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Postoperative exercise rehabilitation after elective colorectal cancer surgery

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Declaration of contributorship

I hereby declare that the work presented in this thesis is my own.

Statistical support was provided by Dr Brett Doleman, who provided help with statistical analysis within my systematic review (Chapter 2).

Melanie Paul

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I List of Abbreviations

1-RM	Leg press 1-repetition maximum
6MWT	6-minute walk test
ADL	Activities of daily living
AET	Aerobic exercise training
AT	Anaerobic threshold
ASA	American Society of Anaesthesiologists
BFI	Brief Fatigue Inventory
BMI	Body mass index
CHAMPS	Community Healthy Activities Model Program for Seniors questionnaire
CI	Confidence Interval
CON	Control
CONSORT	Consolidated Standards of Reporting Trials
CPET	Cardiopulmonary exercise testing
CRC	Colorectal cancer
CRC UK	Cancer Research UK
CRF	Cardiorespiratory fitness
CRP	C-reactive protein
CR-POSSUM	ColoRectal Physiological and Operative Severity Score for the enumeration of Mortality and morbidity
DNA	Deoxyribonucleic acid

DASI	Dukes Activity Status Index questionnaire
ECG	Electrocardiography
ELISA	Enzyme-linked immunosorbent assay
EMG	Electromyography
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Core Quality of Life of Cancer Patients Questionnaire
EORTC QLQ-STO22	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach Cancer-Specific Module
EQ-5D-5L	EuroQol- 5 Dimension questionnaire
EDTA	Ethylenediaamine tetra-acetic acid
ERAS	Enhanced recovery after surgery
EX	Exercise
FACT-E	Functional Assessment of Cancer Therapy- oesophageal cancer QOL specific items
GOJ	Gastro-oesophageal junction
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS Anxiety Subscale
HADS-D	HADS Depression Subscale
HEPA	Health- enhancing physical activity

HGS	Handgrip strength
HIIT	High-intensity interval training
HRQoL	Health-related quality of life
ICIQ	International Consultation on Incontinence Modular Questionnaires
iEMG	Intramuscular electromyography
IL-6/IL-10	Interleukin –6/-10
IPAQ-SF	International Physical Activity Questionnaire- Short Form
IRAS	Integrated Research Application System
LoHS	Length of hospital stay
LoS	Length of stay
MD	Mean difference
MDT	Multi-disciplinary team
MET	Metabolic equivalent of task
MET.h	Metabolic equivalent of task in hours
MIO	Minimally invasive operation
MPS	Myofibrillar protein synthesis
MRC	Medical Research Council
MUP	Motor unit potential
MVC	Maximum voluntary contraction
MVPA	Moderate-vigorous physical activity
NHS	National Health Service
PEDro	Physiotherapy Evidence Database
PIS	Patient information sheet
POD	Postoperative day

POETTS	Perioperative Exercise Testing and Training Society
POPS	Proactive Care of Older People having Surgery
PREP-GC	Postoperative Recovery Exercise Program Developed Specifically for Gastric Cancer Patients
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of life
RCT	Randomised controlled trial
RDH	Royal Derby Hospital
REC	Research Ethics Committee
RER	Respiratory exchange ratio
RET	Resistance exercise training
RoB2	Cochrane Collaboration's tool for assessing risk of bias tool
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions tool
RPM	Revolutions per minute
SD	Standard deviation
sEMG	Surface electromyography
SF-12/SF-36	Short Form Surveys 12 and 36
SOP	Standard operating procedure
STS	Sit to stand
TNFα	Tumour necrosis factor- alpha
TUG	Timed up and go
UHDB	University Hospitals Derby NHS Foundation Trust
UK	United Kingdom
VL	Vastus lateralis

VO2 max	Maximal oxygen consumption
VO2 peak	Peak oxygen consumption
W	Watts
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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Thesis Abstract

Introduction

Colorectal cancer (CRC) is common, accounting for approximately 11% of all new cancer cases, and is primarily a cancer associated with increasing age (Cancer Research UK, 2021). Surgery is usually the most appropriate option (if feasible and depending on staging) to try to achieve cancer free status. However, it carries significant morbidity, especially given the generally older patient population in which colorectal cancer presents (Argillander et al., 2021; Kolarsick et al., 2020). Appropriately stratifying preoperative risk to improve immediate outcomes is an appropriate strategy, but after a significant physiological insult through surgery, patients are not given clear guidance on how to regain their preoperative physical state (Karlsson et al., 2020). A structured exercise programme, such as proposed within this thesis, aims to assess the use of both aerobic and resistance exercises to safely improve postoperative patients' physical and mental fitness and wellbeing, looking at objective measures through cardiorespiratory exercise testing (CPET) but also milestones important to the patient such as the ability to carry out their activities of daily living in order to improve not only their speed of recovery but maintain their mental well-being during a difficult period.

Methods

A systematic review was performed to assess the impact of postoperative aerobic exercise training in patients undergoing surgery for intra-abdominal cancers which included studies that began the exercise regimen within 3 months of surgery and reported on outcomes that included cardiorespiratory fitness. A cohort study (PHYSPAL) was performed to evaluate the quantity and type of immediate in-hospital postoperative activity that patients did was performed. Finally, a randomised controlled trial (RCT) (POSTEX) was undertaken to explore whether a combined aerobic and resistance programme improved physical fitness as well as quality of life parameters in postoperative colorectal cancer patients.

Results

The systematic review showed that there is benefit in exercise training in the immediate postoperative period and is safe. However, due to the heterogenous study designs and exercise regimens, there is no one clear programme that confers the most benefit. The PHYSPAL study showed some increase in activity over time in the immediate postoperative period, but overall step count is low and sedentary time is high. The POSTEX study conferred a potential benefit in preserving muscle strength and fatiguability, likely in response to the resistance component of the exercise regimen. Patients in the exercise group gave excellent feedback with regards to the programme delivery and ability to complete the exercises at home.

Conclusions

The work presented in this thesis shows the importance of and potential benefits in providing patient-focussed, achievable postoperative goal-directed exercise targets to maintain and/or improve activity levels after surgery. Multimodal exercise programmes can be safely performed with indirect supervision, which is an important consideration in a resource-limited healthcare setting. Both functional and patient-related factors, especially with regards to quality of life, are positively impacted but greater focus needs to be on integrating this into direct guidance with enhanced recovery after colorectal surgery protocols.

1 Introduction

1.1 Ageing

Ageing is a constant, multifactorial process describing the gradual decline in function over time of an organism. It affects every cell, tissue and organ in the human body. As people age, this is reflected not only in how they look, move and feel, but also at a cellular level by changes in cell quality and turnover.

Over the last 100 years, due to not only an increasing population (Roser et al. 2013), but also an increase in the proportion of the population who are over the age of 85 (Christensen et al. 2009), interest in ageing from both a basic sciences and clinical viewpoint has increased. Although lifespan has increased across most of the Western world due to societal advancements such as improved sanitation and healthcare (Schoeni et al. 2008), there is a significant disconnect between lifespan and 'health-span' (i.e., the number of healthy years lived), with clear individual and societal (i.e., economic and healthcare) impacts (Marešová et al. 2015; Connolly, Postma 2010).

1.2 Exercise and ageing

Although consensus on a single theory of ageing has not been reached and there are multiple cellular processes which contribute to an ageing phenotype, the magnitude and trajectory of these changes does appear to be influenceable by environmental factors (i.e., exercise, nutrition, smoking and alcohol consumption (Annear et al. 2014)).

As an umbrella term for many different forms of structured physical activity, exercise confers a huge benefit in reducing the risk of developing disease and mortality (Naci & Ioannidis 2013), especially for older adults. The cardiovascular benefits of aerobic exercise, for example, are well documented, with regular exercise reducing the risk of cardiovascular disease even in previously sedentary individuals (Seals et al. 2009). In addition, most forms of exercise are also known to improve psychosocial

wellbeing and reduce symptoms of anxiety and depression. For example, a large cross-sectional study of Finnish participants (1856 women and 1547 men) assessing exercise habits and depression, anger and stress (Hassmén et al. 2000) reported that, perhaps unsurprisingly, those who were unable to exercise due illness or disease had the highest depression scores. Beyond this, they also reported that the lowest anger scores were associated with highest exercise levels.

1.2.1 Aerobic exercise training

Aerobic exercise training (AET) is a form of exertional activity that places demand on the cardiovascular and respiratory systems and requires aerobic respiration to create energy. It is often colloquially referred to as “cardio” and can be of varying intensity, duration, and type (i.e., running, cycling, and swimming). There is a substantial body of evidence to show that AET has a beneficial effect on reducing morbidity and mortality in healthy adults (Schoenborn, Stommel 2011) and reduces risk factors for diseases such as myocardial infarction (Fernström et al. 2017) and stroke (Crump et al. 2016; Bailey et al. 2013). In patients with cancer (many of whom are older (Balducci, Ershler 2005)), AET has been shown to i) reduce risk of developing cancer (Nilsson et al. 2019), ii) improve recovery from cancer treatment (Onerup et al. 2022; Dimeo et al. 1997a), and iii) reduce risk of cancer recurrence (Brown, Gilmore 2020), as well as iv) improve quality of life and mental health (Murtezani et al. 2014; Courneya et al. 2015).

1.2.1.1 Effect on the vasculature

Our capacity for aerobic exercise declines with age (Weiss et al. 2006) and although this is known to be multifactorial, changes to the vasculature will contribute due to its role in both oxygen and nutrient delivery and also ‘waste’ clearance. With advancing age there is stiffening of the vascular endothelium of large elastic arteries, reducing the production of vascular endothelial growth factors that coordinate the response of the vascular system to increasing metabolic demand (Ungvari et al. 2018). Regular AET into older age can reduce this large

artery stiffening to preserve normal responses to aerobic stress. In women, the decrease in circulating oestrogen as a result of the menopause further compounds the vascular effects of ageing, blunting their adaptive response to AET in terms of improvement in vascular function when compared to men (Yoshioka et al. 2003). The impact of hormonal profile on vascular adaptation to AET is further exemplified by a study showing that, when taking hormonal replacement therapy, there is improvement in endothelial function after AET when compared to oestrogen deficient females (Moreau et al. 2013). One proposed mechanism for the improvement in vascular function seen with AET is that exercising individuals will have lower oxidative stress and circulating inflammatory cytokines which will preserve endothelial vascular function (Seals et al. 2019). Synthesising the evidence around AET and vascular function, a meta-analysis by Campbell et al., showed that long-term, regular AET slowed the age-associated decline in vascular endothelial function compared to sedentary controls (Campbell et al. 2019).

1.2.1.2 Effect on skeletal muscle

In addition to reductions in cardiorespiratory and vascular function with advancing age, skeletal muscle mass and function also decline in a condition known as sarcopenia (Cruz-Jentoft et al. 2019). Derived from the Greek terms for “flesh” (*sarx*) and “poverty” (*penia*) (Rosenberg 1997), the process of sarcopenia begins at the age of ~40 years, with average losses of ~0.64-0.70% in women and 0.80-00.90% in men per year for mass and ~2.5-3% in women and 3-4% in men/year for strength (Mitchell et al. 2012a). There is variation in losses between genders and differing ethnic groups, with studies showing Black populations losing almost 30% more strength than whites over the course of 3 years in a population of older adults (Goodpaster et al. 2006). Although loss of muscle fibre number, rather than a significant decrease in the size of individual muscle fibres, is thought to be the predominant mechanism of sarcopenic muscle atrophy (Mitchell et al. 2012b), the commonly described discrepancy between loss of muscle function being greater than loss of muscle size, indicates that other factors such as

neuromuscular dysfunction (Hepple, Rice 2016) and mitochondrial dysfunction (Ferri et al. 2020) may also be impacting the functional losses seen with sarcopenia. Sarcopenia has a significant impact on the ability to withstand physiological insults of disease, treatments, and other environmental factors (i.e., periods of inactivity) (Cosquëric et al. 2006), hence the clear importance of muscle mass maintenance for older adults.

Although the exact and full mechanisms of sarcopenia are still to be elucidated, anabolic resistance to (protein) nutrition is commonly accepted as a substantial contributor (Burd et al. 2013). Anabolic resistance to resistance exercise training (RET) is also apparent in the literature (Kumar et al. 2009), but there is little to suggest that this is true for AET. For example, a study of 12 healthy older adults (74 y) who completed a 24-week fully-supervised AET programme reported significant improvements in muscle quality, as determined by peak torque divided by leg lean mass (+15.5%, p=0.01), and an increase in basal myofibrillar protein synthesis (MPS) levels (+50.7%, p=0.01) and capillary density (+66.4%, p=0.03) taken from *m. vastus lateralis* biopsies compared to a non-exercise group control (Brightwell et al. 2019). Similarly, a review by Konopka *et al.,* who examined skeletal muscle hypertrophy after AET in adults showed improvements in not only skeletal muscle hypertrophy, but also muscle function and exercise capacity (Konopka, Harber 2014). Of note, the discussion of this review stated that both a sufficient and sustained application of adequate exercise intensity is required for AET to have benefit with specific mention of target heart rate, duration and frequency of exercise.

1.2.1.2.1 Electromyography as a method to assess skeletal muscle function

As alluded to earlier, with age comes a global reduction in skeletal muscle mass and function, termed sarcopenia (Cruz-Jentoft et al. 2019). Neuromuscular changes associated with ageing and cancer include a reduction in the number of motor units and motor unit connectivity (Huot et al. 2021; Faulkner et al. 2007). Electromyography (EMG) is a recognised method to detect and analyse motor unit potentials (MUP),

which are the result of action potentials of multiple muscle fibres of the same motor unit (Piasecki et al. 2016). This can be done via a surface electrode (sEMG) or using intramuscular EMG (iEMG), which detects MUPs from a smaller area; iEMG involves inserting a needle into the desired muscle to record action potentials (Piasecki et al. 2016). Changes in conduction speed can be associated with various physiological disorders, such as demyelinating disease (Scott et al., 2011). With regards to the loss of muscle strength and power associated with ageing, part of this is attributable to a reduction in the ability of motor units undergo voluntary activation. This can be due in part to a reduction in recruitment, i.e., the number of motor units activated in a particular muscle to complete a muscle contraction, combined with the firing frequency of the activated motor units (Enoka et al., 2017). Outside of study into the changes in anal sphincter activity following treatment for rectal cancer (Trybek et al. 2019.), little work has been performed looking at changes in a patient's muscle activation along the surgical treatment pathway for colorectal cancer. This is a potentially useful area of study as there is potential to inform bespoke exercise/rehabilitation programmes for these patients if it is shown there are changes compared to the normal healthy population.

1.2.1.3 Effect on functional capacity

Functional capacity is a term used to describe the ability of a person to carry out activities and tasks that are often seen as vital in day-to-day life (i.e., activities of daily living (ADL)). There are various well-validated tests used to carry out an evaluation of functional capacity which are widely utilised across a plethora of different specialties, each with differing time and equipment requirements and participant burden.

1.2.1.3.1 Timed up-and-go

Modified from the "Get-Up and Go" test developed by Mathias *et al.* in 1986, the timed up-and-go test (TUG) by Podsiadlo and Richardson is one of the most commonly used assessments of functional capacity. Assessing the time taken for a participant to rise from a chair, walk 3 metres, turn, walk back and sit down again, the TUG was originally

developed for use as part of a comprehensive geriatric assessment. Requiring little to no equipment (just a chair and stopwatch) and being quick to carry out (Richardson 1991) has likely led to its popularity and use. In relation to AET, the TUG showed a significant correlation with aerobic capacity in elderly patients with coronary artery disease, after a 12-week AET programme (Chen et al. 2014a), evidencing not only the positive impact of AET on functional capacity, but also the ability of the TUG to detect these changes.

1.2.1.3.2 6-minute walk test

Similar to the TUG, the 6-minute walk test (6MWT) is a quick, inexpensive, easy to administer and safe method of assessment of functional capacity in older adults and/or co-morbid patients. It has also been used to determine cardiorespiratory responses to treatment (Hovington et al. 2009) or exercise interventions (Mendes et al. 2016), especially in co-morbid or frail patients in whom stress testing or ergometry-based exercise may not be feasible or appropriate (Figure 1.1). The 6MWT has been shown to correlate well with VO_2 peak as measured via cardiopulmonary exercise testing (CPET) (Ross et al. 2010), and in relation to AET has been used to evidence good correlation with functional ability (Chen et al. 2014b).

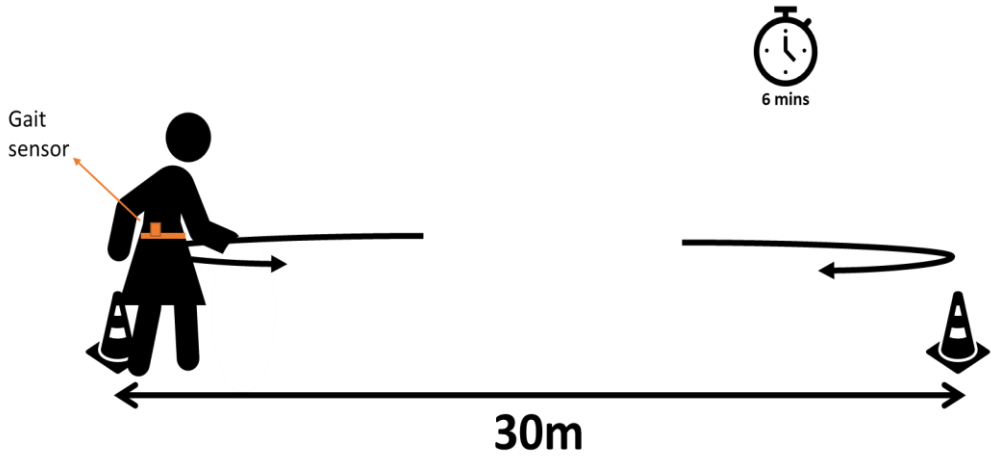


Figure 1.1. Diagram showing how to carry out the 6MWT using a gait sensor over a 30m distance. Note that a gait sensor is not required; it can also be performed using a treadmill noting the total distance walked in 6 minutes.

1.2.1.3.3 Handgrip strength test

Handgrip strength (HGS) testing is often used as part of functional performance battery to give an assessment of overall strength and muscular durability (Trosclair et al. 2011). A systematic review and meta-analysis by Bobos *et al.* scrutinised the quality of eight studies that used HGS measurements and found that in both healthy participants and those with musculoskeletal, neurological and other co-morbidities, HGS was reliable and valid (Bobos et al. 2020). When used to determine the impact of AET on aerobic capacity, HGS has been shown to correlate between a higher aerobic capacity in a healthy cohort in young women (Dag et al. 2021) and a large cross sectional population study (Seong et al. 2020).

1.2.1.4 Effect in cancer patients

In patients with cancer undergoing treatment, aerobic exercise has been shown to help improve patient adherence to treatment (Cheville et al. 2015), reduce the incidence and effect of complications (Steffens et al. 2018; Dimeo et al. 1997b) with improvements in cancer-related fatigue (Velthuis et al. 2010) and physical performance (Dimeo et al. 2004) in multiple different cancer subtypes.

1.2.2 Resistance exercise training

The second of the two most recognised forms of exercise training (alongside AET), RET involves muscle working against a form of resistance (i.e., body weight or an external load). Traditionally, associated with skeletal muscle hypertrophy only, RET is now gaining recognition as an effective way to increase multiple aspects of muscle function (i.e., strength, endurance, and power (Fragala et al. 2014; Talar et al. 2021)), structure (i.e., architecture (Häkkinen et al. 2002) and neuromuscular aspects (Rodriguez-Lopez et al. 2022)) and quality (i.e., reduced myosteatosis (Marcus et al. 2010)). As with almost all forms of exercise training, RET is most effective when personalised to both the participant and the desired adaptation. Although many RET studies conduct their interventions in a formal setting using relatively large and

expensive equipment (e.g., pulley-based machines) (Mende et al. 2022), RET using little equipment or space (i.e., with resistance bands (Kwak et al. 2016) or bodyweight-based) has been proven effective at eliciting benefit (Aerenhouts, D'hondt 2020; de Lima et al. 2018).

1.2.2.1 Effect on skeletal muscle

Known to prolong and enhance muscle protein synthetic responses to protein nutrition (Figueiredo 2019), thus leading to muscle hypertrophy, RET has potential to mitigate both sarcopenia and other situations associated with ageing and catabolic processes, such as cancer. In a meta-analysis of 25 studies totalling 2,267 participants with an age range of 62 to 98 years, Talar *et al*., that RET significantly reduced fat mass and increased muscle mass (Talar et al. 2021). Functional outcomes were also improved in all but one study, evidencing the potential benefit of RET to improve older adults body composition, strength, independence, and quality of life (QoL). In addition, and likely related to increased muscle mass after RET, a recent systematic review by our research group (Smart et al. 2022) has shown that RET also can improve the cardiorespiratory fitness (CRF) of older adults. This is despite the prevailing view that this adaptation is only achievable with AET and/or more novel forms of exercise training such as high-intensity interval training (HIIT) (Karlsen et al. 2017).

1.2.2.2 Effect on functional capacity

In older and/or frail patients, assessment of functional capacity is often more useful than measures of muscle mass or isolated region muscle function (i.e., as measured with handgrip strength), as this will more likely correlate to their ability to perform ADL and maintain independence. RET has the potential to improve functional capacity in older adults as shown across a range of studies, each implementing different RET regimes (Lopez et al. 2018). As a specific example, both high- and low-speed RET for 12 weeks improved multiple functional outcome measures, including the sit-to-stand test, leg press 1-repetition maximum (1-RM) and non-dominant HGS (Ramírez-Campillo et al. 2014).

1.2.2.3 Effect in cancer patients

RET interventions have been prescribed to patients with differing cancers at various points in their treatment pathway, with numerous primary outcomes (i.e., QoL (Cramp et al. 2010), incidence of treatment side effects (Galva˜o et al. 2006), muscle mass (Padilha et al. 2017), physical fitness (Wiskemann et al. 2019)). Patients with abdominal cancer (stomach, colorectal and gynaecological malignancies) self-reported RET as a safe form of exercise, even after cancer surgery (Hashem et al. 2020). In addition, a systematic review looking at RET in cancer survivors who had undergone chemotherapy found that, despite a wide variation in the delivery of the RET programme, there were improvements in cardiovascular and respiratory function, it was well tolerated and was safe (de Backer et al. 2009). Twenty-four studies were included in this review, which covered mainly breast and prostate cancer patients, however six studies had a mixed cancer population. The training programme length varied from 3 to 24 weeks and also included a form of AET in various formats (e.g., cycling, walking, swimming, etc.). Of the seven studies that used VO_2 peak and the four that used peak power output as measures of CRF, they all found a significant improvement after RET. It should be noted that the studies varied in quality, with only 3 studies meeting the full criteria for methodological quality, and a median score of 4/10 was achieved for the studies included in this review using a slightly modified version of the Physiotherapy Evidence Database (PEDro) scale (Maher et al. 2003).

1.2.3 Alternative forms of exercise

The exercise modalities described above (AET and RET) are not exhaustive, and other, more novel types of exercise training have been trialled to try and improve the physiological and/or well-being status of older adults. For example, 12-weeks HIIT in 28 older participants significantly improvement their HGS, QoL, body mass index (BMI) and gait speed (Jiménez-García et al. 2019). In addition, just 4-weeks HIIT improved the CRF (anaerobic threshold: +1.2 ± 0.4 ml/kg/min1, P=0.001) of 28 octogenarians (Blackwell et al. 2021); no adverse events were

reported in either of these studies. HIIT has also been used in patients with cancer as both surgical prehabilitation (Palma et al. 2021), rehabilitation from surgery (Schmitt et al. 2016) and whilst undergoing neoadjuvant therapies (Gonzalo-Encabo et al. 2022). In a cohort of eighteen patients with colorectal cancer (CRC) prior to undergoing curative resection, Boereboom *et al.,* trialled a short-course (<31-days, in keeping with the National Cancer Action Team mandated period between decision to treat and surgery (NHS England 2022)) of fully-supervised HIIT using cycle ergometers 3 to 4 times per week, and found that despite no significant improvement in VO_2 peak, resting heart rate and blood pressure were reduced (Boereboom et al. 2019). Conversely, using the exact same HIIT protocol (5x 1-min exertions, interspersed with 90-seconds rest), Blackwell *et al.,* found a significant improvement in cardiorespiratory fitness VO_2peak following preoperative HIIT in a cohort of 19 urological cancer patients. Potential explanations for this discrepancy include the number of sessions that were able to be scheduled before surgery (8 (range 6-14) vs. 11 (range 10-12)) and the differing systemic disease burden of the 2 cancer types, with higher inflammatory profiles reported in CRC patients. Although it could be suggested that a longer programme may have yielded more consistent results, a study by Herrod *et al*., showed that 4-weeks HIIT was superior to 2-weeks for improving anaerobic threshold in older adults, with a further improvement in VO2 peak with 6-weeks training (Herrod et al. 2020).

