pre-operative exercise as an intervention for optimising cardiometabolic fitness (‘physiological reserve’) and improving post-operative recovery outcomes after major cancer surgery [16-19]. Post-operative complications cause prolonged hospital stays, increase the number of readmissions and treatment costs, and have implications for the patient’s long-term wellbeing and risk of mortality [16, 20]. Since Older *et al.* (1993) first reported an association between low cardiopulmonary fitness and poor outcome following major surgery in

elderly patients [21], further studies have reported an association between cardiopulmonary fitness and post-operative recovery outcomes in cancer patients, including those undergoing colorectal resection [22-24]. Furthermore, supervised pre-operative aerobic and resistance exercise have been shown to improve cardiopulmonary fitness, maintain lean body mass and augment tumour regression grading in colorectal cancer patients following neo-adjuvant chemoradiotherapy [24-27]. There is also evidence of improved functional (walking) fitness and maintenance of lean body mass in colorectal cancer patients throughout the peri- and post-operative periods following home-supported exercise programmes as a component of trimodal prehabilitation incorporating nutritional and psychological support [9-13]. This means an attenuation of the functional impairments and loss of lean body mass normally seen in the peri- and post-operative periods.

Rigorous randomised controlled trials (RCTs), including studies that are designed to test the clinical and cost effectiveness of different exercise delivery methods (e.g., hospital-supervised versus home-supported exercised programmes), are now clearly needed. Home-supported exercise avoids the use of limited hospital resources, may be adoptable by more patients (e.g. those unwilling to travel to supervised sessions) and can be successfully continued soon after major cancer surgery [9, 10]. However, more closely supervised programmes (e.g., hospital-supervised exercise) might be more effective for improving cardiopulmonary fitness in the short time-window before major abdominal surgery [28] and the potential advantages of supervised vigorous intensity aerobic interval exercise have been highlighted [29-32]. Post-operatively, programmes that provide ongoing support via intervention contacts are likely to have the greatest impact on long-term health-related quality of life. In this respect, systematic reviews have shown that maintaining intervention contacts (e.g., via “booster” sessions) is more successful in achieving sustained physical activity behaviour change than withdrawal of follow-up support [33, 34]. However, the provision of exercise is also likely to have resource implications, both in terms of resources required to provide the exercise interventions, and any effect it may have on the use of health care resources for those with colorectal cancer. In order to

make good decisions about the provision of exercise for colorectal patients it is also important to establish the cost-effectiveness of the service.

PREPARE-ABC has been designed to assess the clinical and cost-effectiveness of pre- and post-operative hospital-supervised and home-supported exercise in relation to 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 clinical and cost-effectiveness data to underpin clinical guidance on how exercise programmes should be implemented in the routine management of colorectal cancer patients awaiting surgical resection.

METHOD

Study design

A multi-centre, parallel group, randomised controlled trial with three arms: (1) hospital-supervised exercise; (2) home-supported exercise; (3) treatment as usual control (Figure 1).

Internal pilot

An internal pilot will be conducted for one year, following 6-month site set-up, allowing an assessment of stop/go criteria to aid decisions on whether or not to continue with the RCT. The objectives of the internal pilot phase are to confirm feasibility of site set-up and recruitment, acceptability of, and adherence to, the exercise interventions and to assess implementation fidelity to the intervention and any potential sources of contamination in the control arm. All data collected in the internal pilot phase will be included in the main analyses. Stop/go criteria are defined as: (1) 75% of sites open by recruitment month 12; (2) ≥30% of eligible patients recruited to the study; (3) 50% of sites are achieving recruitment rates sufficient to sustain an adequately powered RCT (4-5 patients per month during recruitment months 10-12); (4) 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.

Setting

Patients will be recruited from colorectal surgery units within UK NHS Trusts at the point of diagnosis, where principal investigators (PIs) are able to demonstrate the potential for recruitment and capacity to conduct the exercise interventions, and all required set-up tasks have been completed. Exercise will take place in hospital or home/community settings, depending on the treatment arm to which patients are allocated.