Beyond HIIT, other forms of exercise including Tai-Chi (Penn et al. 2019), yoga (Denham-Jones et al. 2022) and low-intensity RET with blood flow restriction (Centner et al. 2019) have also been trialled to try and improve the physiological status/resilience of older adults. In older adults, a review by Rogers *et al.* looking at Chi and Qigong found mixed results with regards to observed functional performance parameters, despite self-reported functional performance generally showing significant differences in a variety of validated questionnaires, including the Short Form Surveys 12 and 36 (SF-12 & SF-36) and Western Ontario and

McMaster Universities Osteoarthritis Index (WOMAC) (Rogers et al. 2009). Yoga appears to have positive effects on motivation and energy levels but has mixed results with regards to any improvement in physiological function (Adams et al. 2019; Yao, Tseng 2019).

1.3 Ageing and cancer

As previously highlighted, many diseases, such as cognitive disorders, arthritis and those related to the cardiovascular system, are generally associated with advancing age (Ungvari et al. 2018). As we age, we enter a more chronic pro-inflammatory state, also increasing our risk of developing inflammatory disorders, of which cancer can be also considered (Vasto et al. 2009). Further, cellular abnormalities seen in ageing are also seen in the development of cancer at the microscopic level. The development of cancer is heralded by uncontrolled cell growth and lack of apoptosis, usually due to the deactivation of tumour suppressor genes combined with the activation of oncogenic pathways. The progression towards metastasis is secondary to breaching of tissue basement membranes and increased cellular motility, allowing cancer cells to spread (Sarkar et al. 2013). There are usually processes for the detection of DNA damage in order to repair it, however these processes become impaired as we age (de Magalhães 2013), possibly contributing to the increased risk of cancer over time. In breast cancer patients, a significant reduction in apoptotic responses to radiation has been reported, with further reductions with advancing age (Camplejohn et al. 2003). As cancer is primarily a disease of older age, age itself can be considered to be a potential carcinogen. This relationship between age and cancer is thought to be due to a combination of i) increased duration of exposure to other environmental carcinogens, ii) the cellular ageing process itself being a risk factor, and iii) increased susceptibility to other diseases/processes that may contribute (e.g., duration of endocrine exposure increasing the risk of breast and endometrial cancers) (Balducci, Ershler 2005). Unfortunately given the heightened prevalence of cancer with advancing age, some cancers also show a worse prognosis due to poor treatment response with increasing age, such as

ovarian and non-Hodgkins's lymphoma (Cloven et al. 1999; Morrison et al. 2001). It is known that some physiological features of ageing such as diminished muscle mass negatively impact cancer treatment outcomes due to, for example, elevated risk of chemo-toxicity in those with low muscle mass (Gérard et al. 2016).

1.3.1 Colorectal cancer

Colorectal cancer (CRC) is a malignant growth in the lining of the colon or rectum, often having a pre-malignant neoplastic phase in a colonic polyp. Over time the neoplasia has a malignant change and crosses the basement membrane to invade the surrounding structures with the potential to metastasise to other areas of the body. CRC is almost exclusively adenocarcinoma. Risk factors for CRC include advancing age, smoking, family history of CRC, high alcohol consumption and chronic intestinal inflammation, such as seen in ulcerative colitis. Protective factors include a low animal protein diet and physical activity. Between 2016 and 2018 there were, on average, 42,886 new cases of CRC diagnosed each year in the UK alone (Figure 1.2). It accounts for over 10% of all new yearly cancer cases, with 43% of new cases in people aged 75 years and over (Cancer Research UK, 2021). Given its high incidence, but also a modifiable disease trajectory, screening for CRC is imperative to identify pre-symptomatic patients, to offer the best chance at curative intervention.

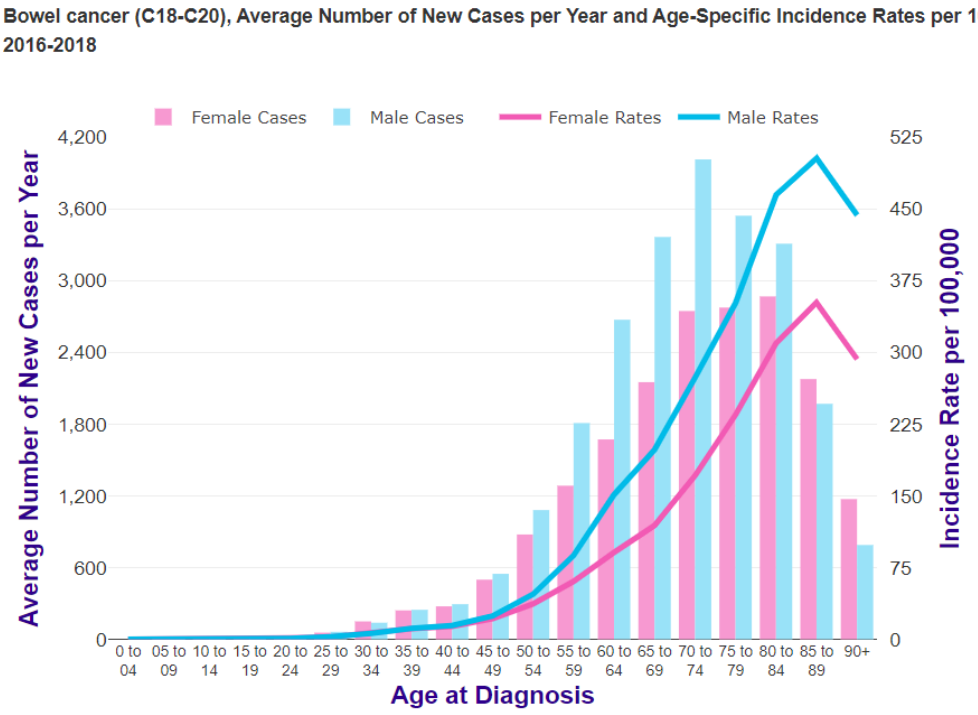


Figure 1.2. Average number of new cases of colorectal cancer per year and age specific incidence rates per 100,000 population, UK, 2016-2018. (Cancer research UK [CRC UK], https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence. Accessed 28th December 2022). Permission to use CRC UK content as per website.

1.3.1.1 Colorectal cancer and surgery

Surgery is the gold standard treatment for cure in CRC patients, with over half of patients surviving their disease for ten years or more. In 2023, 85% of patients who underwent surgery with curative intent were alive 2 years after surgery (National Bowel Cancer Audit Project Team., 2024). However, as CRC increases in incidence with age, patients often have more co-morbidity associated with ageing, which can affect their overall fitness for surgery. To improve fitness before surgery in the UK, interventions should be delivered within the 31-day window between decision to treat and surgery. The postoperative focus has not been on improving fitness but has been directed towards “enhanced recovery” to achieve target-driven goals such as length of hospital stay (LoHS) and improve the pathway of immediate postoperative recovery. This is most notably via the use of enhanced recovery after surgery (ERAS), a concept discussed in more detail in section 1.3.1.4. Once patients have been discharged, however, there is little or no structured guidance on how to rebuild strength and fitness to return to preoperative levels of

activity. This lack of a structured exercise recovery programme may be a factor in prolonged times to full recovery after surgery for CRC (Bhalla et al. 2014)

1.3.1.2 Exercise and physical function in colorectal cancer patients

Surgery for intra-abdominal cancers form a large part of the scope of practice for surgeons. There are guidelines which are enacted via the use of multi-disciplinary teams (MDT) which determine those patients who are eligible for potential resection; this can be for either curative or palliative intent. Those who are staged appropriately for surgery must be physiologically capable of withstanding the surgery involved, whether that comes in open, laparoscopic, or robotic format. This decision can also involve the opinions of other disciplines, such as anaesthetists and geriatricians. There has been a plethora of research into preoperative scoring to help define the appropriate population for surgery (Cohen et al. 2009; Copeland et al. 1991), and, as cancer is primarily a disease of ageing, this is ever more important as an older multi-morbid patient group that have other pathologies that make surgery too high risk. There has also been a substantial body of work in preoperative optimization of patients to help them better withstand the rigors of surgery, known as prehabilitation (Wynter-Blyth, Moorthy 2017). Despite, a lack of mechanistic understanding for how prehabilitation may be optimised, and some facets of physiological resilience seemingly being hard to improve in certain patient groups (Boereboom et al. 2019), prehabilitation has on the whole, shown encouraging results (Blackwell et al. 2020), even within the limited timescale of urgent surgery for malignancy.

1.3.1.3 Preoperative risk prediction and risk reduction

In older patients who require surgery, it is useful to identify those who are at increased risk of mortality or increased morbidity, preferably in the preoperative state. Emergency patients aside, this currently ranges from asking the simple question “can you walk up a flight of stairs” to a detailed preoperative anaesthetic clinic assessment encompassing a cardiopulmonary exercise test (CPET). There are also various risk prediction models that have been validated for use in these patients, for

example the colorectal POSSUM (CR- POSSUM) (Tekkis et al. 2004) which helps guide the consent process between surgeons and patients by delivering a more bespoke estimated predictive risk for individual patients as well monitoring performance between centres. However, none of these measures offer input on *how* to improve perioperative status. One example of a perioperative programme that has been shown to reduce postoperative morbidity and mortality is the Proactive Care of Older People having Surgery (POPS) programme at Guys and St Thomas's Hospital in London, UK. This is a geriatric led service with multidisciplinary input which preoperatively assesses patients who require surgery and attempts pre-optimisation to improve their recovery, as well as continued specialist input during their inpatient stay (Partridge et al. 2018). This involves a full comprehensive geriatric assessment, a medications review, and referral to appropriate specialists where required for expert input.

1.3.1.4 Perioperative programmes

Perioperatively, programmes such as ERAS have put the spotlight on trying to improve postoperative morbidity and mortality by providing goal-directed targets based around enabling patients to be ambulatory, well and discharged safely as quickly as possible. This is a multidisciplinary process involving not only surgeons, but other healthcare professionals such as physiotherapists, dieticians and anaesthetists. The ERAS Society have published guidelines with targets for all stages of the patient journey to improve perioperative care (Gustafsson et al. 2018). This begins preoperatively with lifestyle modification advice such as smoking cessation, preoperative screening and optimisation of any other medical conditions. This continues to intra-operative measures such as, use of a minimally invasive approach where possible and prophylaxis against commonly encountered problems such as nausea and vomiting, thrombosis and hypothermia. Postoperatively, early mobilisation, removal of drains/catheters, etc. and intake of oral fluids and diet are encouraged to help support early discharge (Figure 1.3). In a meta-analysis of ERAS for patients having open CRC surgery, Varadhan *et al*.,

found six RCT's that assessed the efficacy of the ERAS pathway (Varadhan et al. 2010) and reported that LoS and complication rates were significantly reduced in those who had experienced ERAS-based care.

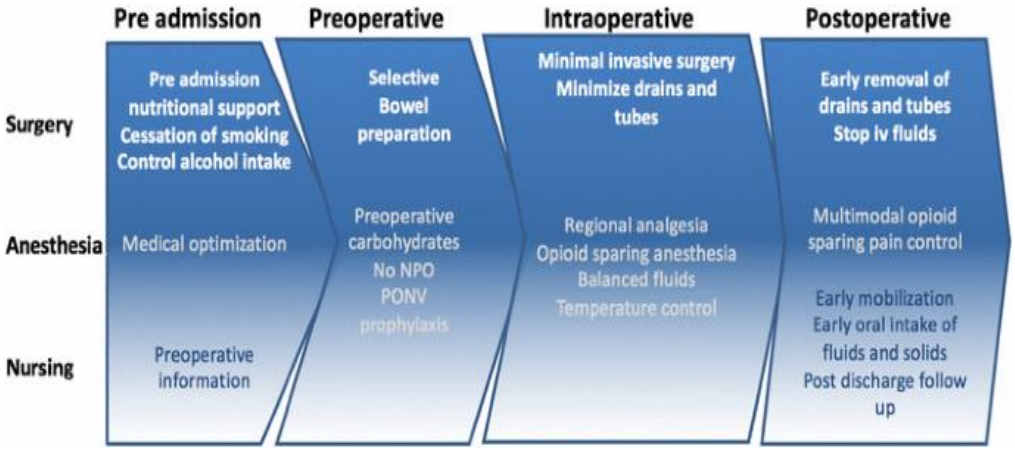


Figure 1.3. ERAS multimodal/multidisciplinary model. Taken from Ljungqvist, O., Hubner, M. Enhanced recovery after surgery—ERAS—principles, practice and feasibility in the elderly. Aging Clin Exp Res 30, 249–252 (2018). Accessed 28th December 2022.

Although many studies assessing the benefit of ERAS (or other pre/peri-operative interventions) focus on shorter LoS, this should be seen as a derived effect of higher quality care rather than the focus being on a quick discharge. The effects of these programmes are also commonly measured against parameters of 30 and 90-day morbidity and mortality outcomes, with limited conclusions with regards to patient-related QoL measures. Longer term, post-discharge exercise programmes in cancer patients after surgery are less well-studied, with little advice given during routine follow-up appointments with regards to what exercise can be undertaken. Patients can also suffer long-term emotional effects of cancer and surgical treatment that are also addressed with limited frequency (Mosher et al. 2016).

1.3.1.5 Exercise and quality of life in cancer patients

A diagnosis of cancer is a major cause of anxiety, uncertainty, and stress. QoL in cancer patients is an extremely important outcome, and often therapies are directed towards QoL improvement, especially in the context of incurable disease. By virtue of the catabolic effects of having cancer alone, there is increased fatigue and issues with memory, coupled with systemic cytotoxic therapies such as chemotherapy, it can significantly decrease patients' overall QoL. In a cohort of CRC survivors, Vallance *et al.,* showed that patients who had high moderate-vigorous physical activity (MVPA) scores reported significantly less anxiety and higher satisfaction with life (Vallance et al. 2015). However, in a systematic review by Cramer *et al.,* investigating the use of physical exercise in CRC patients to improve fatigue, physical fitness and quality of life, the 3 studies included in the meta-analysis of QoL did not demonstrate any significant improvement over the short or longer-term (Cramer et al. 2014). Another study showing a positive impact of exercise for CRC cancer survivors was conducted by Brown *et al.,* in 2018. Comparing low dose (150 minutes per week) and high dose (300 minutes per week) AET for six months, against a usual care control, Brown and colleagues found a statistically significant improvement in multiple QoL domains, especially in the high dose group, including physical health and fatigue (Brown et al. 2018). Similarly, Patel and Bhise prescribed 6-weeks low to moderate intensity (50-70% of maximum heart rate) AET to cancer patients reporting cancer-related fatigue for 20-40 minutes/day for 5 days/week (Patel, Bhise 2017). Patients in this study suffered from a range of cancers including breast, head and neck, gastrointestinal and gynaecological tumours. Fatigue was assessed using the brief fatigue inventory (BFI) - a patient-reported validated questionnaire for use in this cohort of patients (Mendoza et al. 1999), and a statistically significant improvement in fatigue was found. As fatigue is a major contributor to perceived QoL in cancer patients, the ability to improve this may be a major driver for cancer patients to feel a significant improvement in other QoL domains.

1.3.1.6 Patient perceptions of exercise during colorectal cancer treatment

Despite there being a body of evidence promoting the benefits of perioperative physical activity in colorectal cancer patients (Minnella et. al 2018; Barberan-Garcia et al. 2018; Van Rooijen et al. 2019), it is still not ubiquitous in terms of advice given and programmes delivered. Patients often decline offered preoperative exercise interventions, but those who agree often show high rates of compliance (Karlsson et al., 2019). From a series of semi-structured interviews, Karlsson *et al.* explored the attitudes of older patients with colorectal cancer towards preoperative physical activity and exercise (Karlsson et al. 2020). Previous experiences with regards to physical activity had a big influence on perceptions both positively and negatively, depending on the type of previous experience. Attitudes towards being able to perform preoperative physical exercise mainly came down to confidence as self-motivation as well as support to enable the patient to perform the activity. In a postal questionnaire of 479 patients with non-metastatic colorectal cancer, perceived barriers & benefits were surveyed (Fisher et al. 2016). The most frequently cited barrier to physical activity disease/treatment-specific tiredness & fatigue (13.2%), with 12.9% of respondents reporting general age-related aches and pains as another barrier. In terms of perceived benefits, 28.9% reported an improvement in fitness as a benefit, and 23.4% claimed it promoted weight loss. 7.2% reported that it decreases tiredness/increases energy. Very few patients in the study reported cancer-specific beneficial outcomes from physical activity, with overall low levels of self-reported activity (active patients were those who reported ≥ 5 sessions of activity per week on the Godin Leisure Time Exercise Questionnaire (Amireault et al., 2015)). This study did not include subset analysis depending on the stage of the respondent's treatment pathway, however, so although it gives a good overview of themes to take into account when attempting to devise perioperative exercise programmes in this cohort of patients, they may not be specific to those undergoing surgery.

1.4 Rehabilitation

Rehabilitation (in the healthcare context) is the process of helping an individual return to a prior or achieve an appropriate level of day-to-day function (World Health Organization, 2019). This is usually multimodal, with exercise forming only part of the intervention needed to enable this. It ideally involves a multidisciplinary approach, with roles and responsibilities including dieticians to assess and optimise nutrition, occupational therapists to look at whether any adaptations/changes are required to help support patients, and specialist clinicians to look at other issues, such as reducing polypharmacy and mental health support. In geriatric medicine, this approach is employed often, with many rehabilitation programmes specialising in this cohort of patients. A Cochrane review from 2013 looked at rehabilitation programmes for adult cancer survivors (Scott et al. 2013). They identified 12 RCT's which delivered an intervention with both a physical and psychosocial component by a healthcare professional. Although a meta-analysis was not possible due to the heterogeneous nature of the studies, they did find that rehabilitations programmes that focus mainly on one intervention seem to be more successful at achieving their desired outcome, and that they do not need to be cancer-site specific: with gains seen in mixed cancer groups having the same intervention. However, the results do appear to plateau at ~6 months, and face-to-face delivery is most effective.

1.4.1 Theories of rehabilitation design

With regards to the development of rehabilitation programmes in healthcare settings, there are several theories underpinning the design and development to ensure they are robust, safe, and replicable. In order to give a rehabilitation programme the best chance of success, attention must be paid towards factors that can positively or negatively influence adherence and compliance, as well as stakeholder input into rehabilitation design in order to make sure it is fit for the population it will

serve. Goal setting by the participant is seen as an integral part of rehabilitation. There are two main phases of goal behaviour, the *motivational phase*, where expectations are outlined, and the *action phase*, where the behaviour is performed to initiate and maintain a course towards achieving the goal. Scobbie *et al.,* conducted a qualitative review to scrutinise the literature for behavioural change theories that influence the setting and/or achieving of goals in patients with clinical conditions (Scobbie 2009). They found multiple relevant theories of behaviour change with regards to goal setting/achievement in the rehabilitation setting which helped patients to set effective, achievable goals which led to increased adherence. The common thread of the identified theories was that they aimed to work on either or both phases of goal behaviour. Ormel *et al.,* looked more specifically at predictors of adherence to exercise interventions during and after systemic cancer treatment in a systematic review (Ormel et al. 2018). They found fifteen eligible studies, giving a total of 2279 patients (1383 randomised to an exercise intervention). The studies included a range of cancer types including breast (n=6), mixed (n=4), prostate (n=2), head and neck (n=1), lymphoma (n=1) and CRC (n=1). Significant predictors of adherence after treatment completion included male gender, family support, trainer feedback, and interestingly in breast cancer patients, older age. Home-based interventions were found to not allow for effective monitoring of adherence as compared to supervised programmes, but with good family support and regular supervisor feedback can be an excellent choice, especially in patients who may find regular visits difficult with regards to transportation. As alluded to prior, exercise is not the sole component of rehabilitation, but it will be the main element discussed here.

1.4.2 Exercise as part of postoperative rehabilitation

There is a plethora of evidence in the literature that show that exercise after various types of surgery is safe and can improve postoperative outcomes even in major surgery that causes a significant reduction in mobility. For example, AET immediately after cardiac surgery has been

shown to be both safe and beneficial. Supporting this, Doyle *et al.* conducted a systematic review and meta-analysis of studies reporting safety and efficacy outcomes of patients taking part in an AET programme within two weeks of cardiac surgery (Doyle et al. 2019). They included a total of twenty studies; 6 who exercised patients in the immediate postoperative period and 14 that reported early (post discharge but within 2 weeks of surgery) exercise interventions. The 6 studies who reported on adverse events showed no significant difference in the overall adverse event rate in the exercise group compared to usual care. In the 4 studies that reported peak oxygen consumption, there was a significant increase in the exercise group compared to usual care. Similarly, in cancer patients postoperative exercise has been shown to improve quality of life and mood, although this is complicated by the fact that adherence to postoperative exercise programmes is variable, suggesting a need for understanding of motivational factors behind those who succeed over those who do not. For example, logistical issues such as travelling to a gym or group physiotherapy session may not be achievable for some patients, especially those who may potentially benefit the most (i.e., more infirm/frail), whereas others may prefer a more hands on approach/accountability and may not adhere well to an independent/home exercise approach. Programmes that offer flexibility, the option between these two approaches may yield more success.

1.4.2.1 Biopsychosocial predictors of exercise rehabilitation

In exercise rehabilitation, biopsychosocial predictors of prognosis in many disorders has been researched in order to outline a clear set of important factors. In a cohort of 120 stroke patients, Kobylańska *et al.* found that factors such as age (mean age in years, 58.0, SD 8.6), duration since the stroke, comorbid status, family support status with regards to ability to care and depressive symptoms were associated with a low efficacy of rehabilitation (Kobylańska et al., 2019). Similarly in patients with chronic rotator cuff related shoulder pain, a younger age and fewer depressive symptoms related to a high step count (Rosa et al., 2025). However, in the cancer-specific cohort, this is less well-

understood. Studies have shown a favourable relationship between rehabilitation programmes and psychosocial outcomes of adult patients with cancer (Kudre et al., 2020), but analysing the factors that determine or improve specific outcomes is yet to explored. Erlik *et al.* looked at reasons for non participation in rehabilitation programmes in a scoping review (Erlik et al., 2024). With a total of nine studies as part of their results, they found (surprisingly to them) that the presence of social/familial support meaning that patients did not feel that they needed extra support was the major theme noted. Despite low socioeconomic status being a well-recognised barrier to engagement in rehabilitation (Costas-Muniz et al., 2016; Oksbjerg Dalton et al., 2019), they were unable to identify any themes that could potentially explain this from the studies included.

1.4.2.2 Exercise Prescriptions

Exercise prescriptions are poorly undertaken by clinicians generally and are not always well documented amongst other healthcare professionals who may use it more frequently (Zenko, Ekkekakis 2015). It is based on using specific prescriptions to tailor exercise towards the individual to improve physical function and quality of life. The 5 principles of exercise prescription which must be included is type, duration, frequency, volume and intensity (Swain, Brawner 2014). The American College of Sports Medicine have developed a set of expert-led evidence-based guidelines specific to cancer survivors, although the research involved is heavily weighted on breast and prostate cancer cohorts (Schmitz et al. 2010).

1.4.2.3 Impact on cancer recurrence rates

Exercise seems to have a beneficial effect on disease-free survival in cancer patients, although the reasons why are still poorly understood. Cormie *et al.,* conducted a systematic review analysing the impact of exercise on (all types of) cancer mortality and recurrence (Cormie et al. 2017). Thirty-six articles were included: 32 prospective cohort studies and 4 RCT's. A significantly lower risk of cancer-specific mortality was

observed for patients with higher exercise levels in 17 of the 30 studies that reported cancer-specific mortality. Of the studies that reported cancer recurrence, there was a significantly lower risk observed in exercising patients in 4 out of 9 studies. The cancer populations in the four studies were breast, prostate, and CRC. The included studies did have variable lengths of exercise training, differing training modalities and varied time from diagnosis to assessment of exercise levels which limits further inferences of the pooled results. Morishita *et al.* conducted a meta-analysis to investigate the effect of exercise on mortality and recurrence in breast cancer only (Morishita et al. 2020). They found that exercise resulted in 69 fewer cases of recurrence per 1000 in 3 RCT's. The overall patient population was however relatively small (intervention group = 367, control group 294) and the studies had an overall serious risk of bias. Although the mechanisms underlying this potential effect are not well studied, there is suggestion that this is due to improvements in immune function which exert a protective effect against cancer recurrence (Bigley et al. 2013).

1.5 Thesis Aims

The current literature base shows us that exercise of cancer resection surgery is safe but that the short-term benefits are still unclear. Therefore, the aims of this thesis are:

1) To review the existing literature base to assess the impact of postoperative exercise-led rehabilitation programmes in abdominal cancer patients (Chapter 2).
2) To assess levels of postoperative physical activity in the immediate postoperative period by patients on an ERAS pathway (Chapter 3- PHYSPAL study).
3) To deliver a 12-week combined AET and RET programme to CRC patients who have undergone surgery with curative intent to:
    a. assess the efficacy of this exercise programme for improving i) cardiorespiratory and muscle function, and ii) health related QoL, and

b. determine its acceptability (Chapter 4- POSTEx study).

2 A systematic review of the impact of postoperative aerobic exercise training in patients undergoing surgery for intra-abdominal cancers

2.1 Chapter Summary

As discussed in Chapter 1, exercise is not only safe during the perioperative period, it is actively encouraged in order to reduce the risk of postoperative complications and morbidity (Boukili et al., 2022). ERAS has been extensively investigated and audited to look for benefits (Varadhan et al., 2010), but post discharge exercise is less well considered. The following systematic review was undertaken in order to evaluate whether specific exercise regimes have shown any improvements in patients undergoing surgery for intra-abdominal cancers.

2.2 Introduction

Nearly half of all UK adults will develop cancer at some point during their lives (Cancer Research UK, accessed 2022). Surgery remains the gold standard for achieving a curative outcome in many of these cases, especially for intra-abdominal cancers. Various prediction tools and preoperative assessment models such as the CR-POSSUM score are used to try and appropriately triage patients who may need more intensive perioperative support, based on an established evidence base showing that physical fitness at the time of operation is strongly associated with improved post-surgical outcomes (Dronkers et al. 2013; Tekkis et al. 2004). In recent years, prehabilitation for cancer surgery has received increasing attention in both research and clinical spheres (C. Boereboom et al., 2016). Designed to improve the functional status of patients prior to surgery (even within the time-sensitive period between cancer diagnosis) to improve postoperative outcomes, the supportive evidence for prehabilitation in cancer patients is most commonly based

around exercise training, although often with adjuvant multi-disciplinary elements such as nutritional advice and/or psychological support (J. E. M. Blackwell et al., 2020; Van Rooijen et al., 2019). However, to date, there is little focus for clinicians on amalgamated evidence and therefore advisory body guidance about exercise rehabilitation for this particular cohort of patients. This is despite evidence that rehabilitation in other surgical cohorts significantly improves functional outcomes for patients (Bartolo et al., 2012; K. Kong & Kevorkian, 1996).

It is well known that the presence of cancer has a catabolic effect, with many patients presenting with systemic symptoms including skeletal muscle loss, weight loss, fatigue, and difficulty performing activities of daily living (Nicholson et al., 2020). In those who are eligible for surgical resection with curative potential, reduced physical activity levels, often attributed to fatigue and weakness, can impact their ability to withstand the physical demands of this treatment (Tung et al., 2016). In addition, when considering cancer as a disease of ageing (e.g., despite the increase in diagnoses in younger adults, the incidence of colorectal cancer rises sharply after the age of fifty years, (Haggar & Boushey, 2009)), other age-associated conditions such as sarcopenia may also negatively impact physiological resilience for surgery (Reisinger et al., 2015).

Recognising the importance of optimal surgical recovery, not only for the patient, but also for healthcare systems in terms of length of stay and associated costs, has led to the design and implementation of ERAS programmes (Roulin et al., 2013). Providing targets for both patients and healthcare professionals, the primary aim of these programmes is to reduce the length of postoperative stay and complication rate (Gustafsson et al., 2018). A meta-analysis of RCTs assessing the effect of ERAS programmes on morbidity, complications and length of stay showed that they did shorten length of hospital stay without increasing

rates of readmissions, although there was no difference in surgical complication rate (Greco et al., 2014).

Similar to prehabilitation regimes which cease at the point of surgery, ERAS programmes often stop at the point of hospital discharge. With little in the way of clear guidelines for what patients can aim to achieve after surgery, especially in cancer patients, patients are commonly provided with little clear instruction on what they should aim to do when at home until their follow-up appointment, which can often be many weeks later. UK government guidelines state that all healthy adults should aim to do either 75-minutes of vigorous exercise or 150-minutes of moderate exercise per week, with at least 2 resistance exercise sessions per week to promote whole-body health (Davies et al., 2019). In patients with active cancer, aerobic exercise training, even at a vigorous intensity has been shown to be both safe and effective for improving health-related outcomes (i.e., cardiorespiratory fitness, fatigue, patient-perceived fitness, and sleep) (Singh et al., 2020). In addition, when combined with appropriate dietary intake (i.e., adequate protein), resistance exercise training has also been shown to improving muscle mass and function in various populations of cancer patients (Kamel et al., 2020; Lee, 2022; Padilha et al., 2017). However, bespoke guidelines for patients after cancer surgery are not available. As both cardiorespiratory and muscle function are each associated with favourable health outcomes, especially in older adults (Galva˜o et al., 2006; Padilha et al., 2017; Wiskemann et al., 2019), the physiological benefits of exercise for this patient cohort are clear. In addition, the psychological benefits of exercise are also well-established, an aspect of heightened importance for patients dealing with a cancer diagnosis and the impacts of treatment (Kim et al., 2019; Lund et al., 2020).

Given the well-established benefits of perioperative exercise for cancer patients including a growing body of evidence for exercise based

prehabilitation yet a lack of tailored exercise advice for postoperative intra-abdominal cancer patients, the aim of this work was to review the current literature to determine if aerobic exercise training as rehabilitation, either alone or in conjunction with another exercise modality: i) is feasible in the postoperative setting; ii) confers any physiological benefits in terms of aerobic capacity; and iii) has any significant effect on patients' psychological well-being or health-related quality of life (HRQoL).

2.3 Methods

2.3.1 Study design

The review was registered on PROSPERO prior to literature searches (registration number CRD42021175427). Cohort studies, randomised, and non-randomised controlled trials were included, with abstracts and case reports excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart was used to assess papers for inclusion in the final review (Page et al., 2021).

2.3.2 Inclusion and exclusion criteria

Only studies of adult patients (aged 18 and over) diagnosed with an abdominal malignancy and who had undergone resectional surgery with curative intent were included. Full details on the inclusion and exclusion criteria are detailed in Table 2.0.1. All intra-abdominal cancers were included as the method of entry to abdomen is similar and the focus of this review is the impact of rehabilitation on post-surgical recovery.

Inclusion Criteria
• Adult patients over the age of 18 years with an abdominal malignancy
• Patients undergoing any mode (i.e., open, laparoscopic, robotic, etc) of resectional surgery with curative intent
• Postoperative exercise programme (inpatient, outpatient or mixed) with an aerobic exercise training component
• A reported outcome of cardiorespiratory fitness
• Studies that compare either pre- and postoperative measures, or compare an exercise group to control
Exclusion Criteria
• Patients who have not undergone intra-abdominal surgery with curative intent
• Palliative patients or those undergoing surgical resection for benign disease
• Preoperative exercise only or studies that only compare prehabilitation to rehabilitation, with no reference to baseline changes within the two groups
• Exercise programmes that start more than 12 weeks post operatively
• Qualitative only studies
• Studies that assess the impact of an ERAS protocol

Table 2.0.1. Inclusion and exclusion criteria for article selection.

2.3.3 Search strategy and article selection

A clinical librarian (ST) conducted searches of OVID Medline, OVID Embase, OVID Emcare, EBSCOhost CINAHL, ProQuest BNI, PubMed, Cochrane databases (see Search Strategy in Appendix 7.1). Articles searched for were in any language and with no date restriction. Abstracts

from the initial search results were filtered using Rayyan systematic review software (Ouzzani and Hammady 2016) to exclude duplicates and identify papers to be further screened for inclusion. The process of article identification and exclusion is shown in Figure 2.0.1**.**

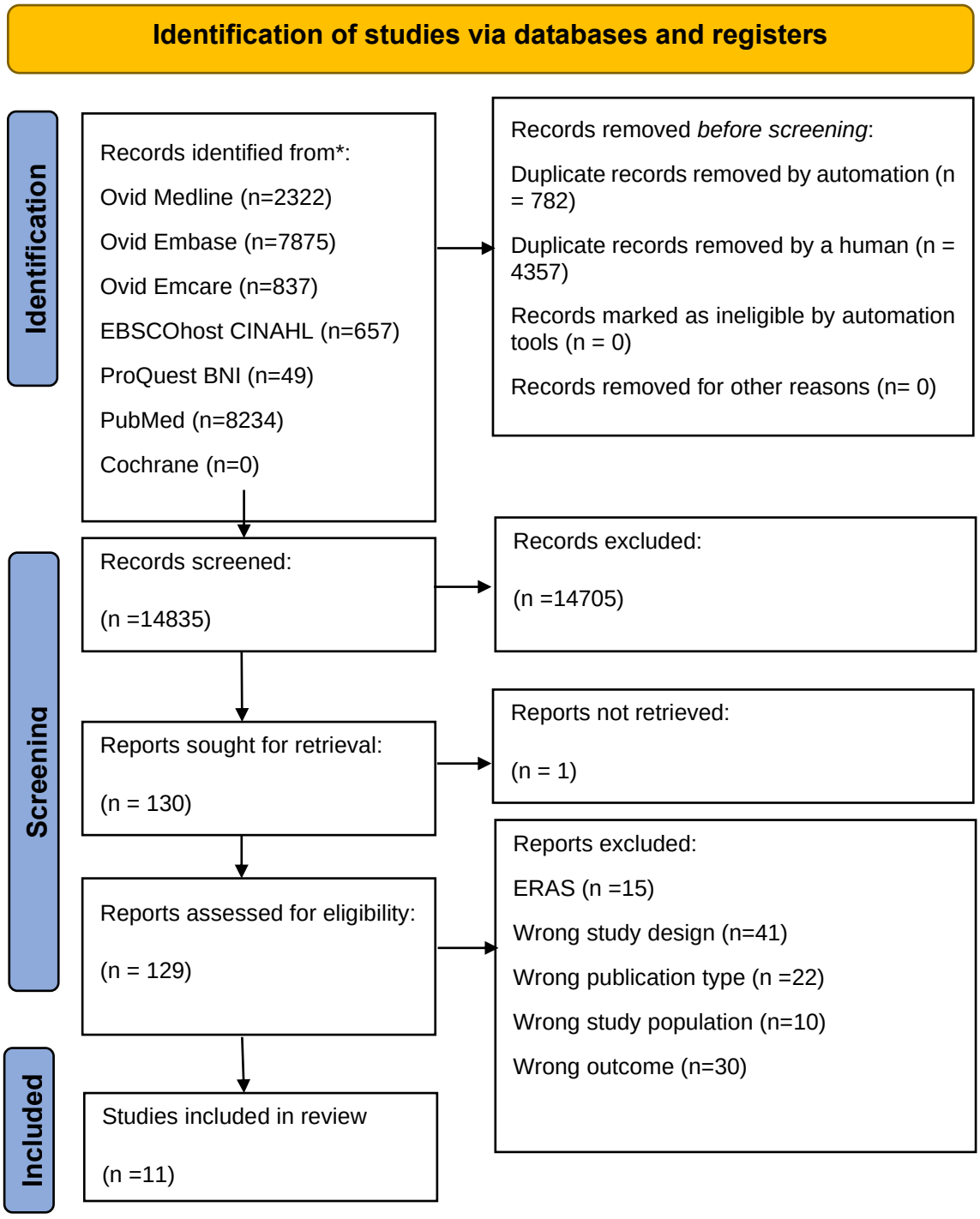


Figure 2.0.1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart showing the process of article identification and inclusion.

2.3.4 Outcomes

The primary outcome was a measure representing aerobic capacity, to determine if exercise rehabilitation elicited any physiological benefit. Other clinical outcomes included length of hospital stay, rates of postoperative complications, and postoperative morbidity and mortality. Patient-centred outcomes included BMI, HRQoL (via questionnaire) and markers of physical function such as 1-repetition maximum (1-RM) and 30-second chair stand. Outcomes related to feasibility included adherence and compliance of the exercise regimes.

2.3.5 Quality assessment

Study quality in randomised trials was assessed using the Cochrane Collaboration's tool for assessing risk of bias (RoB2) (Sterne et al., 2019). For non-randomised studies, the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was used (Sterne et al., 2016).

2.3.6 Data extraction and statistical analysis

Abstract screening was performed by one individual and rescreened in a blinded manner by another researcher within the same group, with differences resolved by consensus agreement.

Effect estimates are reported as mean differences (MD) with 95% confidence intervals (CI). Due to inconsistent reporting of mean changes and change standard deviations (SD), these were calculated using formulae from the Cochrane Handbook (Higgins et al., 2023). A correlation coefficient of 0.7 was assumed between baseline and final values based on previous similar data (Blackwell et al. 2018). Means were estimated from medians, and SD from range (Wan et al., 2014). For outcomes with sufficient data, meta-analysis using a restricted maximum likelihood random-effects model was performed. Statistical

heterogeneity was assessed using the I^2 statistic. GRADE was used to assess the certainty of evidence for the 6MWT (Guyatt et al., 2008) and all analyses were conducted using Stata Version 16.

2.4 Results

2.4.1 Included studies

Eleven studies were included: 6 RCT's, 1 pilot study, 1 retrospective cohort study and 3 feasibility trials (Carli et al., 2020; Chang et al., 2020; Cho et al., 2018; de Almeida et al., 2017; Do et al., 2022; Frawley et al., 2020; Gillis et al., 2014; Mascherini et al., 2020; Nusca et al., 2021; Porserud et al., 2014; Simonsen et al., 2020). Studies were conducted between 2014 and 2022, and all were published in the English language. The total number of patients across all studies was 734, with colorectal cancer the most prominent cancer type studied (n=). Other cancer types included gastric, oesophageal and urological. Details of the included studies can be seen in Table 2.2.

Study first author & year	Country	Study design	ERAS–type	Surgical approach n (%)	Total no. of	Intervention	Control group no.	Cancer type	Inpatient, outpatient or mixed	Primary outcome	Type of exercise	Length of exercise (weeks)	Location of exercise	Aerobic capacity outcome	QoL assessment tool
de Almeida (2017)	Brazil	Single blind RCT	Yes	Laparoscopic – 24 (22%) Open – 84 (78%)	108	54	54	Mixed abdominal	Inpatient	Inability to walk without human assistance at POD5 or hospital discharge	Aerobic, core, gait, isometric and isotonic	Until discharge	Ward-based	6MWT	EQ-5D-5L
Do (2022)	South Korea	Retrospective cohort	NES	Robotic-38 (64%) Open- 21 (36%)	59	29	30	Oesophageal	Inpatient	Not specified	Aerobic, pulmonary rehab and resistance	Until discharge	Ward-based	6MWT	EORTC QLQ-C30
Cho (2018)	South Korea	Single arm interventional feasibility study	Yes	Laparoscopic – 8 (40%) Robotic 12 (60%)	20	20	n/a	Gastric	Mixed	Feasibility	Aerobic and resistance	10	Mixed inpatient, outpatient supervised, and	VO_2 peak	EORTC QLQ-C30, EORTC

													home-based		QLQ-STO22
Simonsen (2020)	Denmark	Non-randomised controlled feasibility study	NES	Robotic assisted-2 (4%) Hybrid – 7 (14%) Open 33 (67%)*	49	20	29	GOJ	Outpatient	Feasibility	Aerobic and resistance	12	Hospital based supervised	Peak power output	FACT-E
Chang (2019)	Taiwan	RCT	NES	All open	88	44	44	Oesophageal	Outpatient	Quality of life	Aerobic	12	Home-based	6MWT, mean VO2 max	EORTC QLQC30, EORTC QLQ-OES18
Gillis (2014)	Canada	Single blind RCT	Yes	Laparoscopic – 72 (94) Open – 5 (6%)	77	39	38	colorectal	Outpatient	Functional exercise capacity (6MWT)	aerobic and resistance	8	Home-based	6MWT	SF-36, HADS
Porserud (2014)	Sweden	Single blind RCT	Yes	Open – 18 (100%)	18	9	9	Urological (cystectomy)	Outpatient	Not specified	Aerobic mobility, strength and stretching	12	Group hospital-based	6MWT	SF-36

Mascherini (2020)	Spain	RCT	NES	Laparoscopic 6 (100%)	6	3	3	Colorectal	Outpatient	Not specified	Aerobic and resistance	26	Mixed supervised and home-based	6MWT	n/a
Frawley (2020)	Australia	Non-randomised controlled	NES	Method of access NES	188	84	104	Mixed abdomino-pelvic	Outpatient	Feasibility	Aerobic and resistance	8	Supervised group at rehabilitation site	6MWT	ICIQ, IPAQ-SF, HADS, EORTC QLQ C-30
Carli (2020)	Canada	Single blind RCT	Yes	Open – 23 (21%) MIO – 87 (79%)	110	55	55	Colorectal	Outpatient	30-day complications	Aerobic and resistance	4	Hospital and home-based	6MWT	HADS, CHAMPS, SF-36
Nusca (2021)	Italy	Pilot	NES	Laparoscopic – 11 (100%)	11	6	5	Colorectal	Outpatient	EORTC QLQ-C30 for QoL improvement	Aerobic and muscle strengthening	8	Hospital based supervised	6MWT	EORTC QLQ-C30, HADS

*Table 2.0.2. Included studies. (Carli et al., 2020; Chang et al., 2020; Cho et al., 2018b; de Almeida et al., 2017; Frawley et al., 2020; Gillis et al., 2014; Mascherini et al., 2020; Nusca et al., 2021; Porserud et al., 2014; Simonsen et al., 2020). Abbreviations: RCT, randomised controlled trial; SOP, standard operating procedure; NES, not explicitly stated; MIO, minimally invasive operation; POD, postoperative day; 6MWT, 6-minute walk test; EQ-5D-5L, EuroQol- 5 Dimension; VO2 peak, peak volume of oxygen consumed (during exercise); EORTC QLQ-C30, European Organisation For Research And Treatment Of Cancer Core Quality of Life questionnaire; EORTC QLQ-STO22, European Organisation For Research And Treatment Of Cancer Quality of Life questionnaire- Gastric Cancer Module; GOJ, gastro-oesophageal junction; SF-36, 36-Item Short Form Survey; HADS, Hospital Anxiety and Depression Scale); ICIQ, International Consultation on Incontinence Modular Questionnaires; IPAQ-SF, International Physical Activity Questionnaire- Short Form; CHAMPS, Community Healthy Activities Model Program for Seniors questionnaire; QoL, quality of life. *7 patients excluded as no surgery performed or tumour not resected.*

2.4.2 Bias Assessment

Across all the studies eligible for inclusion in this review, risk of bias was elevated in non-controlled compared to controlled trials. The full results of this assessment are seen in Figures 2.2A and 2.2B. The overall GRADE certainty of evidence for the studies included in the meta-analysis of 6MWT is low. This is mainly due to the overall risk of bias, as 1 study was not a randomised controlled trial.

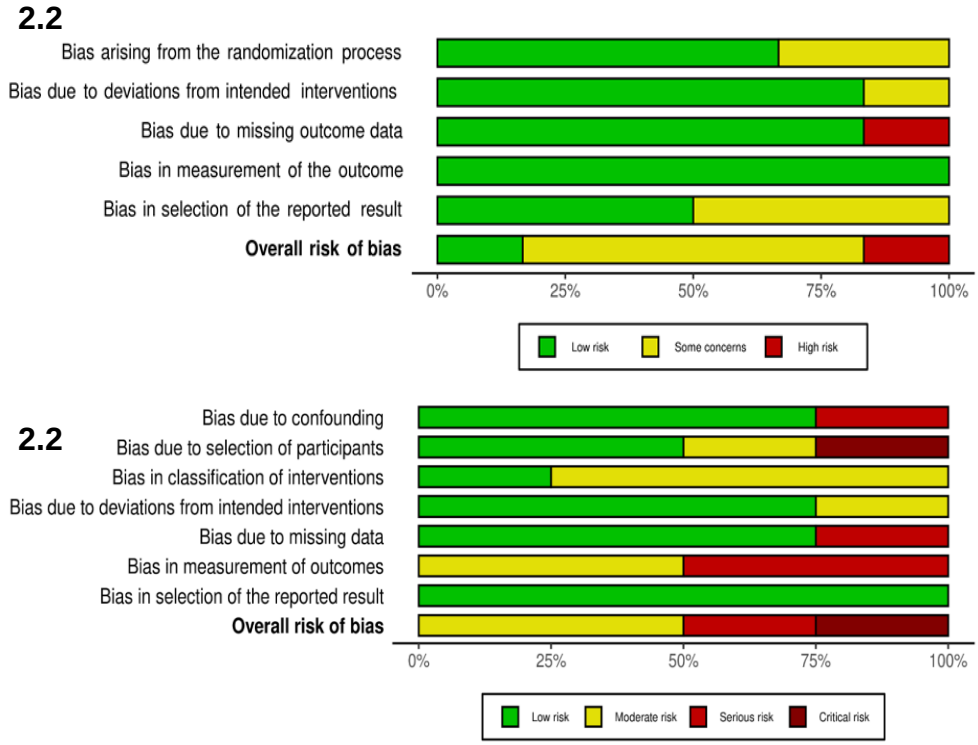


Figure 2.2A & 2.2B. Result of bias assessment of the randomised controlled studies using ROB2 tool (3A) and non-randomised studies using ROBINS-I tool (3B).

2.4.3 Inpatient-based studies

Two studies had an aerobic outcome in patients undergoing a dedicated postoperative exercise programme prior to discharge (de Almeida et al., 2017; Do et al., 2022), with the majority of screened inpatient studies focussed on ERAS regimens to reduce hospital length of stay (LoS) without an outcome related to aerobic capacity. de Almeida *et al.,* randomized 108 patients who had undergone major abdominal oncological surgery into an early mobilization (exercise) group (EX, n= 54) or standard postoperative care (CON, n=54). The exercise protocol involved core, gait, isometric, isotonic and aerobic training. Patients underwent a baseline preoperative assessment, measuring thigh circumference and performing a 6-minute walk test (6MWT), with 6MWT and HRQoL also assessed at postoperative day (POD) 5. The primary outcome for this study was ability to cross a room without human assistance postoperatively. 16.7% of patients were unable to cross the room unassisted in the EX-group compared to 38.9% in CON (P=0.010; relative risk (RR): 0.42, 95% CI: 0.22-0.85). Although the EX-group performed significantly better in the 6MWT compared to CON [212m (56-299) vs. 66m (0-228), p=0.004], there was no significant different in LoS (EX: 8 days (6-13) vs. CON: 8 days (7-13), p=0.25). Despite a lack of difference in LoS, the EX-group did have better HRQoL scores (via the EQ-5D-5L index, which reports on mobility, self-care, usual activities, pain/discomfort and anxiety and depression) at POD5 compared to CON (0.71 (0.48-0.88) vs. 0.34 (90.19-0.73), p<0.001). However, this benefit appeared to be short-lived as there was no significant difference between the groups at POD 30.

Do *et al.,* introduced a new multimodal rehabilitation programme to replace an existing pulmonary rehabilitation regimen for a cohort of patients who underwent surgery for oesophageal cancer (Do et al., 2022). They compared QoL outcomes, 6MWT and other markers of physical function including 30-second chair stand test and grip strength,

between the two groups. There were no significant differences between the two groups at baseline, including for surgery type and disease staging. They found significant within group differences between pre- and post-surgery in left handgrip strength, 30-second chair stand and 6MWT (mean difference between pre- and post-operative 6MWT distance: multimodal rehabilitation versus pulmonary rehabilitation: 73.1±52.6 *vs.* 28.4±14.3, $p<0.001$, $d=1.15$). The authors posited that a potential cause for the differences seen was the introduction of aerobic and resistance training to attenuate the effects of reduced physical function and to improve cardiorespiratory function, especially given the surgical approach often employed (through the chest wall).

2.4.4 Mixed studies (inpatient and outpatient)

Only one study had a programme that started during inpatient stay and continued post-discharge (Cho et al. 2018). Most screened mixed studies were excluded due to no aerobic capacity outcome assessment, with the majority of outcomes related LoS, readmissions and/or complication rates. Cho *et al.,* developed and piloted a postoperative exercise recovery program for patients who had undergone either laparoscopic or robotic gastrectomy for gastric cancer, called PREP-GC. Twenty patients completed the program following surgery, which started during their postoperative inpatient admission. The inpatient exercise component consisted of isokinetic exercises, stretches and walking, which continued for a week post discharge at home. For the subsequent 8 weeks, patients underwent a supervised aerobic and resistance exercise programme consisting of aerobic and stretch-based warm up and cool down movements and a variety of resistance exercises. The primary outcome for this study was incidence of adverse events during the exercise programme with feasibility also assessed by rates of adherence and compliance. All patients completed the exercise programme with no adverse events. The adherence and compliance rates were 95.2% and 80%, respectively. 11 patients required minor

modifications to the outpatient exercise programme, totalling 17 (0.6%) of the 2,908 individual exercise components performed.

In terms of aerobic capacity, absolute VO_2 peak increased ($p<0.001$) after the exercise programme, returning, from an initial decrease postoperatively ($p<0.05$), to levels numerically similar to preoperative levels (preoperative, 2.27±6.18; postoperative, 1.80±4.38; post PREP-GC, 2.16±5.05 L/min). Other measures of physical function including 30-second chair stand and half-squat test also improved following the exercise programme compared to preoperative assessment.

As expected, HRQoL scores using the EORTC QLQ-C30 and EORTC QLQ-STO22 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach Cancer-Specific Module) were reduced in the period after surgery but improved significantly following the PREP-GC exercise programme ($p<0.05$), including in symptom-related domains such as fatigue, nausea and pain. Using the EORTC QLQ-C30, physical, social, cognitive and role functioning parameters were shown to decrease immediately after surgery before increasing during the postoperative period. Conversely, a sustained improvement in emotional functioning was shown, even during the immediate postoperative period; perhaps attributable to the exercise programme given that this is at odds to what has been shown in previous studies who report a sustained reduction in emotional functioning during the short-term (within 1 month) postoperative period (Hellstadius et al., 2015; Kobayashi et al., 2011; H. Kong et al., 2012).