Participant recruitment and eligibility

Recruitment will be organised on a regional basis with the support of National Institute for Health Research (NIHR) Local Clinical Research Networks (LCRNs). PIs will identify potential participants and assess their eligibility for inclusion in the trial. Following consent, the site staff will send a letter to the patient's GP to inform them of their participation in the study. The trial inclusion criteria are: male and female participants ≥ 18 years old; awaiting a curative elective colorectal resection for cancer (minimally-invasive/laparoscopic or open); American Society of Anaesthesiologists (ASA) physical status I-III [35]; able and willing to provide informed consent; able to understand verbal and written instructions in English. The trial exclusion criteria are: presence of a comorbid contra-indication to exercise, such as lower-limb amputation without prosthesis or a 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.

Patients participating (or who have recently participated) in other trials may be eligible, but this must be agreed in advance by the relevant trial teams. In addition, patients presenting with metastasis and a potentially curative treatment plan (clinical intervention to treat primary and metastasis with curative intent) may also be eligible, providing all other eligibility criteria are met. Patients found to have had a benign tumour post-operatively may continue to participate in the study as per protocol and patients undergoing long course chemo-radiotherapy for rectal cancer are eligible for inclusion but will not be approached until this treatment has been completed.

Process evaluation

Patients consenting to participate in the trial and healthcare professionals involved in delivering the interventions will be given the option to participate in a process evaluation of intervention delivery and standard care. This will be to: 1) describe usual care prior to implementing interventions; 2) assess how the exercise interventions are delivered and fidelity to the intervention protocol; 3) assess patients' and staff experiences and acceptability of the interventions; and 4) assess any variation in non-receipt of the interventions in the control arm and any sources of contamination. Consent to allow a researcher to observe pre- and post-operative consultations and to conduct interviews with patients and healthcare professionals will be obtained. Patients and healthcare professionals will have the option of consenting to observations and interviews, or to only one of these components.

Qualitative data collected from sites will be analysed to provide a 'thick description' [36] of how each arm of the study was delivered, maintained and experienced by staff and patients. The analysis of the interview and observational data will be iterative, with knowledge gained from observations of both standard care and intervention delivery used to strengthen interview topic guides and provide additional insights during analysis. Coding and analysis will be undertaken by one researcher and validated by a second researcher, who will review a sample of the transcripts.

Sample size

To detect a 25% reduction (relative risk 0.75) between standard care and each of the exercise arms (90% power, alpha 2.5%), 343 patients are required for each arm (1146 patients in total, allowing for 10% attrition). In addition, based on a mean ± SD SF-36 score of 52 ± 10 a year after surgery [37], 276 patients are required in each arm to detect a difference of 3 units between standard care and each of the exercise groups (1035 patients in total, allowing for 20% attrition). These sample sizes are based on 90% power and an alpha of 2.5%. A Bonferroni correction to the alpha rate was made due to having two primary outcomes. Anticipated attrition rates of 10% for 30-day complications and 20% for longer-term HR-QoL are consistent with those used previously for exercise studies by members of the research team. The effect sizes used were based on a pragmatic decision that would have a meaningful impact as no agreed minimally important difference was published in the literature. Based on these sample size calculations, an overall sample size of 1146 patients (randomised 1:1:1) provides 90% power to detect clinically important improvements in the primary outcomes.

Randomisation and allocation concealment

Randomisation to treatment arm will take place after all baseline assessments have been completed and entered into the electronic case report form (eCRF). Participants will be randomised (1:1:1) using a web-based randomisation sequence generated by NCTU data management staff who are not involved in the delivery of the intervention. Email notification of the patient's treatment arm allocation will be sent to the study team. Allocations will be stratified by centre using permuted block randomisation, with randomly varying block sizes.

Intervention training

Hospital-supervised and home-supported exercise sessions will be delivered by healthcare professionals who are part of the local care team after receiving trial-specific training and demonstrating competency to deliver the interventions consistently, to all participants. Trial-specific

training-days held at a central location and delivered by members of the trial team include practical 'hands-on' sessions in which the healthcare professionals develop and practice the skills needed to set-up and run supervised exercise classes and provide face-to-face and telephone behaviour change support.

Exercise interventions

The hospital-supervised and home-supported exercise interventions are separated into pre- and post-operative phases and last for 12 months post-randomisation in total. Following GP referral for symptoms of bowel cancer, patients are normally investigated within 31 days and treated within 62 days, but the duration of the pre-operative phase will be dictated by local scheduling of surgery. However, where possible, clinical teams will consult with patients about the trial before scheduling surgery to give them every opportunity to make an informed decision about participation and engage in as many pre-operative exercise sessions as possible if allocated to an intervention arm. Patients allocated to the intervention groups will also receive treatment as usual before and after curative colorectal cancer surgery.

Theoretical approach

Both exercise interventions are underpinned by self-determination theory (SDT) [38]. The theory posits that developing intrinsic forms of motivation towards a health behaviour is central to long-term behaviour change, a process that is supported by satisfaction of the basic psychological needs for autonomy (feeling volitional), competence (feeling effective), and relatedness (sense of belonging) [39, 40]. On this basis, the interventions are designed to provide support by offering a clear rationale, acknowledging the patient's perspectives, providing choice, promoting competence, avoiding the use of external incentives, providing positive feedback, and showing care and concern [41]. These strategies will be implemented via an intervention manual, face-to-face contacts and semi-structured motivational telephone calls.

Pre-operative phase

Both exercise interventions will begin with a 45-minute exercise counselling session in the hospital setting, informed by SDT and using skills associated with motivational interviewing [42]. Patient perceptions of the pros and cons of being physically active and ways to overcome perceived barriers will be explored. In addition, patients will work with the healthcare professional to set achievable structured exercise/physical activity goals. Patients will also receive instructions on how to complete an exercise diary for recording exercise sessions (e.g., exercise modality, duration, intensity) before and after surgery and will be given a pedometer to record daily step counts. Fidelity to the content of both exercise programmes will be recorded in the eCRF from pedometer data and patient completed exercise diaries.

After the exercise counselling session, patients in the hospital-supervised exercise arm will be offered up to three aerobic interval exercise sessions per week on a cycle ergometer over the 3-4 weeks prior to surgery. Each exercise session will comprise of 6 x 5 min repetitions at 60-80% of heart rate reserve (~60-80% peak $\dot{V}O_2$; Borg RPE Scale 13-15) [43], with 2.5 minutes active rest intervals at 50 W. Heart rate, clinical signs, blood pressure and perceived exertion (via Borg RPE Scale) will be recorded regularly throughout exercise. The programme will be progressed by increasing the number of intervals to a maximum of six and/or adding further load to the flywheel. Patients in this arm will also be instructed to undertake two home-based resistance exercise sessions per week using resistance bands (Theraband, Akron, OH, USA).

After the exercise counselling session, patients in the home-supported exercise arm will be encouraged to achieve a minimum of 150 min of moderate-vigorous intensity aerobic exercise per week (e.g., brisk walking/jogging/cycling/ swimming), equating to a score of 13-15 on the Borg RPE Scale [43] over the 3-4 weeks prior to surgery. Patients in this arm will also complete two sessions of

resistance exercise using resistance bands (Theraband). Home-supported exercise programmes will be tailored to each patient, taking previous level of activity, mobility and any barriers to exercise into consideration. Patients will receive weekly 15-minute telephone support to encourage adherence to the exercise programme.