2.4.5 Outpatient-based studies

Eight studies had exercise programmes which started after hospital discharge to outpatient status (Carli et al., 2020; Chang et al., 2020; Frawley et al., 2020; Mascherini et al., 2020; Nusca et al., 2021; Porserud et al., 2014; Simonsen et al., 2020). These interventions started between

0 and 11 weeks postoperatively and were between 4 and 12 weeks in duration.

2.4.5.1 Adherence and compliance

Six of the eight outpatient studies reported on adherence (30–32,35,36) and/or compliance (29,37). Of the six studies that did report compliance, four (Frawley et al., 2020; Gillis et al., 2014; Porserud et al., 2014; Simonsen et al., 2020) reported the attrition rate after the exercise programme had started (23% (range 7-45%)), with attrition between randomisation and study completion slightly lower (21% (range 0-50%)) based on all six outpatient studies. Further details on compliance can be seen in **Table 2.3**.

Study first author & year	Location of exercise	Exercise completion rate
Simonsen (2020)	Hospital-based	19 randomised to exercise group, 16 started programme, 13 finished. • 90.4% completion rate of aerobic exercise • 75.5% completion rate of resistance exercise
Gillis (2014)	Home-based	44 randomised to exercise group, 42 started programme, 39 finished. • Postoperative compliance rates; mean % (SD): • 0-4 weeks: prehab group 53% (30%), rehab group 31% (26%) • 4-8 weeks: prehab group 53% (33%), rehab group 40% (31%)
Porserud (2014)	Group session; hospital-based	9 randomised to exercise group, 5 started programme, 4 finished. • 76% (67-95) attendance rate at group exercise training sessions

Frawley (2020)	Group sessions; rehabilitation site	84 randomised to exercise group, 75 finished. • 81% attended 85-100% of 16 scheduled training sessions • 56% received scheduled telephone coaching sessions
Carli (2020)	Hospital and home-based	60 randomised to rehab exercise group, 55 included in intention-to treat-analysis, 30 finished.
Nusca (2021)	Hospital-based	6 randomised to exercise group, 6 finished. • 100% exercise adherence rate (note enrolment rate of 29% for all eligible patients).

Table 2.3. Exercise completion rate from included studies that employed outpatient exercise interventions (Carli et al., 2020; Frawley et al., 2020; Gillis et al., 2014; Nusca et al., 2021; Porserud et al., 2014; Simonsen et al., 2020). Chang et al., did not document compliance rates (Chang et al., 2020).

2.4.5.2 Aerobic outcomes

Of the 8 studies included in the results, seven reported the 6-minute walk test (6MWT) as one of their outcomes related to aerobic capacity (Carli et al., 2020; Chang et al., 2020; Frawley et al., 2020; Mascherini et al., 2020; Nusca et al., 2021; Porserud et al., 2014). 6MWT has been shown to correlate with both aerobic capacity and functional performance (Rikli & Jones, 1998; Q. Zhang et al., 2017). Carli et al., and Gillis et al., were excluded from this analysis as they were directly comparing groups having undergone prehabilitation versus rehabilitation with no control group (Carli et al., 2020; Gillis et al., 2014). Frawley et al. was excluded as there was no data available for the control group (Frawley et al., 2020).

Therefore, meta-analysis of the remaining four studies showed a significant increase in 6MWT distance in the intervention groups compared to the control groups (MD: 74.92; 95% CI: 48.52 to 101.31; p<0.01) (Chang et al., 2020; Mascherini et al., 2020; Nusca et al., 2021; Porserud et al., 2014) as seen in **Figure 2.3**. There was no statistical heterogeneity between these studies (I^2=0%).

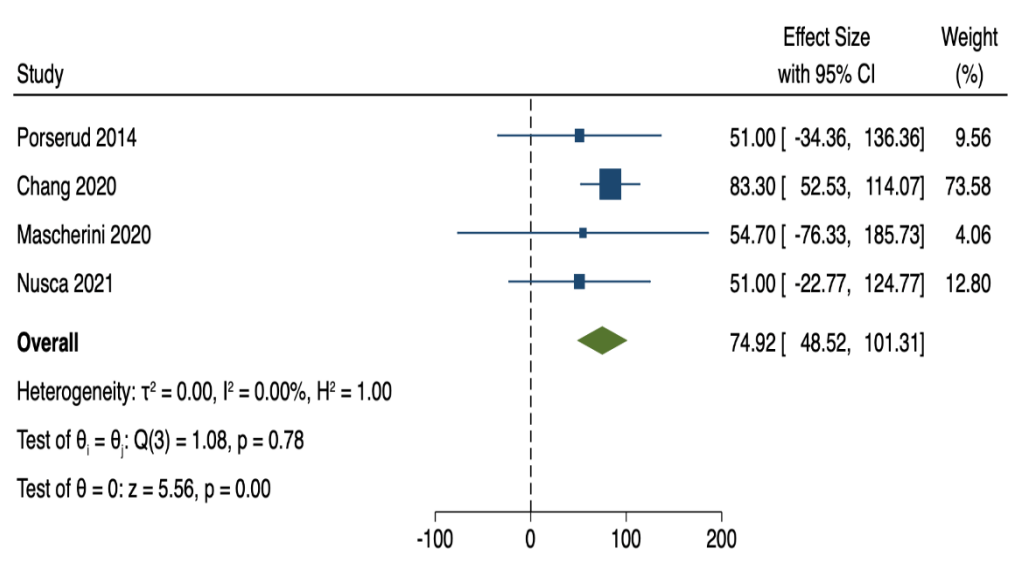


Figure 2.3. Forest plot showing the difference in 6-minute walk test (6MWT) distance between exercise and control groups from 4 studies that employed 6MWT as an outpatient exercise outcome measure.

Simonsen *et al.* used either a stationary bicycle or a treadmill to measure peak power output as their primary aerobic capacity outcome. As expected, there was a reduction in mean peak power output in the exercise group in the immediate postoperative period, but this returned to, or improved from, baseline by the end of exercise training in the intervention group. The control group did not undergo aerobic testing, limiting the inference of the impact of the exercise intervention on recovery.

2.4.5.3 Health-related quality of life

To assess changes in HRQoL a range of different validated questionnaires were used. All included studies assessed HRQoL except for Mascherini *et al*. The most commonly used questionnaire was the SF-36 followed by the EORTC-QLQ C30. Other questionnaires used included EORTC cancer specific subsets, and the Hospital Anxiety and Depression Scale (HADS) questionnaire. A summary of HRQoL findings is presented in **Table 2.4**.

Study, (first author & year)	Questionnaire used	Outcome	
Simonsen (2020)	FACT-E	Total score at 7-14 months - no between group differences	
		Exercise group: significant improvement in total score at 7-14 month follow up (within group) (i.e. post exercise programme); Control no significant change in total score	
Porserud (2014)	SF-36	Exercise group: Role physical: significant improvement in score at T2 (post exercise) assessment compared to pre-exercise (p=0.031). No other significant difference seen at any other timepoint measured in either group	
Nusca (2021)	EORTC QLQ C30	Exercise group: significant difference seen in the following domains: physical functioning (PF2), cognitive functioning (CF) and fatigue (FA).	
	Domain:	End of exercise (2 months postoperatively):	4 months postoperatively:
	PF2	0.03	0.018
	CF	0.018	N/A
	FA	0.017	0.045

	HADS	No significant difference between groups at any timepoints in any domain
Gillis (2014)	SF-36	No significant difference between groups at any timepoints in any domain; no within-group differences reported
	HADS	No significant difference between groups at any timepoints in any domain; no within-group differences reported
Carli (2020)	SF-36	No significant difference between groups at 4 weeks post-surgery
	HADS	No significant difference between groups at 4 weeks post-surgery
Chang (2020)	EORTC-QLQ-C30	Exercise group: significantly lower scores (less severe symptoms) for insomnia than controls at 3 months (β β = −12.81, 95% CI −2.74, −0.89, p < .05, respectively). Scores for nausea and vomiting were also significantly lower for the intervention than control groups at 3 and 6 months (β=−12.62, CI −20.48, −4.79, p < .01; and β=−11.67, 95% CI −20.77, −2.57, p < .05, respectively)
	EORTC-QLQ-OES18	At 3 months the intervention group had significantly lower scores for dysphagia than controls (β=−12.56, 95% CI −21.34, −3.76, p < .01). Loss of taste was also significantly lower at 6 months (β=−13.66, 95% CI −2240, −4.93, p < .01 respectively)

Table 2.4. Summary of HRQoL outcomes in the outpatient studies (Carli et al., 2020; Chang et al., 2020; Gillis et al., 2014; Nusca et al., 2021; Porserud et al., 2014; Simonsen et al., 2020). Abbreviations: FACT-E, Functional Assessment of Cancer Therapy- oesophageal cancer QOL specific items; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-OES18, European Organisation for Research

and Treatment of Cancer Quality of Life questionnaire- Oesophageal Cancer Module; SF-36, 36-Item Short Form Survey; HADS, Hospital Anxiety and Depression Scale.

2.5 Discussion

Given the known multiple benefits of exercise training for healthy adults (Muscari et al., 2010; Stein et al., 1999) and numerous different clinical cohorts (Kadoglou et al., 2007; McKelvie et al., 2002), it may seem obvious that exercise after surgery would confer both physical and psychological benefits to patients, as shown in this review. However, the magnitude of benefit is highly variable even across a relatively small number of studies and is likely multifactorial, involving factors such as format and length of exercise programme and method of delivery. Despite an evidence-based supposition (Loh & Musa, 2015; Tenconi et al., 2021) and emerging direct evidence (Wong et al., 2016) for the benefits of exercise training in the postoperative period, there is still very little in the way of established guidance for patients or healthcare professionals pertaining to exercise in this phase of a cancer patients' journey. This may be due to the postoperative rehabilitation period falling between the purview of different healthcare professionals, i.e. physiotherapists rather than the surgical team. In addition to providing advice for those who are not educated in exercise prescription, such guidelines may also help with complex patient perceptions. Although some cancer patients and associated healthcare practitioners do view exercise as a tool to help with both emotional and physical well-being, others may believe it to do "more harm than good"; although this is most commonly not the case (Bland et al., 2022). As can be seen from the studies included in this review, adverse event rates were very low in those completing postoperative exercise training.

Another consideration for exercising patients with cancer is the logistical burden of their diagnosis and treatment plan. Patients will likely already be faced with multiple cancer-related commitments (i.e., clinic visits) and as such exercise delivery method will likely contributes to patient adherence. For example, multiple trips to an external centre/hospital may

reduce the rate of enrolment and/or compliance. For example, Frawley et al., used patients who were unwilling or unable to complete the exercise programme as their control group. Only 24% of patients approached consented to enrol on their exercise programme, with those in the control group living significantly further away from the rehabilitation site than the exercise group. Conversely, Gillis et al., delivered a home-based rehabilitation programme, in which 89% of eligible patients agreed to randomisation and only 3 out of 42 patients were lost to follow-up after the start of the programme. Although these findings suggest that home-based exercise may be favourable due to the logistical burden of 'on-site' exercise training, the impact of supervision must also be considered. If a home-based exercise programme is used, remote supervision using telehealth tools may be invaluable to help maintain compliance, such as in Chang et al., where a two-way informatics system encouraged communication between the healthcare team and patients (Chang et al., 2020).

In relation to optimal timing of intervention delivery, two studies included in this review compared prehabilitation to rehabilitation and showed inconsistent results. Carli et al., showed that there was no difference in recovery of walking capacity between the two groups at 4 weeks postoperatively, whereas Gillis et al., showed more favourable results from the prehabilitation group at 2 months post-surgery (mean difference 45.4 m [95% CI, 13.9 to 77.0]). There were, however, differences between these studies. Carli et al., had an older patient population (median age of rehab group 82 (IQR 75-84) than Gillis et al., (mean age 66 (SD 9.1)) and there were also differences in the length of the training. The programme delivered by Carli et al., was 4 weeks, whereas Gillis et al., employed an 8-week programme. This suggests that a longer exercise programme may lead to a larger improvement, however, despite a relative wealth of recent data showing the positive impact that exercise prehabilitation can have on physical (Awasthi et al., 2019; Jones et al., 2011), clinical (Dronkers et al., 2013) and psychological (Lund et al.,

2020) outcomes for surgical cancer patients, the mandated limited time-frame (of <31-days) between decision to treat and operation for cancer patients undergoing surgery with curative intent can limit the degree of possible improvement (C. L. Boereboom et al., 2019). For example, 6-weeks high-intensity interval training (an exercise modality commonly employed in prehabilitation) has been shown to be needed to improve peak oxygen uptake in individuals age-matched to those most commonly presenting for colorectal cancer resection (Herrod et al., 2021). In addition, with its origin in anaesthetics, prehabilitation efforts also tend to have a focus on improving short-term clinical outcomes after surgery such as LoS, complication rate and 30/90-day mortality, rather than focusing on return to baseline QoL and/or activities of daily living. Conversely, postoperative rehabilitation exercise programmes can be delivered over a longer period of time and can also be adapted and/or extended until the patient reaches specific goals. This goal-setting approach may help to improve patient adherence and compliance, especially if the targets are developed in concordance with the patient (Holliday et al., 2007). Considering the benefits of both pre- and rehabilitation, one proposition is that for those patients who are both willing and able, both these intervention strategies could be used in tandem to prime patients to be resilient to the physiological insult of surgery and to help them return to their pre-illness activities and quality of life as quickly as possible.

This review does have limitations which need to be acknowledged. Firstly, studies which delivered exercise only as part of an ERAS programme were excluded as such programmes tend to be multi-faceted (i.e., including intraoperative targets) and often start preoperatively, and so may not give an accurate account of the value of exercise alone. This has likely impacted the number of studies eligible for inclusion in this review. Secondly, although all the scores used to determine QoL were obtained via well-validated questionnaires, that different questionnaires were used across studies prohibited meta-analysis. A consensus on the

use of, or development of one comprehensive questionnaire that can be used to assess QoL at various time points in a cancer patients' clinical pathway regardless of cancer type would be beneficial for future research. Thirdly, some of the studies had small sample sizes, including those in the meta-analysis of 6MWT and therefore this meta-analysis was heavily weighted. It should be noted that 6MWT was not the primary outcome for some of these studies, and as such they may not have been powered appropriately for this endpoint. There was also insufficient included studies to conduct assessment for publication bias or investigate heterogeneity.

In summary, this review supports the development of formal exercise guidance for postoperative cancer patients to aid their physical and psychological recovery, with questions around postoperative exercise being commonly asked by patients at surgical follow up. This review suggests that exercise rehabilitation for these patients may be valuable not only in improving physiological parameters, but also in improving psychosocial functioning. However, how this would be delivered in a pragmatic, cost-effective way is yet not clear. Only once the evidence base in this field is established, e.g. via a multi-centre, prospective RCT as an example of the high-quality research required in this space, can the true benefit of postoperative exercise be realised, allowing development and implementation of formalised guidelines in a multi-disciplinary manner for intra-abdominal cancer patients facing surgery.

To attempt to improve this area of study, the main study of this thesis (Chapter 4) will look to deliver a semi-structured aerobic and resistance exercise rehabilitation training programme for patients with colorectal cancer undergoing elective resectional surgery.

3 Characterising inpatient postoperative physical activity (the *PHYSPAL* study)

3.1 Introduction

In addition to the physiological impact of their disease, patients with colorectal cancer also carry a significant psychological burden, presenting with high levels of anxiety and depression (Pitman et al., 2018). This further inhibits their motivation to keep active at a time when it is especially important to do so. This is also often coupled with poor nutritional intake/absorptive capacity (the former of which can also be impacted by psychological upset) which together can reduce physiological resilience at diagnosis and surgery, even in patients who were previously well. As more patients are presenting asymptomatically via the Bowel Cancer Screening Programme, the opportunity to give curative treatment is there, but must be coupled with low morbidity and favourable outcomes with regards to post treatment quality of life. As well as the technical aspects of surgical procedures such as favouring minimally invasive approaches over traditional open incisions to reduce the need for significant durations of postoperative opioid analgesia (Mujukian et al., 2020) and reduce rates of wound infection (Kulkarni & Arulampalam, 2020), preoperative physiological resilience can play a significant part in the postoperative course. As described earlier, colorectal ERAS programmes are now a standardised international approach to optimise various aspects of perioperative interventions so that there is an overall significant cumulative improvement in perioperative morbidity and mortality from this “minimal gains” approach. A high adherence rate to ERAS components has been shown to have better early outcomes, including reduced morbidity and LoHS (Olson et al., 2021; Seow-En et al., 2021). As part of ERAS, the approach to surgery is extremely helpful in trying to reduce the postoperative length of stay, however the requirements for “early postoperative mobilisation” are not well characterised. Early mobilisation after surgery is known to be associated with a reduced risk of developing numerous postoperative complications including venous thromboembolic events (Pellino et al., 2016)and chest infections (Haines et

al., 2013). Surgery-related muscle loss in colorectal cancer patients is prevalent, with reductions in both quality and quantity (van Wijk et al., 2021). Various strategies to attenuate this loss have been attempted, such as neuromuscular muscle stimulation, which has shown some promise in reducing the loss in both muscle mass and function during the immediate in-hospital postoperative period (E. J. Hardy et al., 2022). Furthermore, as discussed in Chapter 2, there is potential for physical rehabilitation to be started during the immediate postoperative inpatient stay with a positive effect on functional capacity and with no significant safety concerns (de Almeida et al., 2017; Thörn et al., 2022). Additionally, there is a scarcity of good quality evidence-based goal directed movement targets for patients to achieve for during their time spent in hospital. To exemplify the disparity in detail between specific components of ERAS guidance, the quality of evidence for preoperative nutrition is strong, with strong recommendation gradings for its inclusion in ERAS. It details screening tools to be used and a length of nutritional supplementation and route advice. However, for postoperative mobilisation, although there is strong evidence and a strong recommendation for mobilisation, there is no detail of frequency, targets or resources required in order to achieve adequate adherence to a mobilisation protocol (Gustafsson et al., 2018). The current ERAS protocol at University Hospitals Derby NHS Foundation Trust (UHDB) is not bespoke to the Trust but aim to follow UK CRC ERAS (Gustafsson et al., 2019). Adherence to postoperative inpatient physical rehabilitation is not regularly monitored and audited, limiting the strength of evidence for recommending a set mobilisation regime, as variable resource allocation of AHP specialists (such as physiotherapists) may limit the ability to provide bespoke exercise prescriptions for individual patients. Just as there are few specifics in the mobilisation guidelines for the immediate postoperative period, there is also very little evidence quantifying how much physical activity CRC patients perform in the immediate postoperative period, but with the increasing development of wearable devices this is becoming feasible (Kavallieros et al., 2024). This is even more true if looking for information beyond step count. This is important as the intensity and type of postoperative activity may reflect the ability/motivation of a patient to engage in postoperative exercise/activity, especially given the heterogeneity of

patients' preoperative fitness levels. The other limitation of ERAS is that its focus is mainly on short term morbidity, mortality and LoHS. Patient related factors that may be as important to them such as time until return to normal ADLs, work or social activities are not taken into account, but often for a significant part of the questions asked during patient-clinician interactions.

3.1.1 Aims

This was an observational cohort study of postoperative physical activity at UHDB using accelerometry to quantify the type and frequency of inpatient activity performed by CRC patients during their immediate postoperative in-hospital stay. The primary aim was to assess if there was a significant increase in 30-day complication rate in patients who achieved lower daily metabolic equivalent of task in hours (MET.h) rates during their in-hospital postoperative period. The secondary aim was to ascertain whether lower physical activity directly correlated with higher Hospital Anxiety and Depression Scores (HADS).

3.2 Methods

3.2.1 Ethics

The study was registered with ClinicalTrials.gov (NCT05934643) and received ethics approval via Proportionate Review from London - Westminster Research Ethics Committee on 23rd June 2023 (see Appendix 7.3.1). Research and Development Approval was obtained from University Hospitals Derby and Burton (RDH site) prior to the study start date. The outline of the study is shown in Figure 3.1.

3.2.2 Study Overview

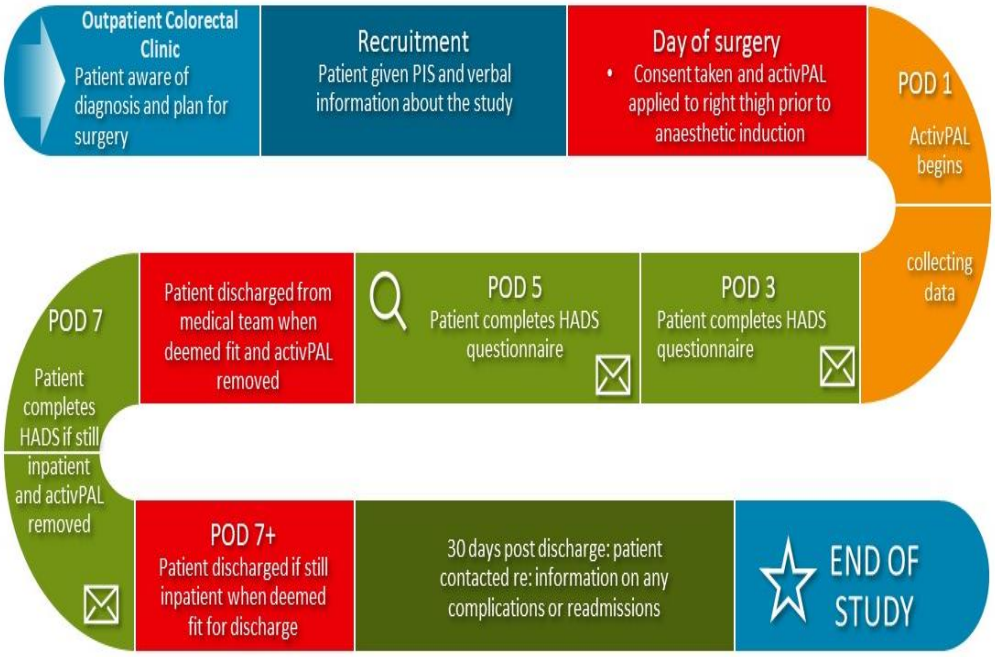


Figure 3.1. Schematic representation of the PHYSPAL study.

3.2.3 Recruitment

17 volunteers with CRC, both male and female, aged between 40 and 85 years, due to undergo resectional surgery with curative intent on a colorectal ERAS pathway were recruited from the CRC clinic at Department of Surgery, Royal Derby Hospital, UK. They were given the study PIS at the time of discussion of surgery, or it was sent by email if the patient agreed to this. Both approaches gave the patients adequate time to read the PIS and consider their inclusion. All participants gave written informed consent in-person, and their usual preoperative assessment was used for screening as they would be considered eligible to take part if they were cleared for surgery by their clinical care team.

3.2.4 activPAL™ accelerometery

On the day of surgery, ActivPAL™ monitors were applied to the participants' right thigh (see Appendix 7.6.1). The accelerometers were pre-programmed to start at a given time and to run for a period of 7 days, automatically collecting data second by second, which was stored on the

device prior to download. The monitors were removed with data collected until that point if a participant was discharged home prior to the 7th postoperative day.

activPAL™ monitors are non-invasive tri-axial accelerometers which for this study were worn on participants' right anterior thigh for up to one week (see Appendix 7.6.1 for application instructions). Compared to other methods of measuring physical activity, the activPAL™ monitors are able to make measurements every 20th of a second for up to fourteen days, and can discriminate between standing, sedentary and lying activity whilst being small enough to not encumber the patient.

3.2.4.1 Overall physical activity

Overall physical activity was estimated using the variables step counts, sit-to-stands and metabolic equivalent of task in hours (MET.h) as surrogate measures.

3.2.4.2 Metabolic equivalents (METs)

One way that overall physical activity can be expressed is using metabolic equivalent of task in hours (MET.h), or sometimes in minutes (MET/min). This is a validated method to describe the intensity of activity by using the ratio of metabolic rate during exercise compared to that at rest, (i.e., 1 MET is the oxygen consumption of a person sat not moving, equal to 1 kcal/kg/h and 3.5 ml/kg/h of oxygen consumption (Balke, 1960)). This can help to amalgamate different types of exercise into one measurable output for comparison between activities, populations and/or situations, especially with regards to cardiorespiratory fitness (Franklin et al., 2018). In this study, participants had their daily activity scored in MET.h calculated by the activPAL™ during the wear period as described above.

3.2.4.3 Step counts

One of the most measured and reported indices of physical activity, step counts are, as the name suggests, simply a measure of the number steps taken over a fixed period. It is measured by most commonly available wearable activity trackers, is simple to understand, requires no accessory equipment to achieve aside from a pedometer or equivalent and provides

an easy-to-understand target for the user. Use of a step count monitor in itself has also been shown to increase user step count (Chaudhry et al., 2020). Originally a marketing campaign from the 1960s Tokyo Olympics, large population studies have shown that increasing daily step count targets up to 10,000 steps per day (and 8,000 steps per day in adults aged over 60 years) is associated with a reduction in risk of mortality for cardiovascular disease and cancer (del Pozo Cruz et al., 2022; Paluch et al., 2022).

Given the previously reported constraints to physical activity in the postoperative period (drains, feeding tubes etc. (ref)) and aspects of the hospital build environment (i.e., the size and layout of wards), achieving even the lower step count guidance mentioned above is not likely in the immediate postoperative period. In this study, the activPAL™ monitors provided daily step count data for the entirety of the wear period or inpatient stay, whichever came first.

3.2.4.3.1 Sit to stand

Sit-to-stands are used as a testing measure of functional capability (often as part of the SPPBT), and difficulty in performance can be associated with muscle weakness and loss of power (Losa-Reyna et al., 2022). As patients should be encouraged to be sitting out for most of the day as well as mobilising, it was chosen as a measure of assessment as it signifies the transition from sedentary to ambulatory behaviour.

3.2.4.4 Total Sedentary time

In addition to physical activity measures, the activPAL™ monitors also provided data relating to sedentary behaviours. They measured the total sedentary time in the day (in minutes). This included sitting time, seated transport time and secondary lying time (any time of at least 60 minutes in duration spent lying down; primary lying time is usually equivalent to an individual's time spent in bed overnight as it is the longest single lying period in a day).

3.2.4.5 Sitting time

Prolonged sitting is associated with increased cardiometabolic dysfunction and poor health outcomes (Buffey et al., 2022). The total

sitting time in a 24-hour period (in minutes) has been used in the final analysis. This accounts for any seated transport time which is included in the total sedentary time but is also individually measured to give a more accurate representation of the participants' time spent seated not in transit or lying down as explained above. As this is an inpatient study, transit would usually be related to short periods of patient transfers from the ward to other parts of the hospital only.

3.2.4.6 Questionnaires

All participants were given a HADS questionnaire on postoperative days 3, 5 and 7 to complete if they were still an inpatient (see Appendix 7.7.1). The HADS questionnaire consists of twenty-one questions to screen for anxiety (HADS-A) and depression HADS-D). It consists of a self-assessment mood scale to be administered in non-psychiatric settings, aiming to eliminate potentially confounding physical symptoms that may be attributable to physical illness (Zigmond & Snaith, 1983). It is widely used in cancer research (Sharma et al., 2007) and has been validated for use in patients with cancer in detecting anxiety and depression (Annunziata et al., 2020).

3.2.4.7 Post discharge follow-up

Participants were contacted by telephone on day 10 and day 28 post discharge to check that they had not developed any complications that required reattendance or readmission. If so, the details were documented to confirm if there was a postoperative complication. The participant's enrolment in the study finished after the second follow-up phone call. If patient could not be contacted for follow up, attendances were checked on the RDH computer system (Lorenzo). Phone calls were used as not all attendances to RDH are accurately logged with Lorenzo discharge summaries at the time of presentation, so were an addition in order to improve the accuracy of post-discharge follow-up.

3.3 Results

Seventeen participants recruited to the study were included in the final analysis. This was the number of participants that had completed the study at the time of analysis. Table 3.1 shows the baseline demographics of the cohort.

Number of participants	17
Age (y) [SD]	64.59 [12.35]
Gender M:F (%) [n]	65:35 [11:6]
Body mass index (kg/m^2) [SD]	28.53 [6.03]
Ethnicity (%) [n]	White British: 94.12 (16) Eastern European: 5.88 (1)
ASA Grade (%) [n]:	
1	17.65 [3]
2	17.65 [3]
3	58.82 [10]
4	5.88 [1]
Operation Type (n) [%]:	
Anterior resection	5 [29]
Right hemicolectomy	8 [47]
Extended right hemicolectomy	2 [12]
Left hemicolectomy	0 [0’
Hartmann’s	2 [12]
Surgical Approach	
Open	5 [29]
Laparoscopic	7 [41]
Laparoscopic converted to open	0 [0]
Robotic assisted	1 [6]
Robotic	4 [24]
Defunctioned at index operation	23.53 [4]

% use of spinal anaesthesia (%) [n]	100 [17]
Clavien-Dindo Complications (%) [n]:	
Grade 1	17.65 (3)
Grade 2	11.76 (2)
Grade 3	5.88 (1)
Grade 4	11.76 (2)
Grade 5	0 (0)
Reoperation rate (%) [n]:	11.76 (2)
Length of hospital stay (days) [range]	11.9 [3-65]
Patients still admitted at each POD (%) [n]:	
1	100 (17)
2	100 (17)
3	88.24 (15)
4	76.64 (13)
5	58.82 (10)
6	58.82 (10)
7	47.06 (8)
Reattendance rate (%) [n]:	11.76 (2)
Readmission rate (%) [n]:	0 (0)

Table 3.1. Baseline demographics of the PHYSPAL cohort. Reattendance was defined as any unplanned reattendance that did not result in admission to hospital (for example, review in same day emergency care). Abbreviations: SD, standard deviation; n, number; ASA, American Society of Anaesthetists; POD, post-operative day.

3.3.1 Postoperative inpatient physical activity

3.3.1.1 Step count

There was no significant difference in step counts between any postoperative day, with a weighted mean daily step count across all 7 days of 630 steps (weighted SD 140.76 steps). Considering only days 1-4, the period where over 75% of participants were still included in the study, the weighted mean step count was 611.35 steps (weighted SD 150.36 steps).

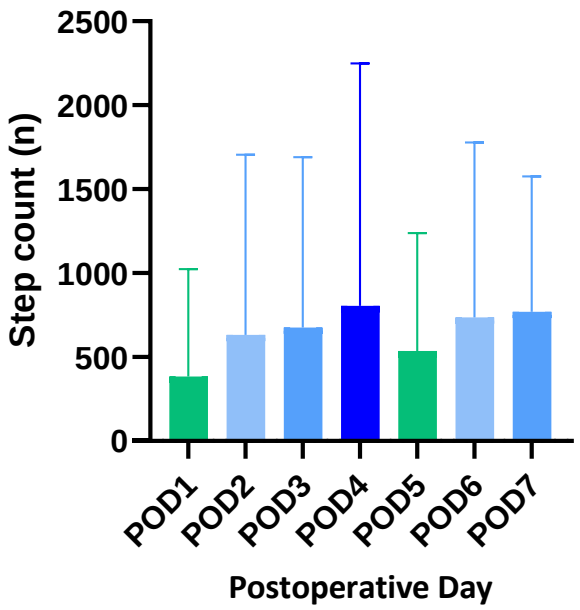


*Figure 3.2. Mean step count on each postoperative day in the PHYSPAL cohort after elective colorectal resection on an ERAS pathway. Analysis via one-way ANOVA. *=p<0.05, **=p<0.01, ***=p<0.001.*

3.3.1.3 Sit-to-Stands

There was no significant difference in sit-to-stands between any postoperative day, with a weighted mean daily sit-to-stand count across all 7 days of 17.36 (weighted SD 4.84). Considering only days 1-4, the period where over 75% of participants were still included in the study, the weighted mean sit-to-stand count was 15.18 (weighted SD 4.11).

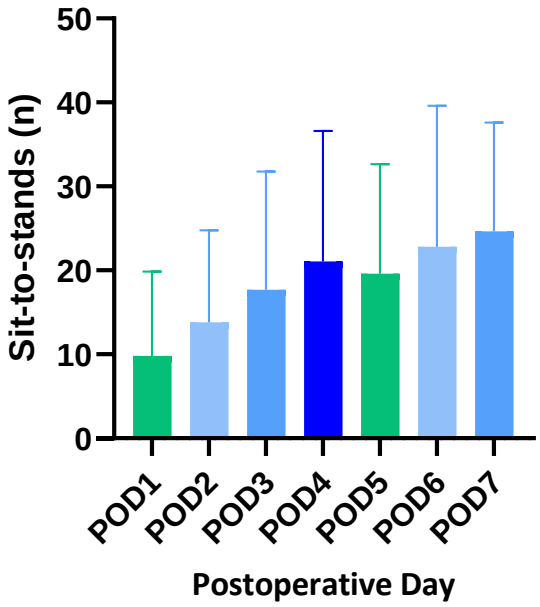


*Figure 3.3. Mean number of sit-to-stands on each postoperative day in the PHYSPAL cohort after elective colorectal resection on an ERAS pathway. Analysis via one-way ANOVA. *=p<0.05, **=p<0.01, ***=p<0.001.*

3.3.1.4 Total Sedentary time,

There was a significant difference in total sedentary time across the in-hospital stay (p=0.005), seen within the first 5 days and all compared with POD1. There was a difference between POD1 and POD2 (MD -340.2m; 95% CI -609.2m to -71.30m, p=0.005) POD3 (MD -325.2m, 95% CI -602.9 to -47.39m, p=0.01), and POD5 (MD -335.4m; 95% CI -647.8 to -22.86m, p=0.03).

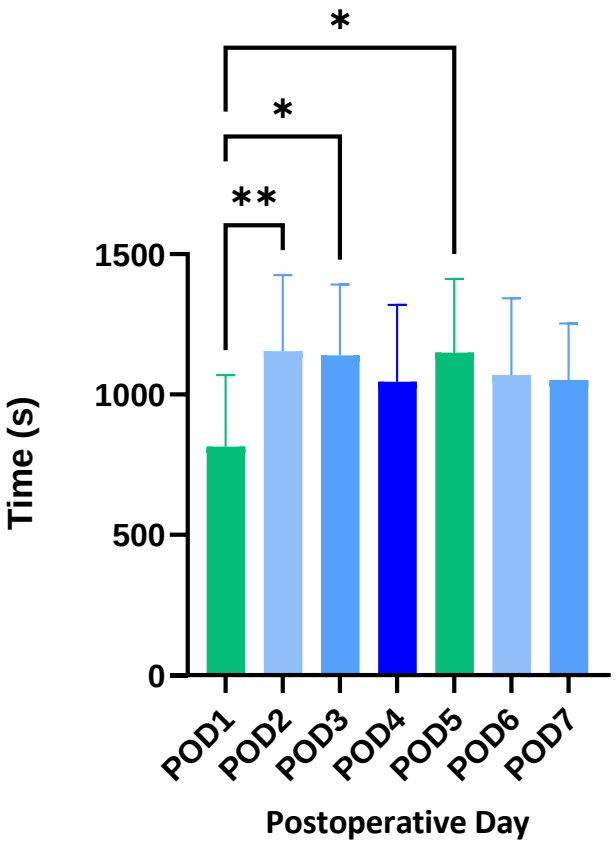


*Figure 3.4. Mean total sedentary time in seconds on each postoperative day in the PHYSPAL cohort after elective colorectal resection on an ERAS pathway. Analysis via one-way ANOVA. *=p<0.05, **=p<0.01, ***=p<0.001.*

3.3.1.5 Sitting time

There was a significant difference in sitting time across the in-hospital stay (p=0.01), seen within the first 3 days and both compared with POD1. There was a difference seen between POD1 and POD2 (MD -352.1; 95% CI -648.0 to -56.11, p=0.01) and POD3 (MD -337.3; 95% CI -642.9 to -31.60, p=0.021).

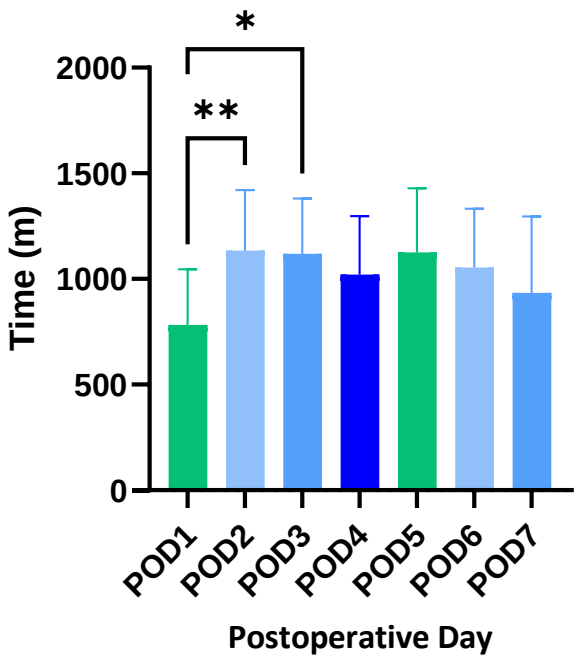


*Figure 3.5 Mean sitting time in seconds on each postoperative day in the PHYSPAL cohort after elective colorectal resection on an ERAS pathway. Analysis via one-way ANOVA. *=p<0.05, **=p<0.01, ***=p<0.001.*

3.3.1.6 Standing time

There was no significant difference in standing times at any timepoint comparison during in-hospital stay (p=0.44), with a weighted mean daily standing time across all 7 days of 48.61m (weighted SD 12.17m). Considering only days 1-4, the period where over 75% of participants were still included in the study, the weighted mean standing time was 43.50m (weighted SD 10.65m).

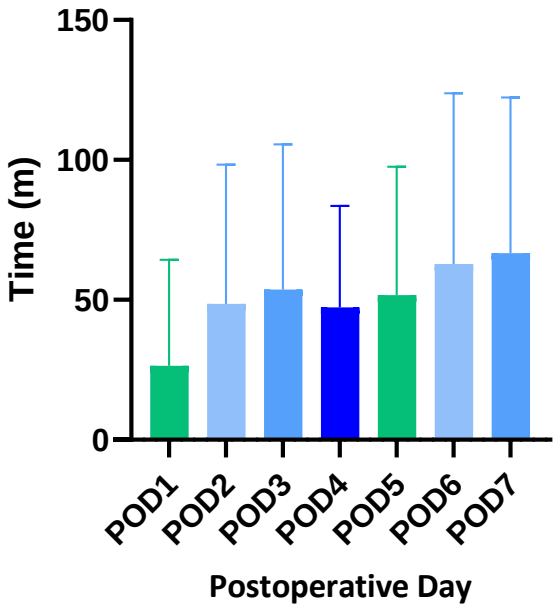


*Figure 3.6. Mean standing time in seconds on each postoperative day in the PHYSPAL cohort after elective colorectal resection on an ERAS pathway. Analysis via one-way ANOVA. *=p<0.05, **=p<0.01, ***=p<0.001.*

3.3.1.7 MET.h

There was no significant difference in MET.h at any timepoint comparison during in-hospital stay (p=0.63), with a weighted mean across all 7 days of 30.12 MET.h (weighted SD 0.33 MET.h). Considering only days 1-4, the period where over 75% of participants were still included in the study, the weighted mean was 30.08 MET.h (weighted SD 0.38 MET.h).

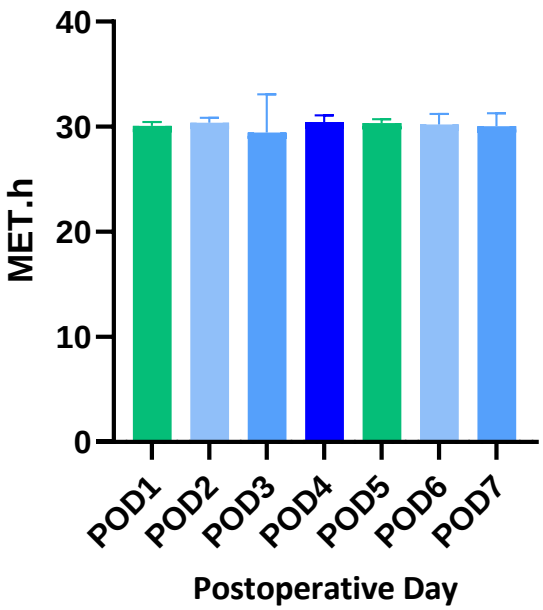


*Figure 3.7. Mean MET.h on each postoperative day in the PHYSPAL cohort after elective colorectal resection on an ERAS pathway. Analysis via one-way ANOVA. *=p<0.05, **=p<0.01, ***=p<0.001.*

3.3.2 Postoperative inpatient HADS score

The total score for the HADS questionnaire is out of 21. For depression and/or anxiety subscales, 0-7 is classed as normal, 8-10 borderline, and 11-21 is abnormal (see Appendix 7.7.1). For the scores relating to both anxiety and depression there was no significant difference in scores between each timepoint (HADS-A p=0.37; HADS-D p=0.84)

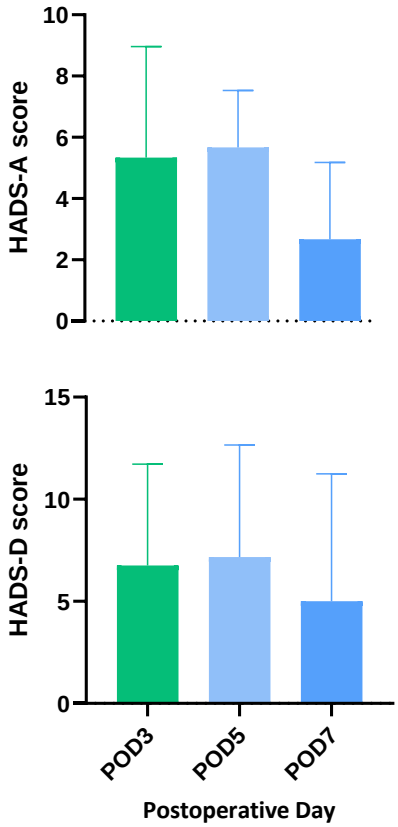


*Figure 3.8. Mean HADS-A (anxiety) and HADS-D (depression) scores of the PHYSPAL cohort after elective colorectal resection on an ERAS pathway. Analysis via one-way ANOVA. *=p<0.05, **=p<0.01, ***=p<0.001.*

3.3.2.1 Correlation of HADS scores with activity

There was no correlation between POD and mean HADS-A score (r=-0.80), mean HADS-D score (r= -0.77), nor mean step count and mean HADS-A (r=0.75) or HADS-D scores (r=0.713).

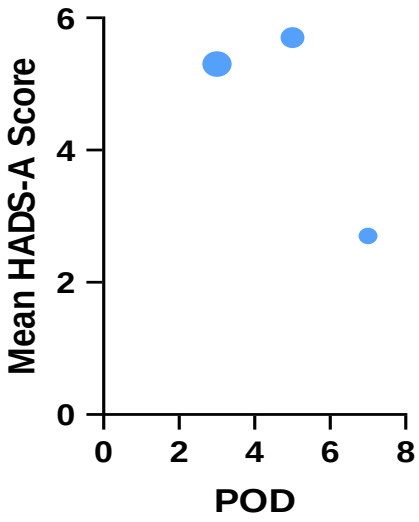


Figure 3.9. Bubble plot showing correlation between HADS-A scores and mean step count at each postoperative day timepoint. A Pearson r correlation coefficient was performed. The size of the circles corresponds with the mean step count.

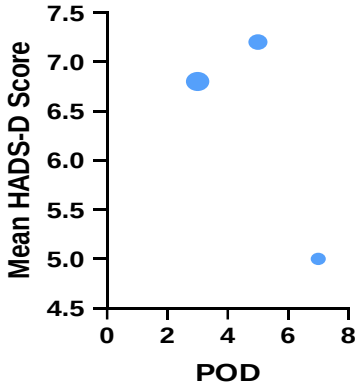


Figure 3.10. Bubble plot showing correlation between HADS-D scores and mean step count at each postoperative day timepoint. A Pearson r correlation coefficient was performed. The size of the circles corresponds with the mean step count.

3.4 Discussion

The initial results of the PHYSPAL study have suggested that there is a modest increase in activity, but the mean step count of 676.5 steps at POD3 and 535.6 steps at POD5 are still below what would be expected. Both step count and sit-to-stand figures follow the same general trend. The drop-off from POD4 to POD5 relates to the time period where most postoperative complications tend to become clinically apparent, so the expectation of an uncomplicated recovery and discharge at approximately day 5 would fit with this observation. At POD7 there were 8 patients still admitted, with a mean step count of 769.0 steps (SD 806.7 steps). There is little change over time, also potentially implying either a non-serious postoperative complication, or other practical factors delaying discharge in an otherwise fit -for-discharge patient.

For total sedentary time, there is a significant increase in sedentary time between POD1 and both POD2 (MD -340.2s; 95% CI -609.2s to -71.30s, p=0.005) and POD3 (MD -325.2s; -602.9s to -47.39s, p=0.0114). A lot of focus in the first postoperative day is spent clinically in trying to but this increase in time could potentially reflect a drop-off in initial pressure/support. Another potential reason is less time spent lying/asleep over the first 3 days, which is supported by the same pattern of significance in mean sitting times (POD1 vs POD2: MD-352.1s; 95% CI -648.0s to -56.11s, p=0.01; POD1 vs POD3: MD -337.3s; 95% CI -642.9 to -31.60, p=0.0210). There was no significant effect in standing times at any timepoint, however, and it is important to note that most patients did not reach at least an hour of standing time at any point during the first 5 days of their inpatient stay.

In general, HADS scores did not hugely differ throughout the hospital stay, with no correlation seen with step count for either depression or anxiety; patient mood is not an obvious factor in motivation to be active postoperatively. There were individual patients who did score highly on the HADs questionnaire, patients who were not necessarily subject to a

postoperative complication; this screening questionnaire is important in identifying those patients who may need some further psychological support, even post-discharge.

The relatively high open approach rate of 29% shows early deviation from ERAS guidelines, although there is likely justifiable reasons for the early decision to not attempt a minimally invasive approach. Nearly 59% of the cohort were ASA 3, and so their co-morbid status may have driven the decision although it was not always documented or obvious as to why. This may also explain the higher-than-expected mean length of hospital stay of 11.9 days. Other factors such as stoma training (4 patients were defunctioned at their index procedure) may have contributed to the increased LoS.

The major limitation to the PHYSPAL study was the inability to recruit every patient who came through. Reasons for this included was patients not being picked up in time to receive information and sign consent, changing operation dates, and being unable to contact them due to other commitments (e.g. their work schedules). The best time to recruit patients is in clinic, but they are often overwhelmed with information at a distressing time, so it is a fine balance between wanting to capture as many participants as possible and not giving the patient too much take on at an already challenging time.

The logistical use of the ActivPAL™ accelerometers was also a factor that quickly became a challenge. The theatre staff and nurses on the postoperative wards required education in their presence and use. Their application needed to be considered with practical issues such as diathermy plate placement and postoperative washing/care. This required education of both day and nighttime staff on multiple wards including on the Critical Care Unit. When patients were discharged a safe drop-off point for the monitors on the ward to prevent loss needed to be considered, especially during discharge periods where no study team members were available. In future, a short information sheet for staff

would be useful, to outline their usage and familiarise themselves with the monitors.

The PHYSPAL study is ongoing, so only the first 17 patients have been included in this analysis. To carry this further, there is a plan for it to be run at other centres to see if the outcomes are Trust-specific or indicative of a wider issue that may need to be addressed.

Other potential uses or developments from this observational cohort include providing patients with preoperative information on step count targets for each postoperative milestone. For example, post removal of urinary catheter, they can be given a target goal of a minimum number of steps and sit-to-stands throughout the day to perform, which with a simple tracker (or existing smartphone/watch) can be easily self-monitored and give patients some power and ownership in taking charge of their own rehabilitation. Of course, postoperative complications (Clavien-Dindo I/II should not massively reduce a patient's capacity for mobilisation) do occur which can often reduce their capacity for achieving these goals and does extend LoHS, but target-driven goals that are simple and require little extra resource could be a good method of improving in-hospital postoperative activity.

As previously discussed in Chapter 1, ERAS in colorectal surgery has been a key driver in improving patient-related outcomes, as well as reducing LoHS (Olson et al., 2021). However, regular scrutiny of postoperative movement is less well-documented. This is multifactorial; for example early removal of catheters/epidurals, etc. as well as physiotherapy availability and input will all contribute to early postoperative mobilisation.

The in-hospital course is ultimately a short although crucial part of the patient journey, and the ability to make a significant impact on a patient's overall function and fitness in the short to medium term is limited by focussing solely on interventions based in this period. There are resource limitations as well such as AHP availability to provide personalised patient rehabilitation that mean alternatives should be considered. As

such, Chapter 4 will present the results of a post-discharge early aerobic and resistance training intervention in a randomised controlled trial format in an effort to address this.

4 A randomised controlled trial (RCT) exploring the efficacy of a multi-modal postoperative exercise training programme to improve physical fitness in colorectal cancer patients *(the POSTEx study)*

4.1 Introduction

As detailed in Chapter 1, surgery is still the gold-standard for treating colorectal cancer with curative intent (Oliphant et al., 2013). The advances in surgical approach (i.e. the development of minimally invasive/robotic assisted surgery over conventional open surgery resulting in large wounds) have helped to reduce the physiological insult of operative intervention (Kolarsick et al., 2020), but there is still an issue regarding long recovery times, especially in elderly patients (Novello et al., 2019). Some patients, especially older cohorts, do not return to their baseline level of function at all (Lawrence et al., 2004), even in the absence of adjuvant therapies (De Roo et al., 2020).