Post-operative phase

Surgery and aftercare will follow treatment as usual in all patients recruited to the trial, with no further study exercise interventions until six weeks after surgery. If return to exercise/usual activities is delayed due to post-operative complications, study participants may continue in the study and re-commence the exercise intervention once they are able. Participants in both exercise intervention arms will be supported in identifying local exercise facilities and physical activity schemes in the community. They will be encouraged to comply with current physical activity recommendations of 150-minutes of moderate-vigorous intensity aerobic exercise per week, equating to a score of 13-15 on the Borg RPE Scale [43], and two weekly sessions of resistance exercise using the resistance bands.

Participants in both exercise intervention groups will also be provided with continued face-to-face or telephone support. Participants in the hospital-supervised arm will be offered a monthly supervised "booster" exercise session comprising of aerobic interval exercise (as in the pre-operative period) and participants in the home-supported arm will receive a monthly 15 min telephone support session until 12 months post-randomisation. During supervised "booster" exercise sessions and telephone support sessions, progress will be reviewed and participants will have the opportunity to discuss any issues related to their programme. In addition, behavioural strategies will be reinforced and the importance of keeping exercise diaries up-to-date and properly completed will be emphasised.

Control arm

Participants randomised to the control arm will receive treatment as usual before and after curative colorectal cancer surgery, which does not include support for pre- or post-operative exercise.

Table 1. Assessment schedule

	Pre-Surgery						Post-Surgery			Post randomisation	
	Screening (Diagnosis)	**Baseline**	**Randomisation - 4 weeks to surgery**	**Pre-surgery -4 to -3 weeks**	**Pre-surgery ≤ 7 days**		**Post-surgery discharge ~ 5-7 days**	**Post-surgery 30 days**	**Post-surgery 6 weeks**	**6 month follow up visit**	**12 month follow up visit**
Consent	X										
Eligibility	X										
Demographics		X									
Medical history		X									
Haemoglobin result and document treatment for anaemia		X			X						
Tumour histological stage								X			
Cardio Pulmonary Exercise Test (CPET)		X			X						
Short Form 36 (SF-36) Questionnaire		X						X		X	X
EQ-5D-5L Questionnaire		X						X		X	X
Hospital Anxiety and Depression Scale (HADS)		X								X	X
Self-Efficacy for Exercise Scale		X								X	X
Behavioural Regulation in Exercise Questionnaire (BREQ-3)		X								X	X
Exercise Identity Scale (EIS)		X								X	X
Godin Leisure Time Exercise Questionnaire (modified)		X								X	X
Resource Use questionnaire		X								X	X
Grip Strength		X			X			X		X	X
Full blood count and liver function tests		X									
CT scans (staging/cancer surveillance)		X								X	X
Randomisation			X								
Exercise Intervention (or treatment as usual - Arm C)				←	→				←	→	→
Adverse Events		←	→	→	→		←	→	→	→	→
Record questionnaire data in electronic Case Report Form (eCRF)							←	→			
Clavien–Dindo Classification of Post-Operative Morbidities							X	X			
Blinded assessment of fitness for discharge							X				
Review of adherence to exercise interventions (if applicable)					X					X	X

Surgery

Study outcomes and blinding

Outcomes will be assessed at baseline (prior to randomisation) and at various time points thereafter, as indicated in Table 1. Blinding is not applicable to the delivery of the interventions in this trial. However, the clinical team(s) responsible for the initial surgical and any subsequent admissions are blinded to treatment allocation. Data collection is to be carried out using patient notes, through assessments at face-to-face visits and through paper questionnaires or case report forms. All data are entered onto an eCRF by a member of the site staff and will be handled in accordance with the current Data Protection Act and General Data Protection Regulation. After completion of the trial the identification, screening and enrolment logs will be archived securely for 5 years in accordance with sponsor policy.