Intuitively, exercise after surgery to improve functional outcomes for patients would seem to be beneficial (Chang et al., 2020; Pinto et al., 2009). In terms of evidence, postoperative post-discharge exercise rehabilitation programmes have been previously trialled, some with promising results (as seen in Chapter 2) (Paul et al., 2023). However, the timing after surgery and the length of the programmes vary, making it hard to be certain there is a real benefit. The government guidelines for exercise in healthy adults are well-publicised and accessible online (Davies et al., 2019), and so this exercise dose was chosen as the basis for the *POSTEx* study exercise protocol, as these do not differ significantly from guidance in cancer cohorts (Campbell et al., 2019; Schmitz et al., 2010). Patients have different lengths of postoperative inpatient stays which can be for various modifiable and non-modifiable reasons. Coupled with preoperative behaviours around exercise (anxiety/fear of causing harm) (Agasi-Idenburg et al., 2019) and the

potential for significant postoperative complications (all affecting the ability to be physically active) (Van Egmond et al., 2020), it is a difficult area to confidently assess. The safety of exercise in post-operative patients is well understood (Heitkamp et al., 2023; Singh et al., 2020), but despite this no UK standardised advice or exercise prescription is given to this particular cohort of patients. Most colorectal ERAS will have physiotherapist specialist input (Ljungqvist & Hubner, 2018), but there is little regular post-discharge follow up or monitoring to ensure adherence and confidence in carrying out the exercises once discharged (de Leeuwerk et al., 2022). There is also variable confidence and knowledge amongst healthcare professionals in providing evidence-based information and guidance for postoperative exercise (Zenko & Ekkekakis, 2015). Many patients have their first postoperative review weeks after discharge (Lithner et al., 2015): the period before follow-up is a potential missed opportunity to start regular gentle exercise intended to improve their functional state and aerobic capacity. Other markers that are more patient-centric, such as return to work, are also important, especially to patients, and can be affected by their physical functioning (Bhalla et al., 2014). This is an area that requires further scrutiny.

4.1.1 Aims

The POSTEx study was designed as an RCT looking at whether a 12-week combined aerobic and exercise programme a) is feasible and b) confers any physical, functional and/or psychological benefits for postoperative patients who have had a colorectal cancer resection. The primary endpoint was the mean change in $VO2_{AT}$ in participants at 12 weeks who had the exercise programme compared to those who continued with standard care. Secondary enpoints were the feasibility of delivering the programme for 12 weeks, functional changes and assessment of any quality-of-life changes (using the EORTC QLQ-C30, DASI and IPAQ questionnaires) during the study period.

4.2 Methods

4.2.1 Ethics

This study was registered with ClinicalTrials.gov (NCT05090215) and received ethics approval from the South Yorkshire Research Ethics Committee on 8th December 2021. Two further amendments were made to the protocol to include intramuscular electromyography (iEMG) testing and a post exercise programme feedback semi-structured interview. They both went through REC approval in accordance with the IRAS guidance for submitting amendment requests (see Appendix 6.2.2). Following significant administrative delays, the study gained Royal Derby Hospital NHS Research and Development approval in May 2022.

4.2.2 Sample size calculation

In a previous cohort of cancer patients from the same centre, a 4 week preoperative intensive HIIT exercise program showed a mean difference in VO2AT of 2.26ml/kg/min between the exercise group and control (normal postoperative care) with a 95% confidence interval of 1.25 to 3.26ml/kg/min and an effect size of 0.42 (Blackwell et al., 2018). Using G*Power calculator (Axel Buchner, University of Dusseldorf), to detect a significant increase in VO2AT with 95% confidence and 5% significance we needed to study 23 subjects. Previous studies have achieved a dropout rate of 20%. Given the significantly increased length of this study we have assumed a dropout rate of 30%. With a postoperative readmission rate of approximately 11% and mortality rate of 3% based on the National Bowel Cancer Audit data 2020 34 volunteers, 17 in each arm were required (Association of Coloproctology of Great Britain and Ireland (ACPGBI), 2020).

4.2.3 Study Overview

The outline of the study is as shown in Figure 4.1.

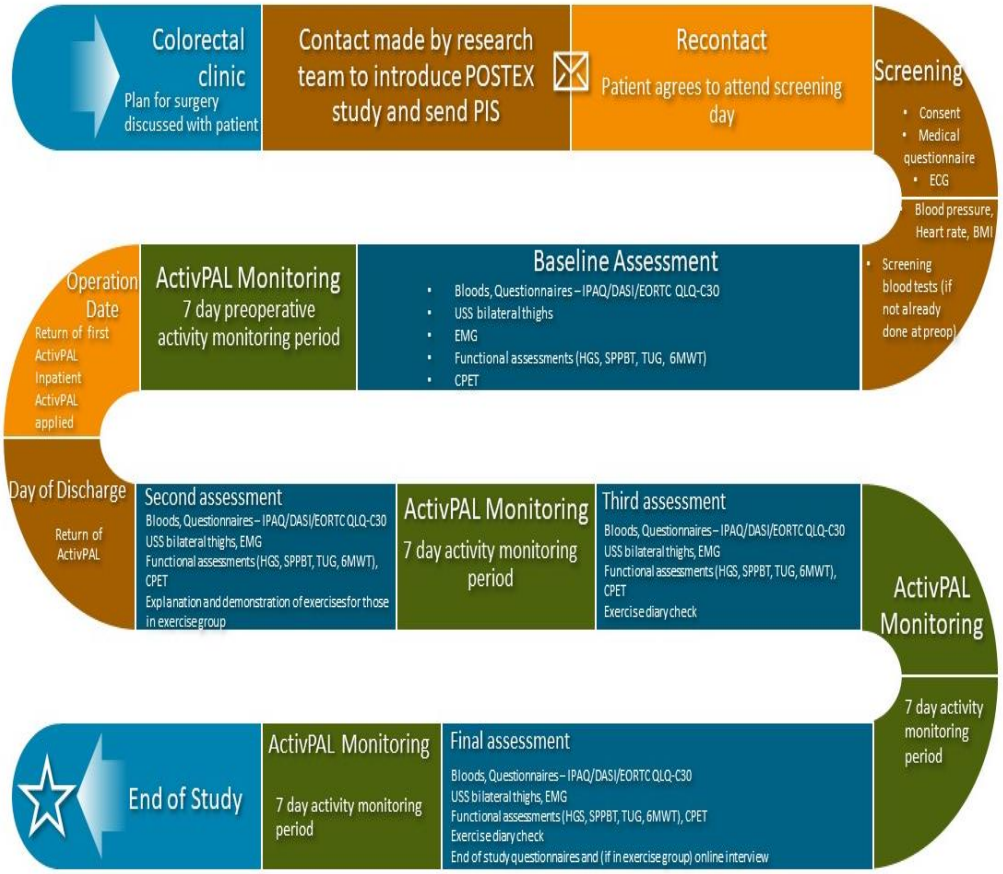


Figure 4.1. Schematic to show the POSTEX study overview.

Recruitment

Twenty-one patients were identified from the Royal Derby Hospital Colorectal multidisciplinary team (MDT) weekly outcome circular following the MDT meetings between May 2022 and September 2023. Potentially eligible patients with a plan for operation with curative intent were approached after being seen in outpatient clinic to discuss their operation with a consultant surgeon. Initially, patients who had neoadjuvant treatment were also included in the study protocol but given the difference in profile compared to newly diagnosed patients and the potential for a long deconditioning period during time spent receiving neoadjuvant chemo+/-radiotherapy, the decision was made to not recruit them into the study. After their clinic appointment potential participants were telephoned or emailed and informed of the study. If there was initial interest, the patient information sheet (PIS; see Appendix 7.4.2) was emailed or posted to them with an invitation to attend the research department for a screening session and to consent for entry into the study. At the screening session they were taken through the PIS and had the opportunity to ask questions. It was reiterated that the study was designed to fit around their usual care and had no impact on any treatment they would be given. They were also informed that they could withdraw from the study at any time. Often this screening session was timed for the same day as the patients' preoperative assessment in order to reduce the burden of preoperative visits. If this was the case, screening bloods were not taken so that the patient avoided venepuncture sampling twice in one day and the preoperative assessment bloods were screened to ensure suitability for inclusion in the study (criteria below). Written informed consent was taken and recorded and a date set for the first assessment day. Inclusion and Exclusion criteria are shown in Table 4.1.

Inclusion Criteria	Exclusion Criteria
Aged 18 years and over	Participants who lack capacity to consent
MDT outcome of proven or high clinical suspicion of colorectal cancer	Participants with a new diagnosis undergoing emergency surgery
Due to undergo either laparoscopic, robotic or open resection with curative intent	Participants with a past medical history including the following: • Recent myocardial infarction (MI) in the last 6 months or unstable angina • Heart failure (New York Heart Association Class III/IV) • Uncontrolled hypertension (BP>160/100mmHg) • Previous stroke/TIA • Cerebral or abdominal aortic aneurysm • Severe respiratory disease including known pulmonary hypertension (>25mmHg) • Exercise induced asthma or brittle asthma
Ability to give informed consent	Abnormal blood and/or ECG results
Must be able to organize own transport to RDH for the duration of the study in order to complete the supervised exercise sessions	Patients who are unable to undergo CPET according to the Perioperative Exercise Testing and Training Society (POETTS)

	published consensus guidelines on performing CPET
Availability for the period of study inclusion	
Ability to exercise on a static bike (in order to complete the CPET, not required for the exercise programme)	

Table 4.1. Inclusion and exclusion criteria for the POSTEx study.

If anything was found at screening that was a potential new diagnosis or could affect their treatment, the patients' care team was informed. The patients' designated GP was also informed of their enrolment into the study via mail (Appendix 7.4.3).

4.2.4 Study day assessments

4.2.4.1 Blood tests

At each assessment day a fasting full blood count, urea and electrolyte, CRP, and thyroid function test sample was taken via venepuncture and sent to the pathology department at Royal Derby Hospital for analysis. After an interim analysis of the first 8 participants showed that there was no significant changes in these parameters, pathology blood samples were no longer taken after initial screening bloods.

4.2.4.2 Functional assessment

Handgrip strength (HGS) was measured using a Takei T.K.K. 5401 digital dynamometer (Takei Scientific Instruments Co., Ltd., Japan) with the patient stood, feet shoulder width apart and arms relaxed by the sides. Measurements were taken in triplicate and verbal encouragement was given to squeeze after a countdown. Both the dominant and non-dominant hand were assessed. The short performance physical battery tests (SPPBT) which include an amalgamation of a 4m walk, balance/gait test and sit to stand speed were part of the functional assessment to assess any changes pre and postoperatively and with the inclusion of the exercise programme.

Patients also performed a series of functional assessments using the G-walk monitor (BTS Bioengineering Corp., Milan, Italy), a sensor that records and analysis motion. These included a counter movement jump (CMJ) test where the participant performed 3 single CMJ jumps 30 seconds apart, the TUG and 6MWT (protocols described in Chapter 1.2.1.3.1 and 1.2.1.3.2) using the G-walk monitor secured to their back in the position according to the test protocol (at the level of L1 for the TUG, and S2 for the CMJ and 6MWT). The results were transferred via Bluetooth to the custom GSTUDIO software application for the G-Walk monitor (BTS Bioengineering Corp., Milan, Italy).

4.2.4.3 Electromyography

4.2.4.3.1 Maximal voluntary isometric contraction

The experimental protocol for the EMG assessment described below was based on previously published procedures by this group(Piasecki et al., 2016). Patients were seated upright on a specially designed chair with a waist belt attached to prevent hip lifting and with knees flexed to 90° with the right leg immobilised just above the ankle to a force transducer. After a 3-second countdown, they were asked to perform a maximal knee extension with verbal encouragement whilst looking at a computer screen which provided real-time feedback of force. Three contractions were performed, and the best effort was subsequently used as the maximum voluntary isometric contraction force (MVC).

4.2.4.3.2 EMG

The right vastus lateralis (VL) was used for all sEMG data capture. The sEMG electrode (disposable self-adhering Ag-AgCl electrodes; 95 mm2, Ambu Neuroline, Baltorpbakken, Ballerup, Denmark) was placed at the mid-point of the lateral right thigh. A reference electrode was placed over the patella tendon and a common ground electrode placed over the patella (both on the right leg) and was used for all sEMG and iEMG data capture. Surface EMG signals were bandpass filtered between 5 and 5 kHz via CED 1902 amplifiers (Cambridge Electronics Design Ltd., Cambridge, UK), sampled at 10 kHz and digitized with a CED Micro 1401 data acquisition unit (Cambridge Electronic Design). Spike2 (version 9.00a,CED) software provided a real-time, on-screen signal display for the participants to follow. For iEMG, A concentric needle electrode (Ambu Neuroline model740 25−45/25, Ambu, UK) was inserted at the VL motor point and contractions were carried out at 10%, 25% and 40% of the participants' MVC following a target line on screen. 3 contractions were recorded at 10 and 25%, respectively, and two at 40% intensity, with the needle electrode position moved to at least two different depths and three different rotations of the needle bevel to pick up a large range motor unit points. These voluntary contractions were held for 15 seconds with approximately 20 seconds rest in between each contraction. Force

steadiness was assessed during the sustained voluntary contractions as the coefficient of variation of the force, averaged at each contraction intensity. Right VL fatigue was measured by asking patients to hold a contraction at 30% of their earlier recorded MVC until they achieved failure. The time held was recorded in seconds.

4.2.4.4 Quality of life assessment

At each visit, participants were given 3 questionnaires to complete: the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire- colorectal subtype (EORTC-QLQ C30) questionnaire, the International Physical Activity Questionnaire (IPAQ), and the Dukes Activity status Index (DASI) questionnaire. A formal application request for use of the EORTC-QLQ C30 questionnaire and scoring manual was granted by the owners (http://www.eortc.org). Patients completed the questionnaires privately at the start of each assessment visit and had no reference to their previous answers.

4.2.4.5 Cardiorespiratory fitness

CPET (Cortex Meta Control 3000, Cortex Biophysik, Leipzig, Germany) was performed using a cycle ergometer (Lode Corival, Lode, Netherlands) and gas analysis system (Cortex Metalyzer 3B, Cortex Biophysik, Leipzig, Germany). A tight-fitting silicone face mask (V2 mask, Hans Rudolph Inc., USA) was applied to the participant's face using custom headgear (Hans Rudolph Inc., USA) and tested by occluding the flow sensor hole against maximal expiration to exclude any air leaks. Participants were asked to mount the bike after checking for an appropriate bike height and comfort of the foot straps. For each session, participants had continuous 12-lead ECG (Custo diagnostic, Custo med, Germany) and pulse oximetry monitoring (Mindray Datascope Trio, Soma Tech Intl, USA) with intermittent automatic non-invasive blood pressure surveillance every 2 minutes during the test (Cortex Medtronik BL-6, Cortex Biophysik, Germany). The flow sensor was then attached to the participants mask and the test was started. There was a 1-minute initial rest period for gas calibration, then had a 2 minute 30 second warm up period with unloaded cycling. Participants then commenced a

modified Bruce ramp protocol that varied between 8 and 15W/min depending on their physical activity status as assessed by the clinician supervising the test aiming to achieve VO_2peak between 8 and 12 minutes. The target RPM was 60-65 and participants were given verbal encouragement to continue cycling to complete fatigue to hopefully reach a respiratory exchange ratio (RER) above 1.0. They were told to speak or verbally indicate if they were having difficulty during the test, and the test would be immediately terminated. If they could no longer maintain a cadence of 60 RPM the test was also terminated. Each session was supervised by at least 2 personnel; one who was trained in Basic Life Support and a clinician trained in Advanced Life Support. The POETTS criteria for termination of CPET testing was present within the CPET testing room to refer to throughout all the sessions (Levett et al., 2018). After the ramp was completed, each participant had a four-minute cool-down period at 10W with a target cadence of approximately 40RPM to ensure a gradual reduction in heart rate and blood pressure. Two independent assessors blinded to group allocation reviewed the results to determine the AT by using V slope and respiratory equivalents (Hull, 2021).

4.2.4.6 Physical activity monitoring

As described in Chapter 3, accelerometers are monitors that can measure the intensity and duration of physical movements, thereby allowing it to be classified by effort. In addition, all patients had the monitor applied for the week either before or after their baseline assessment day depending on the time to surgery, and then 3 more times for 1 week following their assessment days during the postoperative period to capture the activity at home around the same time. Time spent sitting, standing and in bed was captured, along with average MET.h of daily activity, daily step count and sit-to-stands (STS). The PAL software was used for all accelerometer data synthesis and analysis (PAL Technologies, Glasgow, UK).

4.2.5 Exercise training intervention

Participants were randomly allocated to the exercise or control group after completion of the first assessment day (www.sealedenvelope.com). They were given information about the exercises and aerobic component during the second assessment day, which marked the start of their 12 weeks of exercise. The resistance training sessions were demonstrated with a video created by the COMAP group (https://vimeo.com/746255956; password is **resistance**), which was also sent to the exercise cohort by email, so they had reference to it whilst at home. They were given a range of 2-metre resistance bands (Meglio, Oxfordshire, UK) in different strengths, with advice to go up or down on the degree of resistance according to their ability with each individual exercise. They were provided with two diaries, one for recording their aerobic activity and another for the resistance training sessions (see Appendix 6.8). They were told to email to get in contact proactively if they encountered any difficulties. In addition, they had weekly telephone or email follow up to check for any issues. Each week, the following 5 questions were asked:

1. ***Are you managing to do a minimum of 75 mins vigorous or 150 mins moderate exercise in a week and are you happy knowing what the difference is?***
2. ***Are you managing all of the resistance exercises in the video?***
3. ***Do you need a different sized or tensioned band?***
4. ***Are you managing to document it in the diary?***
5. ***Any other issues/questions?***

The exercise diaries were reviewed to ensure compliance with the sessions during the third assessment day, and at the final visit they were given an end of study exercise acceptability questionnaire to complete privately (see Appendix 6.7.6).

4.2.6 Post exercise feedback semi-structured interview

Within two weeks of study completion, participants in the exercise programme were invited to have a semi-structured interview to give more

detailed patient-centred feedback on the exercise programme and the study itself. This took placed via video conferencing software (Microsoft Teams, US) with the camera off and no identifying information used. Prior to the start of the interview, both participants gave recorded verbal consent. They were asked a series of questions (see Appendix 7.9) and were given the opportunity to give free feedback. It was transcribed but as only 2 participants opted to take part, coding software was not used, and thematic analysis was not performed.

4.3 Results

Twenty-one patients were enrolled. Due to concurrent studies with similar target participants in our department, not all eligible participants were approached to take part in this research study (i.e., some we recruited into other trials). As such, the CONSORT diagram below does not start with all potentially eligible participants identified at MDT, but rather those who were approached to take part in this specific study. The Consolidated Standards of Reporting Trials (CONSORT) diagram below shows the participant recruitment and movement through the study (Figure 4.2).

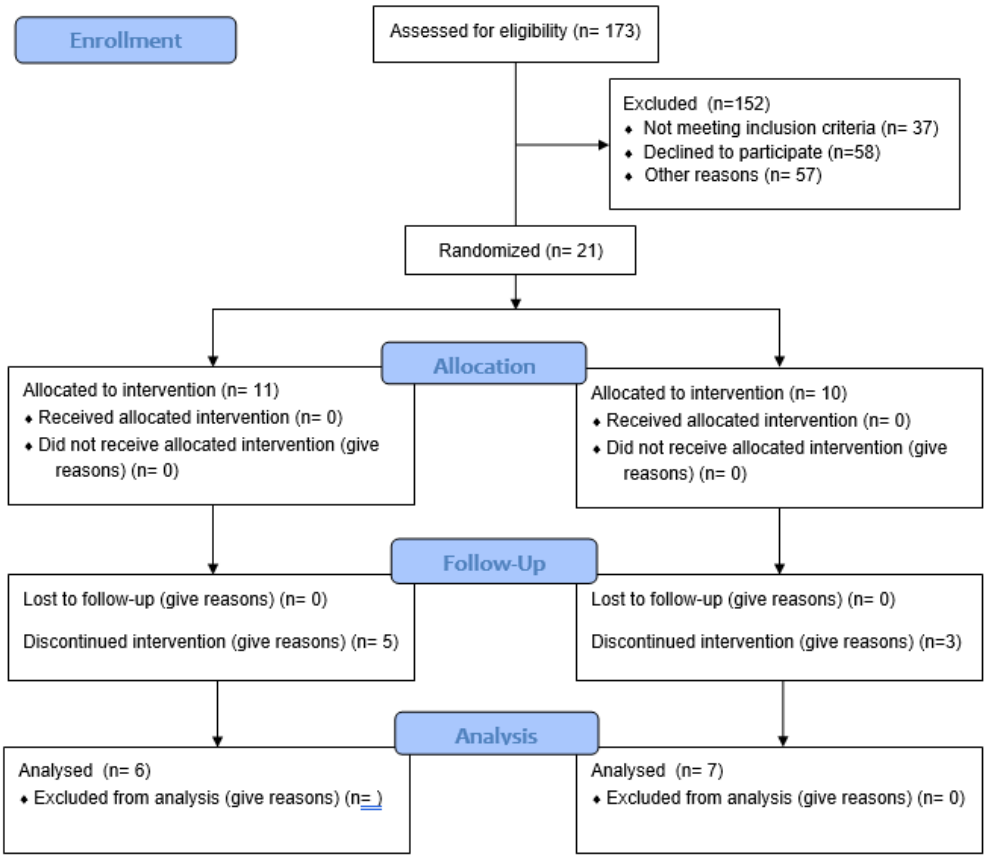


Figure 4.2. CONSORT diagram to show participant progression through the POSTEx study. Adapted from https://www.consort-spirit.org/. Accessed on 2nd April 2025.

Seventy six percent (n=16) of patients completed at the 3rd assessment day and 62% (n=13) completed the study (completion of A4 assessment day). The TiDIER Checklist for reporting of exercise interventions is shown in Table 4.2.

Item number	Item	Where located Primary paper (page or appendi number)
	BRIEF NAME	
1.	Provide the name or a phrase that describes the intervention.	Chapter 4 Title
	WHY	
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Chapter 4.1
	WHAT	
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Chapters 7.6.1; 7.10
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Chapters 7.4.2 & 7.10
	WHO PROVIDED	

5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Not explicitly stated
	HOW	
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Chapter 4.2.4
	WHERE	
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Chapters 4.2.4 & 7.2.2
	WHEN and HOW MUCH	
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Chapter 4.3.6
	TAILORING	
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	N/A
	MODIFICATIONS	

10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A
	HOW WELL	
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Chapter 4.3.6
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Chapter 4.3.6

Table 4.2. The TIDieR (Template for Intervention Description and Replication) Checklist. Accessed from https://www.equator-network.org/wp-content/uploads/2014/03/TIDieR-Checklist-PDF.pdf on 17th March 2025.

The baseline characteristics of the participants are seen in Table 4.3.

Characteristic	Whole group	Control group	Exercise group	P value
Participants enrolled % (n)	21	48 (10)	52 (11)	-
Mean age in years at enrolment [SD]	67.43 [11.19]	71.70 [7.21]	63.55 [13.00]	0.091 (T- test)
Gender M:F % (n)	67:33 (14:7)	60:40 (6:4)	73:27 (8:3)	-
Mean BMI [SD]	27.05 [4.14]	26.93 [3.98]	27.15 [4.48]	0.906
Ethnicity	100% White British	-	-	
Mean Charlson Comorbidity Index [SD]	4.48 [1.03]	5.00 [0.67]	4.00 [1.10]	0.021*
Cancer location; % (n)				
Caecum	33 (7)	19 (4)	27 (3)	-
Ascending colon	24 (5)	10 (2)	27 (3)	-
Descending colon	5 (1)	0 (0)	9 (1)	-
Sigmoid	24 (5)	10 (2)	27 (3)	-

Rectosigmoid junction	5 (1)	5 (1)	0 (0)	-
Rectum	10 (2)	5 (1)	9 (1)	-
Final preoperative staging				-
Tx	5 (1)	0 (0)	9 (1)	-
T1	24 (5)	30 (3)	18 (2)	-
T2	14 (3)	10 (1)	18 (2)	-
T3	48 (10)	40 (4)	54 (6)	-
T4	10 (2)	20 (2)	0 (0)	-
N0	76 (16)	60 (6)	91 (10)	-
N1	10 (2)	10 (1)	9 (1)	-
N2	14 (3)	30 (3)	0 (0)	-
Operation type % (n)				
Anterior resection	33 (7)	14 (3)	36 (4)	-
Right hemicolectomy	52 (11)	29 (6)	45 (5)	-
Left hemicolectomy	14 (3)	5 (1)	18 (2)	-

Surgical approach; % (n)				
Laparoscopic	52 (11)	24 (5)	55 (6)	-
Laparoscopic converted to open	5 (1)	5 (1)	0 (0)	-
Robotic assisted	14 (3)	10 (2)	9 (1)	-
Robotic	29 (6)	10 (2)	36 (4)	-
Mean length of hospital stay [SD]	8.24 [6.66]	8.70 [5.98]	7.82 [7.48]	0.768
Readmission rate; % (n)	0 (0)	-	-	-
Reoperation rate; % (n)	5 (1)	0 (0)	9 (1)	-
Clavien-Dindo Complications; % (n)	83 (13)	70 (7)	55 (6)	-

Grade 1	8 (1)	10 (1)	0 (0)	-
Grade 2	8 (10)	60 (6)	36 (4)	-
Grade 3	0 (0)	-	-	-
Grade 4	17 (2)	0 (0)	18 (2)	-
Grade 5	0	-	-	-
Adjuvant chemotherapy; % (n)	29 (6)	40 (4)	18 (2)	-
Mean time in days from A1 to surgery [SD]	16 [21]	8.20 [4.05]	22.55 [27.45] ^	0.116
Mean time in days from discharge to A2 [SD]	32.16 [18.34]	37.67 [13.86]	27.20 [21.08]	0.192
% Completion of A3	76 (16)	90 (9)	64 (7)	-
% Completion of A4	62 (13)	70 (7)	55 (6)	-

Table 4.3. Baseline Characteristics of the enrolled participants. A1= first assessment day; A2= second assessment day. ^Exercise group: 1 patient took a holiday delaying his operation and another had his initial date delayed due to contracting COVID-19. Level of significance = P>0.05.