Primary Outcomes

Short-term (30-day) morbidity will be assessed using the Clavien-Dindo classification of post-operative complications [44]. Data will be collected 30 days after the operation by members of the clinical team who are blinded to treatment allocation using a structured set of questions during the routine post-operative review. Longer-term (12 months post-randomisation) health-related quality of life will be assessed using the total score from the Medical Outcomes Study Health Questionnaire (SF-36) [45].

Secondary Outcomes

Cardiopulmonary fitness will be assessed twice in the pre-operative period using a standard cardiopulmonary exercise test (CPET) to maximum exercise tolerance [46]. For the purposes of this study, CPETs will be performed as per standard local procedures and the following parameters (at a minimum) will be determined using standard techniques: peak oxygen consumption (peak VO2), peak heart rate, peak power output, anaerobic/ventilatory threshold and maximum oxygen pulse (oxygen consumption per heartbeat). In cases where CPETs are carried out as part of standard care

for pre-surgical assessments, these can be used at baseline providing it is within 28 days prior to randomisation. If due to NHS resource constraints or other exceptional circumstances two CPETs are not possible, participants can continue on the trial with data from one CPET or no CPET data. Grip strength will be measured at the same pre-operative timepoints using a standard grip strength dynamometer.

Post-operative recovery will be assessed using the following outcomes: length of hospital stay, 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), morbidity at discharge (measured by Clavien-Dindo classification of post-operative complications), 90-day all cause re-admission rate, 90-day post-operative mortality (defined as % participants who died on or up to 90 days following date of operation), grip strength (30 days post-surgery, 6 and 12 months post-randomisation).

Self-efficacy and motivation for exercise will be assessed using three brief questionnaires: Self-efficacy and motivation for exercise scale [47]; Behavioural Regulation in Exercise Questionnaire (BREQ-3) [48]; and Exercise Identity Scale (EIS) [49]. Psychological health status data will be assessed using the Hospital Anxiety and Depression Scale (HADS) [50] and physical activity behaviour using the Godin Leisure Time Exercise Questionnaire [51]. HR-QoL will be assessed by the SF-36 Mental and Physical Health sub-scales [45] and the EQ-5D-5L [52]. Questionnaires will be posted out to patients for completion in the week prior to scheduled assessment visits and will be checked through for completeness during assessment sessions.

Economic evaluation

An economic evaluation will be conducted as part of the RCT. The form of this evaluation will be a cost-utility analysis and the perspective will be societal (i.e., will include NHS and social care), as well as costs borne by study participants including productivity costs incurred through time off work. Quality adjusted life years (QALY) will be estimated using the EQ-5D-5L. As recommended [53], QALY gains from the two intervention groups compared to the control group will be estimated using regression based methods to allow for differences between groups in baseline HR-QoL and other relevant patient characteristics. 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).

Adverse events and data monitoring for harm

An independent Data Monitoring Committee (DMC) will be provided with safety data for each treatment arm, including frequency of adverse events and serious adverse events for all three arms. In conjunction with the Trials Steering Committee (TSC), the DMC will advise on the continuation or early stoppage of the trial in the unlikely event that there are concerns over harm to participants. The DMC for PREPARE-ABC consists of the Chair, an independent statistician and independent clinician. The TSC for PREPARE-ABC consists of a number of independent panel members including PPI representatives, an independent exercise physiologist and the committee is chaired by an independent colorectal surgeon. Both the TSC and DMC convene on a yearly basis at a minimum.

Statistical analysis

The main comparisons between arms are: (a) standard care versus hospital-supervised exercise; (b) standard care versus home-supported exercise; and (c) hospital-supervised exercise versus home-supported exercise. Comparisons (a) and (b) are the primary comparisons and (c) is an exploratory comparison, as it is inadequately powered. The main analysis will be undertaken as an intention-to-treat analysis including data from all randomised individuals regardless of adherence. For all

comparisons of primary outcomes, the significance level will be set at 2.5% to account for having two primary outcomes, on the basis of the Bonferroni adjustment. Secondary outcomes will be assessed at the 5% significance level. A general linear model will be used to compare the average values between groups, adjusted for site and other potentially prognostic variables, but with the primary analysis being the unadjusted analysis. Multiple imputation will be used for missing data and sensitivity analyses will be conducted to assess the impact of the multiple imputations. In addition, bivariate associations between key baseline variables and changes in post-operative recovery outcomes will be explored using multivariable regression models. A full analysis plan will be agreed prior to the **analysis** being conducted.