The reasons for withdrawal from the study are detailed in Table 4.4.

Study ID and group allocation	Point of withdrawal	Reason
POSTEXEM06 (Control)	Between A3 and A4	Hospitalised for complications relating to adjuvant chemotherapy
POSTEXJM07 (Exercise)	Between A2 and A3	Required emergency eye treatment precluding exercise
POSTEXAS09 (Control)	Between A3 and A4	No reason given
POSTEXDA10 (Control)	Prior to A2	No longer wanted to take part
POSTEXCB11 (Exercise)	Between A3 and A4	Incorrectly performed exercises and no longer felt need to continue as felt back to usual self
POSTEXJL13 (Exercise)	Between A2 and A3	Felt overwhelmed by regimen
POSTEXPH16 (Exercise)	Between A2 and A3	Debilitating knee pain due to osteoarthritis; unable to complete A3 (completed 7 weeks training)
POSTEXPG19 (Exercise)	Prior to A2	Prolonged hospital stay with complications; unable to mobilise independently at 4 weeks post-discharge

Table 4.4. Table showing reasons for study withdrawal.

Data was analysed using GraphPad Prism, v8.0, (La Jolla, Calif. US) and SPSS version 27 (IBM, US), Data was analysed in house by members of the research team with statistical oversight provided by the study statistician. After testing for normality, the data was analysed using

appropriate post-hoc tests to determine differences between the control and intervention groups (one-way ANOVA) and group x time interactions in the exercise groups (i.e. baseline versus 6- and 12-week assessments).

4.3.1 The impact of postoperative exercise training on cardiorespiratory fitness

There was no significant group, time, nor group x time difference between the control and intervention groups in either VO2 max nor VT1, as seen below in Figure 4.3 &Figure 4.4.

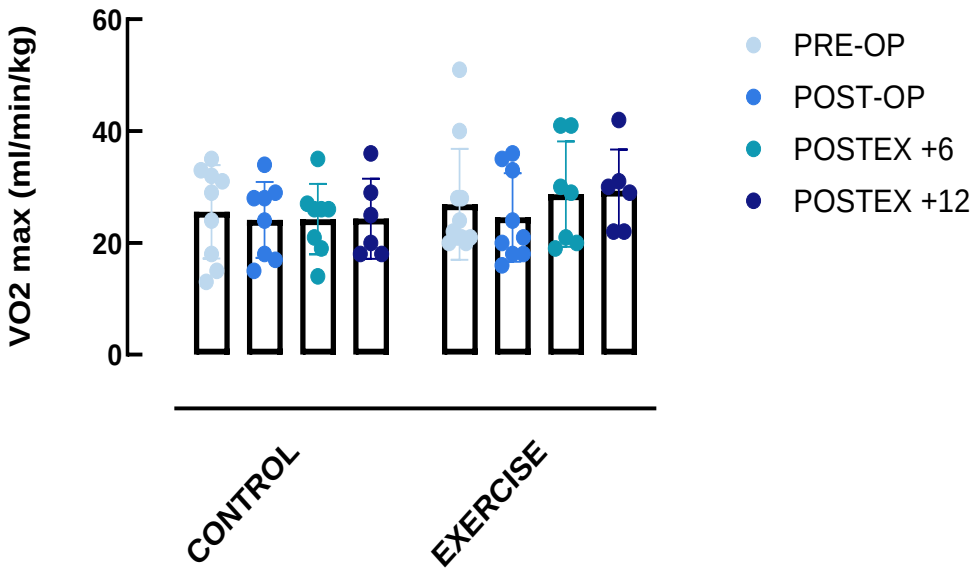


Figure 4.3. Mean difference in VO2 max before (pre-op) and within 6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training or a no-intervention control group. Analysis via a mixed-effects analysis. There was no significant effect of either group (p=0.5942), time (p=0.1077) or group x time interaction (p=0.7639).

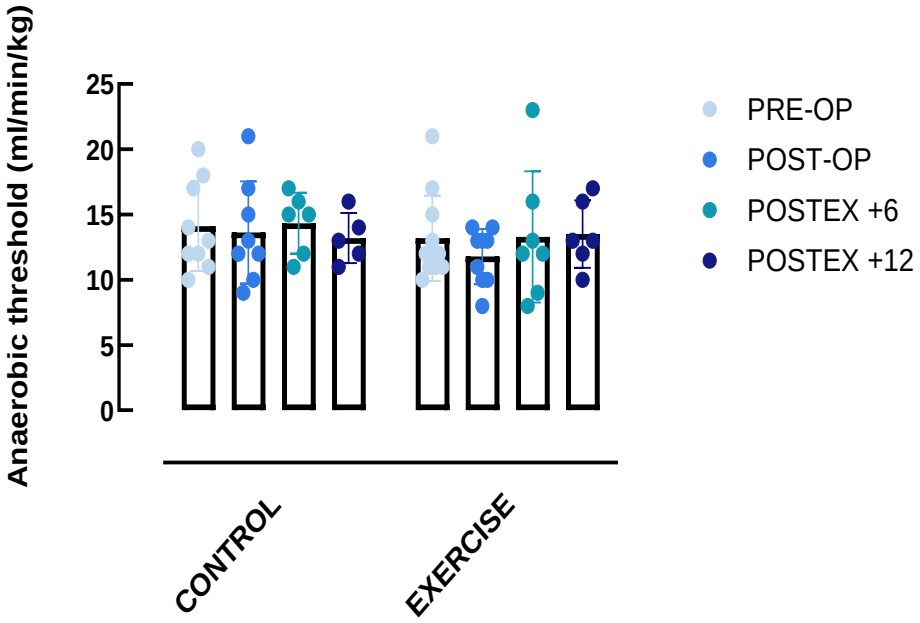


Figure 4.4. Mean difference in anaerobic threshold (VT1) before (pre-op) and within 6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training or a no-intervention control group. Analysis via a mixed-effects analysis. There was no significant effect of either group (p=0.5209), time (p=0.4556) or group x time interaction (p=0.7709).

For max HR, there was no significant difference in group or group x time interaction. There was an intra-group difference between pre-op and post-op max HR in the control group only (mean difference 0.16 seconds; 95% CI 0.281 to 20.04, p=0.0441).

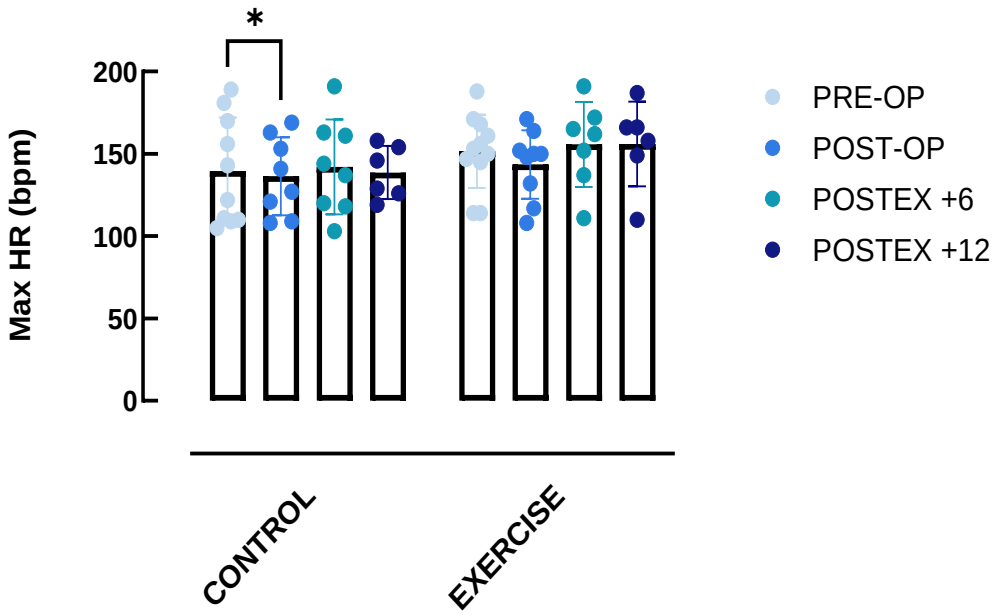


Figure 4.5. Mean difference in max HR before (pre-op) and within 6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training in or a no-intervention control group. Analysis via a mixed-effects analysis. There was no significant effect of either group (p=0.1696), time (p=0.0552) or group x time interaction (p=0.7685).

For max wattage, in the control group there was a significant change in mean difference compared to both the immediate postoperative period (MD 17.80W, 95% CI 3.747W to 31.86W, p=0.0144) and compared to the final assessment (MD 16.57W, 95% CI 1.032W to 32.11W, p=0.0372). There was a significant reduction in the exercise group after surgery but max wattage was higher after both 6 (MD -24.38W, 95% CI -39.02W to -9.736W, p=0.0017) and 12-weeks of exercise (MD -23.76W, 95% CI -39.23W to -8.279W, p=0.0036) compared to post-surgery.

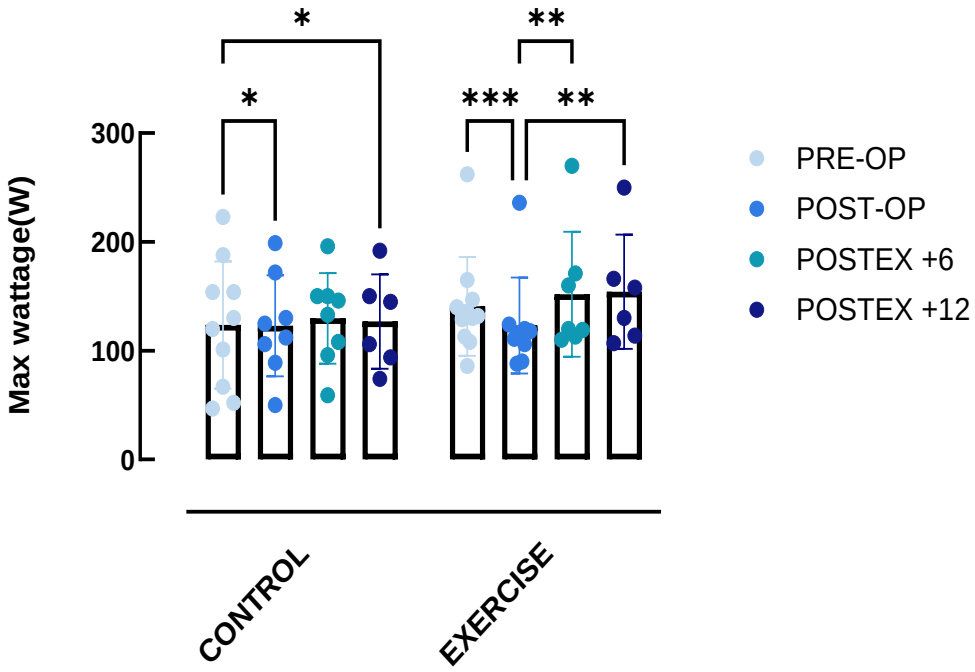


Figure 4.6. Mean difference in max wattage before (pre-op) and within 6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training in or a no-intervention control group. Analysis via a mixed-effects analysis. There was no significant effect of either group (p=0.2992), or group x time interaction (p=0.1494), but a significant time effect (p=0.0009).

There was a significant mean difference in time to VO2 peak. In the control group there was a significant change in mean difference from the preop assessment compared all other assessments (all p>0.05). There was a significant reduction in the exercise group after surgery but VO2 peak was higher after 6 (MD -3.075ml/min/kg, 95% CI -5.442 ml/min/kg to -0.7074 ml/min/kg, p=0.0123) but not 12-weeks of exercise (MD -1.937 ml/min/kg, 95% CI -4.439 ml/min/kg to 0.5653 ml/min/kg, p=0.125) compared to post-surgery.

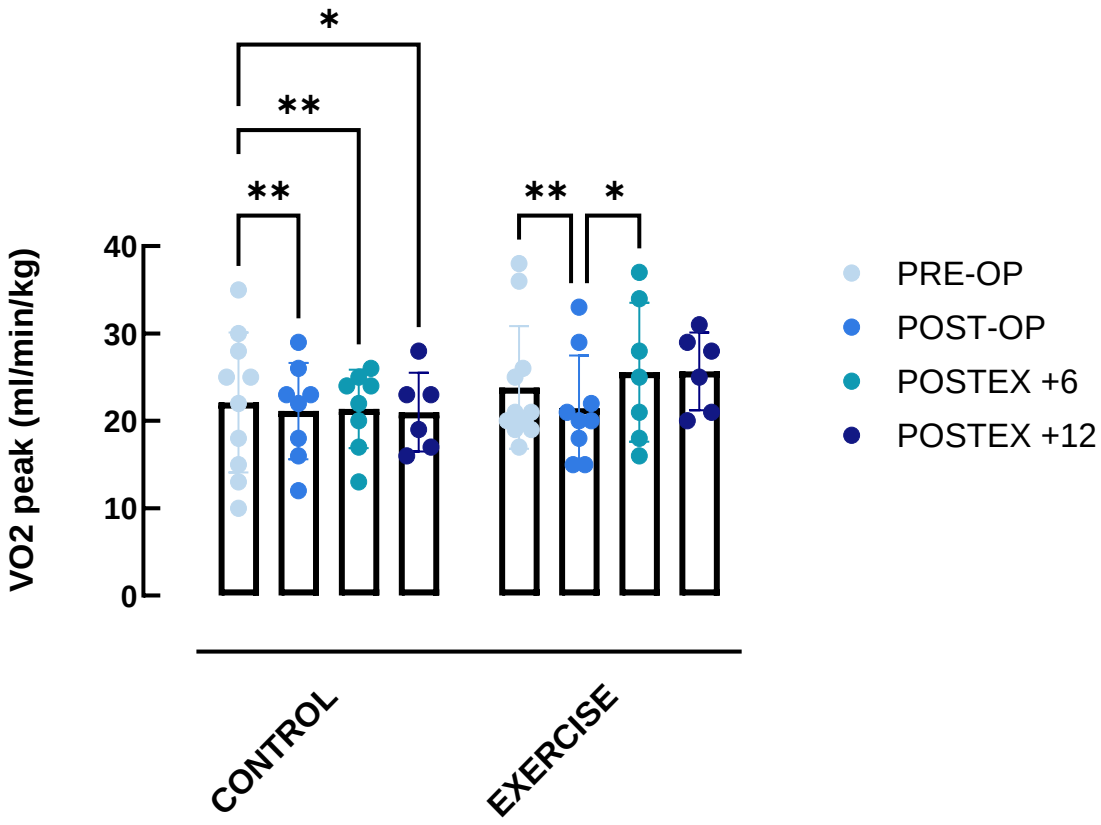


Figure 4.7. Mean difference in VO2 peak before (pre-op) and within 6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training in or a no-intervention control group. Analysis via a mixed-effects analysis. There was no significant effect of either group (p=0.3283), or group versus time interaction (p=0.2574), but a significant time effect (p=0.0013).

4.3.2 The impact of postoperative exercise training on daily activity

Within the exercise group there was a significant decrease in preop and postop step counts (MD 6158 steps, 95% CI 1027 to 5289 steps, p=0.0049), and a significant increase between PREOP and POSTEX+6 step counts (MD 2403 steps, 95% CI -4558 to -247.9 steps; p=0.030).

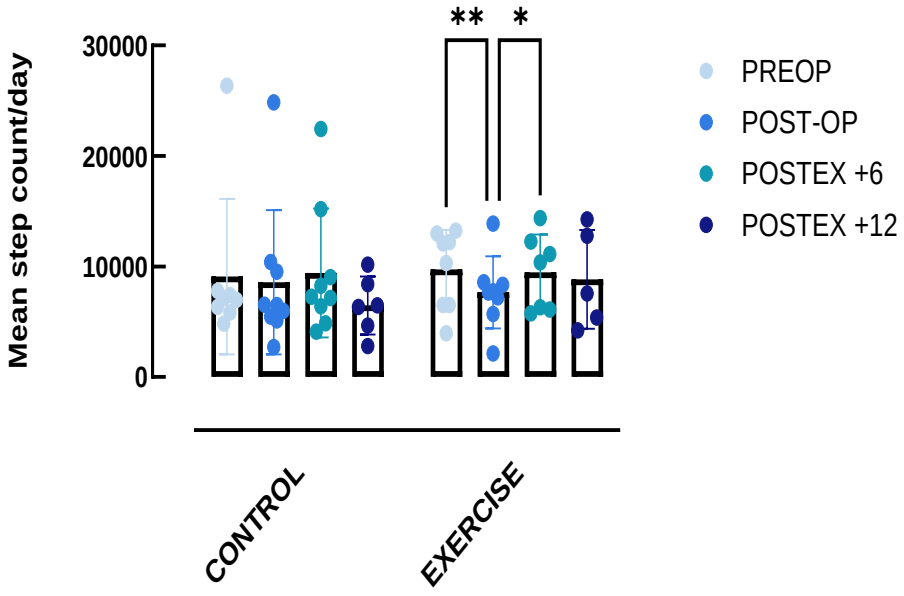


Figure 4.8. Mean daily step count at each assessment period (the preceding or following 7 days); before (pre-op) and within 6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training or a no-intervention control group. Analysis via a mixed-effects analysis. There was a significant time effect (p=0.0247) in the exercise group, but no significant effect of either group (p=0.0.9874), nor group x time interaction (p=0.3966). Note 150 mins of moderate exercise or 75 mins of vigorous exercise (the weekly target) is approximately 15,000 steps.

With regards to mean STS count, there was no group, nor group x time interaction, but there was a significant difference in PREOP and POSTEX+6 STS (MD 6.759, 95% CI 0.4938 to 13.03; p=0.035).

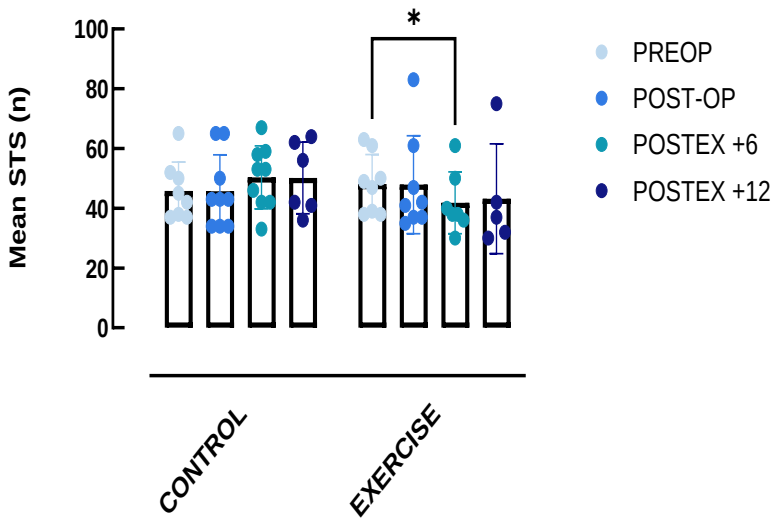
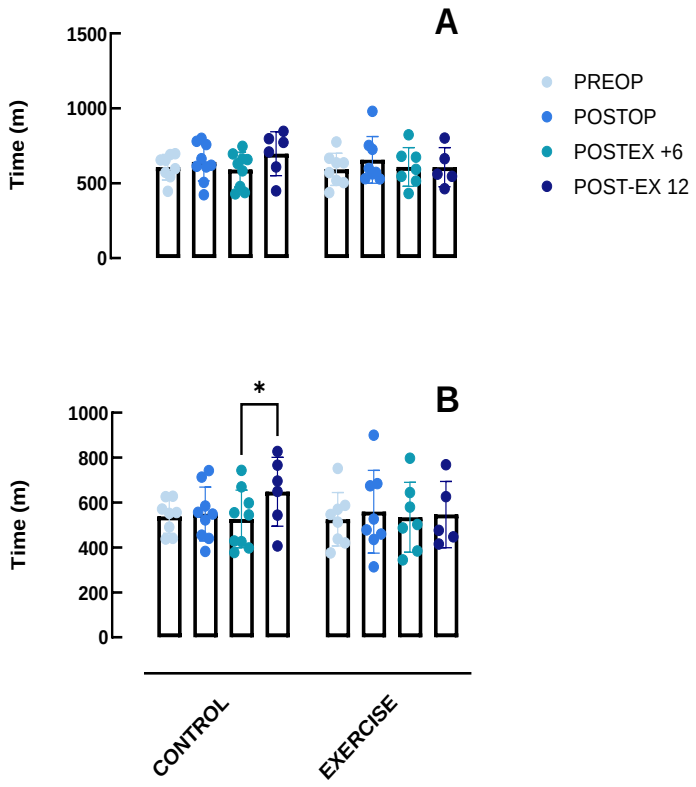


Figure 4.9. Mean sit-to-stand (STS) count at each assessment period (the preceding or following 7 days); before (pre-op) and within 6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training in or a no-intervention control group. Analysis via a mixed-effects analysis. There was no significant effect of either group (p=0.9504), time (0.7260) nor group x time interaction (p=0.692).

There was a single within-group difference between POSTEX+6 and POSTEX+12 in the control group in sitting time, as shown in Figures 4.10B (MD 89.85mins, 95% CI -176.9 to -2.809, p=0.043). There were no other group, time nor group x time interactions.



Figures 4.10A & B. Mean total sedentary (A) and sitting times (B) in minutes at each assessment period (the preceding or following 7 days); before (pre-op) and within 6-weeks of (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training in or a no-intervention control group. Analysis via a mixed-effects analysis. There was no significant effect of either group (total sedentary time: p=0.7472; sitting time: p=0.6486,), time (total sedentary time: p=0.0615; sitting time: p=0.2658) nor group x time interaction (total sedentary time: p=0.3191; sitting time p=0.5345) for either variable.

Both the control and exercise group showed a significant time difference in mean standing times (in mins). The control group had a decrease in mean standing times between the PREOP and all three subsequent timepoints (PREOP and POSTOP MD 61.44mins, 95% CI 20.65 to 82.23, p=0.0018; PREOP and POSTEX+6, MD 62.83mins, 95% CI 2.041 to 63.62, p=0.0374; PREOP and POSTEX+12 MD 69.05 mins, 95% CI 23.52 to 94.59, p=0.0019). The exercise group had an initial decrease in mean standing time from PREOP to POSTOP (MD 64.84 mins, 95% CI 21.60 to 88.09, p=0.0020), but then an increase from POSTOP to POSTEX+6 (MD -43.18 mins, 95% CI -76.83 to -9.526, p=0.0135).

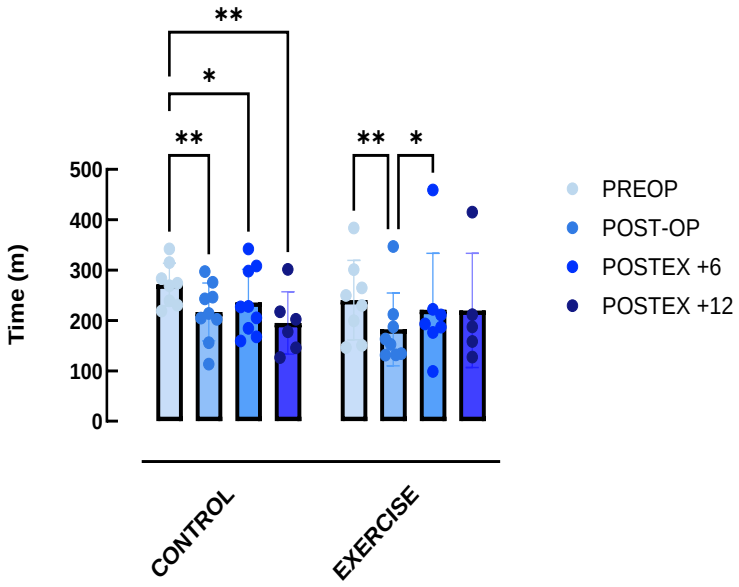


Figure 4.11 Mean standing times in minutes at each assessment period (the preceding or following 7 days); before (pre-op) and within 6-weeks of (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training or a no-intervention control group. Analysis via a mixed-effects analysis. There was a significant time effect (p=0.0003), but no significant effect of either group (p=0.5726) nor group x time interaction (p=0.2917).