Access to Data

Requests for access to trial data will be considered on a case by case basis, and approved in writing where appropriate, after formal application to the TMG and TSC. Considerations for approving access are documented in the TMG and TSC Terms of Reference. Following conclusion of the trial, anonymised data is likely to be added to an open access repository.

Dissemination

Plans for the dissemination of the findings of PREPARE-ABC include: peer reviewed publications (protocol, internal pilot, primary findings, health economics, process evaluation), via conferences, press releases and generating newsletters raising study awareness at patient groups - as well as other methods where appropriate.

DISCUSSION

The role of pre-operative exercise programmes for helping to promote enhanced recovery after cancer surgery has gained increasing interest. In 2019, Macmillan Cancer Support published an extensive report detailing prehabilitation principles and guidance for patients with cancer [54]. This report calls

for changes to the delivery of cancer care across the UK and encourages a greater focus on prehabilitation, including exercise in combination with nutritional and psychological support. It has been argued that prehabilitation represents a shift away from the impairment driven, reactive model of care, towards a proactive approach that enables patients to become active participants in their care [55], potentially impacting the cost-effectiveness and longer-term efficacy of cancer treatment. The health benefits of physical activity and structured exercise for cancer survivors are also recognised by the National Cancer Survivor Initiative (NCSI), a partnership between NHS England and Macmillan Cancer Support [56]. The NCSI recognises the importance of physical activity for cancer survivors in respect of improving physical function, managing fatigue, reducing the risk of cancer recurrence and other major chronic diseases and maintaining independence.

Two recent studies yielded promising evidence of improved post-operative recovery outcomes following pre-operative exercise training (alone or as part of multi-modal prehabilitation) in patients undergoing major abdominal surgery [32, 57]. Barberan-Garcia *et al*. (2018) reported a 51% improvement in post-operative complications for high-risk (>70 y and ASA III/IV) patients undergoing elective major abdominal surgery (75% colorectal resections) following a six-week pre-operative supervised programme of high intensity aerobic interval training and promotion of physical activity [32]. Furthermore, a cross-sectional study undertaken by Howard *et al.* (2019) found that home-supported exercise (walking and breathing exercises) as part of multi-modal prehabilitation before abdominal surgery resulted in significantly fewer Clavien-Dindo grade 3–4 complications in comparison with elective and emergency abdominal surgery without prehabilitation [57]. In the latter study, the authors also reported significant cost savings but only 35% of the prehabilitation group had a cancer diagnosis. However, to date, randomised controlled trials have been unable to evidence 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 [9, 28, 58, 59]. The heterogeneity of study designs and patient populations is likely to account for

inconsistent findings. In addition, most studies of pre-operative exercise training have been small-scale, have not accurately reported changes in cardiopulmonary fitness, and have been insufficiently powered to detect changes in post-operative recovery outcomes [19, 60-62].

PREPARE-ABC is a robustly-designed, innovative multi-centre RCT that will address many unanswered questions and produce definitive evidence of the clinical efficacy of pre- and post-operative exercise training on short and longer-term recovery outcomes. The trial will also provide valuable cost-effectiveness data to underpin new clinical guidance on how to implement exercise programmes for cancer patients awaiting and recovering from major lower-gastrointestinal surgery.

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 is free to 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 without providing a reason. Patients unable to provide written informed consent are deemed ineligible for the trial.

Conflicts of interest

None.

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Appendix

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