4.3.3 The impact of postoperative exercise training on neuromuscular function

4.3.3.1 Maximal voluntary isometric contraction (MVC)

There was a significant effect of group (p=0.0093) and time (p=0.0438) but not a significant group x time interaction (p=0.0566). There was no significant reduction in the exercise group POST-OP compared to PRE-OP (MD 44.30N; 95% CI -26.87 to 115.5, p=0.2155) but MVC was significantly higher at POSTEX+6 compared to both PRE-OP (MD -100.2N; 95% CI -178.6 to -21.86, p=0.0135) and POST-OP (-144.5N; 95% CI -266.3 to -62.78, p=0.0010). MVC was significantly higher in the exercise group compared to control at POSTEX+6 (MD -185.5N; 95% CI -300.6 to -70.44, p=0.0021) and POSTEX+12 (MD -176.7N; 95% CI -297.2 to -56.31, p=0.0047) of intervention.

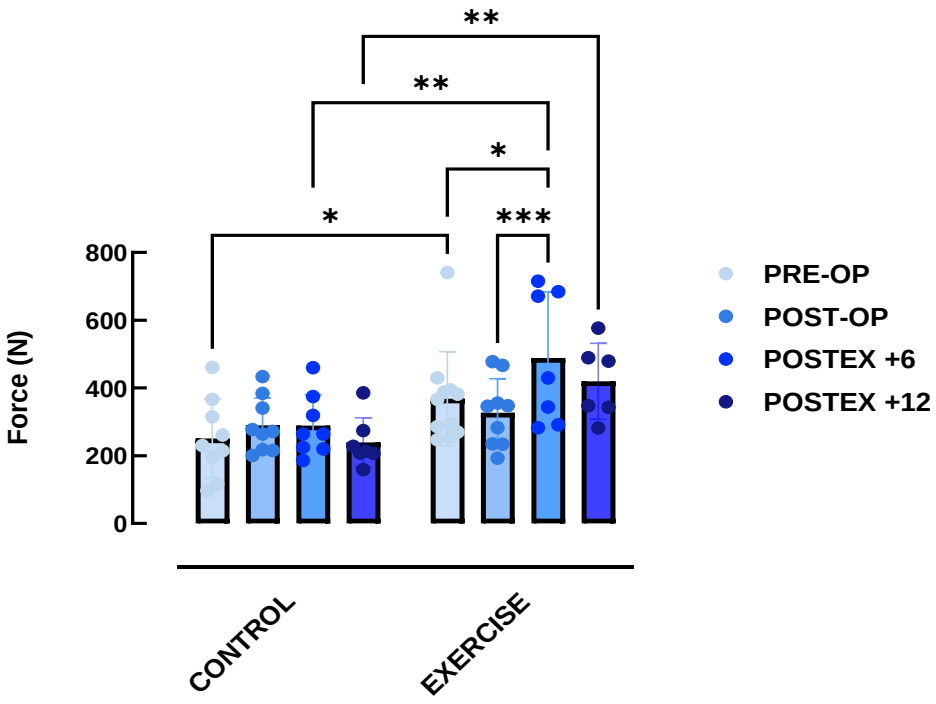


*Figure 4.12. Right vastus lateralis extensor maximal voluntary isometric contraction at each visit before (pre-op), within 6-weeks after (post-op) major abdominal surgery for colorectal cancer, after a subsequent 6 (post-ex 6) and 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training or a no-intervention control group via mixed-effects analysis. *=p<0.05, **=p<0.01.*

4.3.3.2 Force steadiness

At 10% of MVC mean force steadiness showed no significant changes for group (p=0.3280), time (0.0829) nor group x time interaction (p0.0586). No changes were seen at 40% for group (p=0.0805), time (0.8225) nor group versus time (p=0.5937). However, at 25% of MVC mean force steadiness showed a significant effect for group (p=0.0277), time (0.0324) and group versus time interaction (p=0.0191).

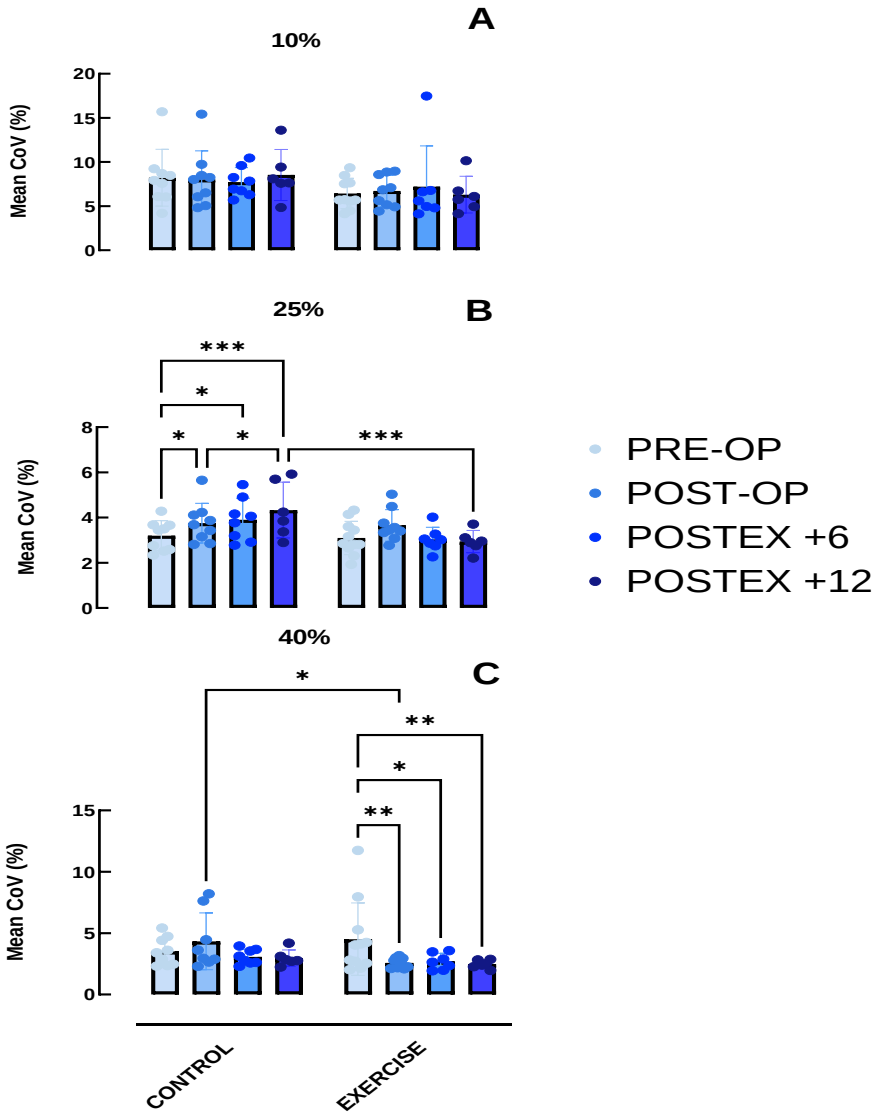


*Figure 4.13 A, B & C. Force steadiness at 10%, 25% and 40% of MVC before (pre-op) and with 6 weeks of (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training or a no-intervention control group. Mixed-effects analysis to account for missing values. *=p<0.05, **=p<0.01.*

4.3.3.3 Fatigue

For fatiguability, there was no significant effect seen in group (p=0.1081), time (p=0.4357), nor group versus time (0.3050). As seen in Figure 4.14, there was a significant reduction in time to fatiguability between PREOP and POSTEX+6 in the control group (MD 167.7s; 95% CI -25.09-310.3s, p=0.0224), although this was not maintained at POSTEX+12.

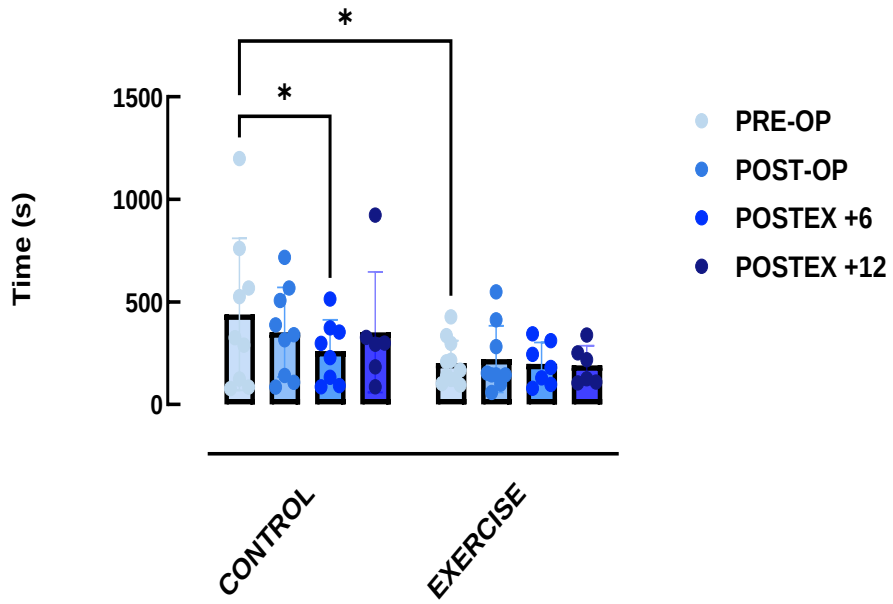
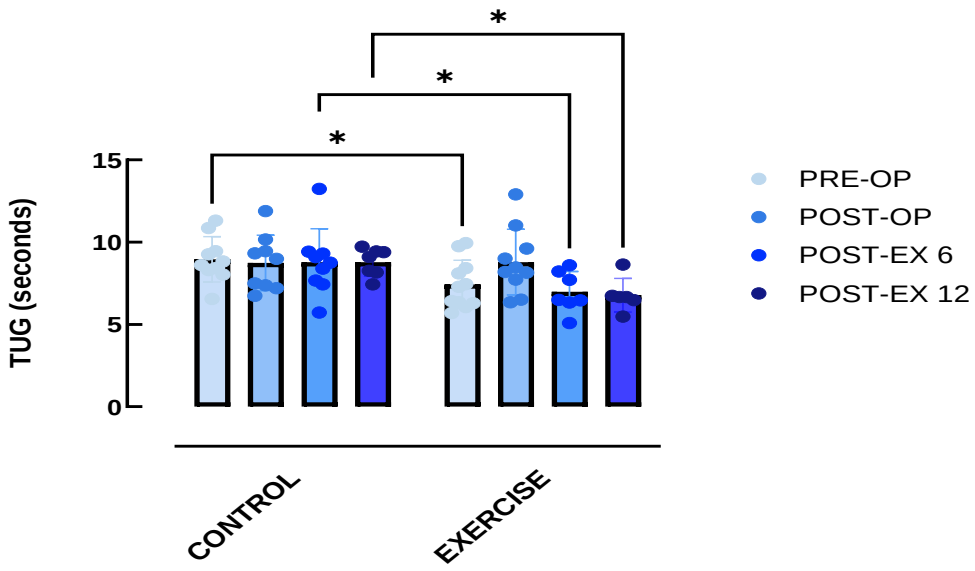


*Figure 4.14. Time to fatigue at 30% of MVC before (pre-op) and with 6 weeks of (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training or a no-intervention control group. Mixed-effects analysis to account for missing values. *=p<0.05, **=p<0.01.*

4.3.4 The impact of postoperative exercise training on physical function

4.3.4.1 TUG

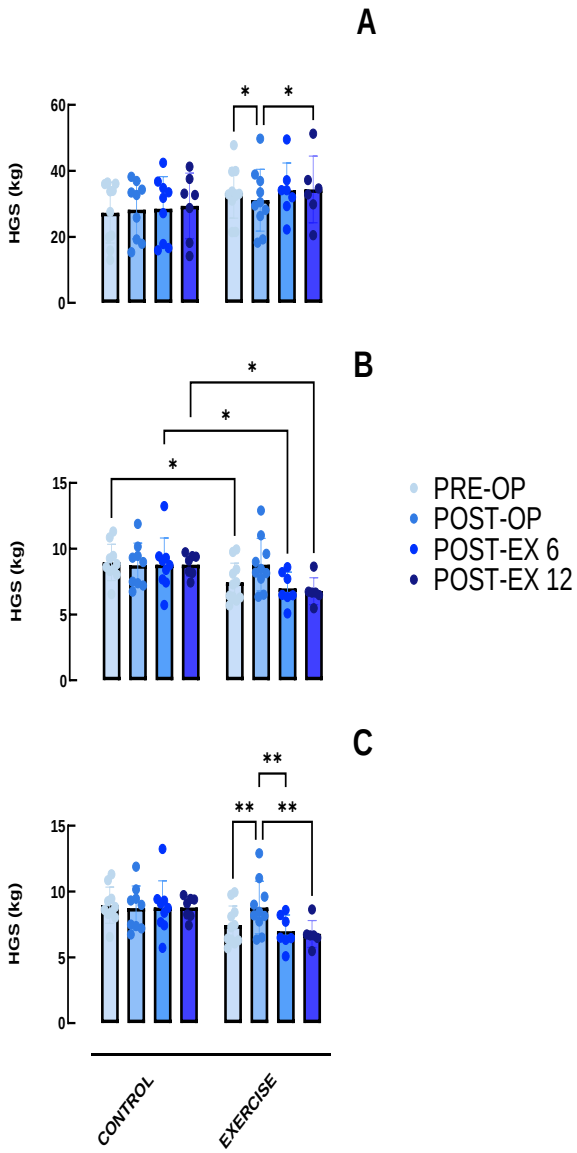
As shown in Figures 4.15a & b, within the exercise group, there was a significant effect from POSTOP to both POSTEX+6 (MD: 0.4687s; 95% CI 0.7412 to 2.847s, p=0.0016) and POSTEX+12 (MD: 0.818s; 95% CI 0.6910 to 2.944s, p=0.0022). There was a significant difference between the two groups at baseline (which normalised at the PREOP assessment day; p=0.9204), POSTEX+6 (MD: 0.898; 95% CI 0.3837 to 3.411s, p=0.0149) and POSTEX+12 (MD: 2.054; 95% CI 0.4428 to 3.665s, p=0.0133), as seen in Figures 4.15b.



*Figures 4.15a & b. Mean TUG times before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training or a no-intervention control group. Analysis via mixed effects analysis to account for missing values. *=p<0.05, **=p<0.01, ***=p<0.001. Note same dataset but split to appreciate both inter and intra-group differences There was a significant group (p=0.0294) and group versus time interaction (p=0.0344), but no significant time interaction (p=0.0730).*

4.3.4.2 Handgrip strength (HGS)

As seen in Figures 4.16A, B & CFigures 4.16, with regards to dominant HGS, there was no significant group (p=0.1342), time (0.2337) nor group versus time interaction (p0.2320). For non-dominant HGS, there was a significant group (p=0.0294) and group versus time interaction (p=0.0344) but no significant time interaction (p=0.0730).



*Figures 4.16 A,B & C. Mean HGS in the dominant (A) and non-dominant (B&C) hand before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training or a no-intervention control group. Analysis via mixed effects analysis to account for missing values. *=p<0.05, **=p<0.01, ***=p<0.001. Note for non-dominant HGS, same dataset but split to appreciate both inter and intra-group differences.*

4.3.4.3 6MWT

For overall distance in the 6MWT, there was a significant effect in both group (p=0.0433) and time (p=0.0002), but not group versus time (p=0.0586). For average speed, there was a significant time effect in the exercise group (p=0.0002) and group versus time interaction (p=0.0043).

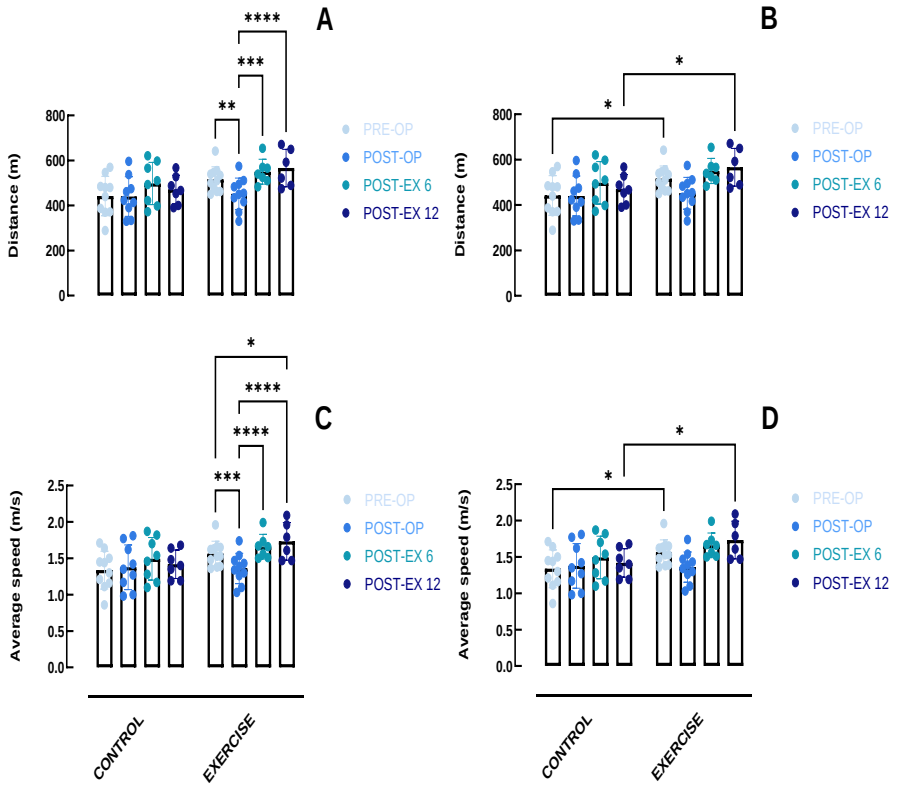


*Figure 4.17. 6MWT total distance (A&B) and average speed (C&D) before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training (exercise) or a no-intervention control group. Analysis via mixed effects analysis to account for missing values. *=p<0.05, **=p<0.01, ***=p<0.001. Note same dataset but split to appreciate both inter and intra-group differences.*

4.3.4.4 SPPBT

As shown in Figure 4.18, there was a significant time effect in the exercise group in the SPPBT scores (p=0.0054), but no significant group (0.1625) or group versus time interaction (0.4199).

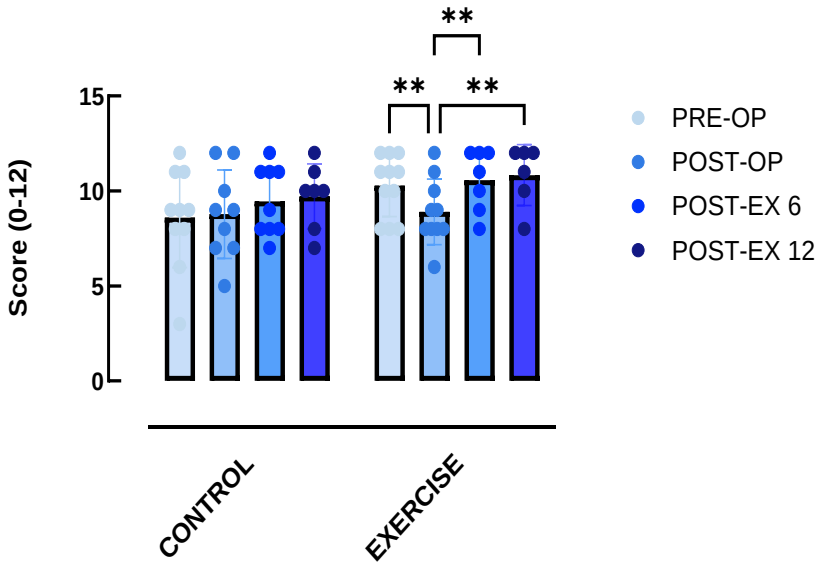
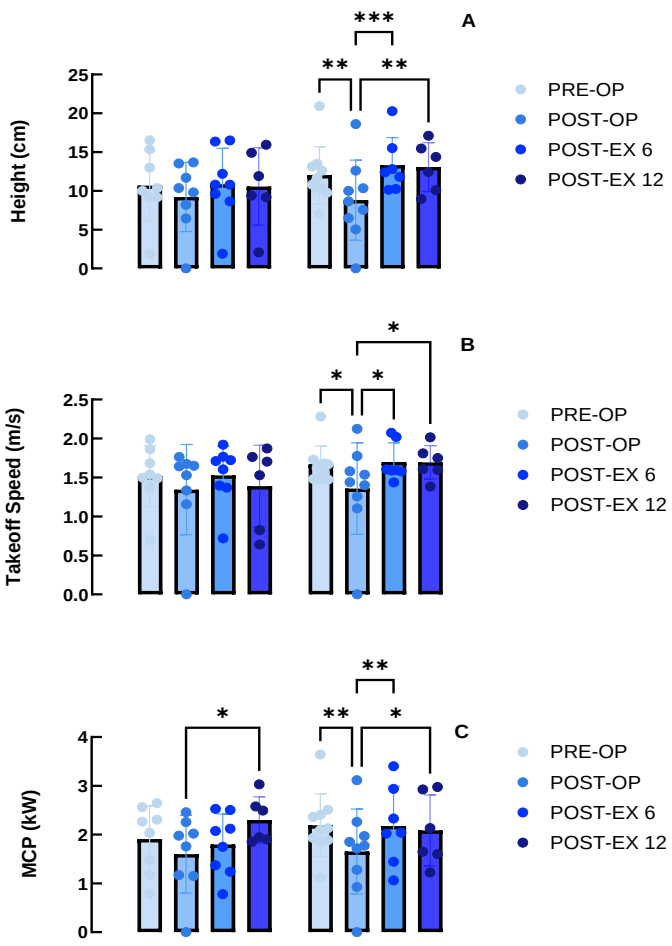


*Figure 4.18 Short Performance Physical Battery Test (SPPBT) scores before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training (exercise) or a no-intervention control group. Analysis via mixed effects analysis to account for missing values. *=p<0.05, **=p<0.01, ***=p<0.001.*

4.3.4.5 Counter Movement Jump

For counter movement jumps, Figures 4.19A, B &C shows the observed differences, most notably seen within the exercise group. For height, there was a significant time effect seen (p=0.0034), most notably between the post-op and POSTEX+6 (p=0.0004) and POSTEX+12 (p=0.0024) timepoints in the exercise group. A time effect was also seen for both take-off speed (p=0.0276) and MCP (p=0.0050). There was a significant difference between POSTOP and POSTEX+12 for both the control (p=0.0465) and exercise (p=0.0225) group; there was a difference seen in the exercise group between POSTOP and POSTEX+6 as well (p=0.0074).



*Figures 4.19A, B & C. Counter movement jump height measurements (A), take off speed B) and mean concentric power (C) before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training (exercise) or a no-intervention control group. Analysis via mixed effects analysis to account for missing values. *=p<0.05, **=p<0.01, ***=p<0.001.*

4.3.5 The impact of postoperative exercise training on quality of life

4.3.5.1 DASI scores

The DASI scores demonstrated a significant time effect (p=0.0001), but no significant group (p=0.5875) or group versus time interaction (p=0.2209). As expected, both groups demonstrated a significant difference between the preop and postop scores (control: MD 9.434, 95% CI 0.08558 to 18.78, p=0.0482; exercise: MD 14.72; 95% CI 10.43 to 19.01, p<0.0001). The exercise group showed a significant difference from POSTOP to POSTEX+6 (MD -9.539, 95% CI -15.57 to -3.512, p=0.0062) and POSTEX+12 (MD -12.37, 95% CI -19.55 to -5.182, p=0.0054). The control also had a smaller but significant difference from POSTOP to POSTEX +6 (MD -7.694, 95% CI -13.73 to -1.655, p=0.0176), but not at POSTEX+12 (MD -0.5185, 95% CI -9.527 to 8.490, p=0.9962).

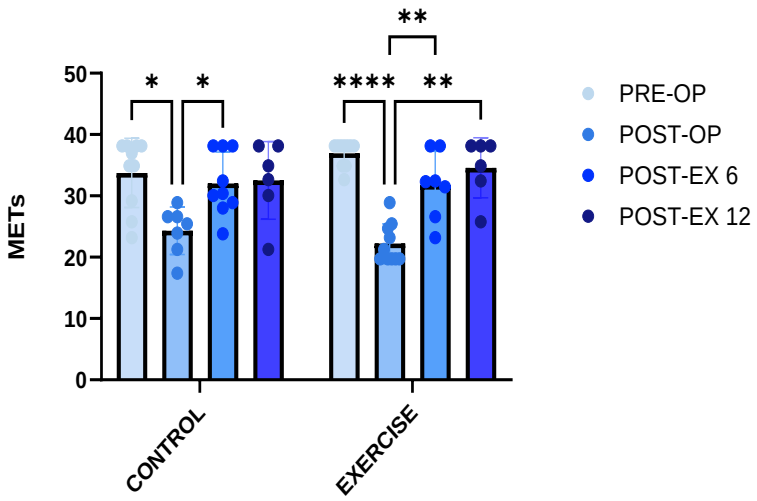


*Figure 4.20. Mean MET scores as calculated from completion of the DASI questionnaire before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training (exercise) or a no-intervention control group. Analysis via mixed effects analysis to account for missing values. *=p<0.05, **=p<0.01, ***=p<0.001.*

4.3.5.2 IPAQ scores

There was no group (p=0.8904), time (p=0.1521) nor group versus time (p=0.2915) interaction with IPAQ scores.

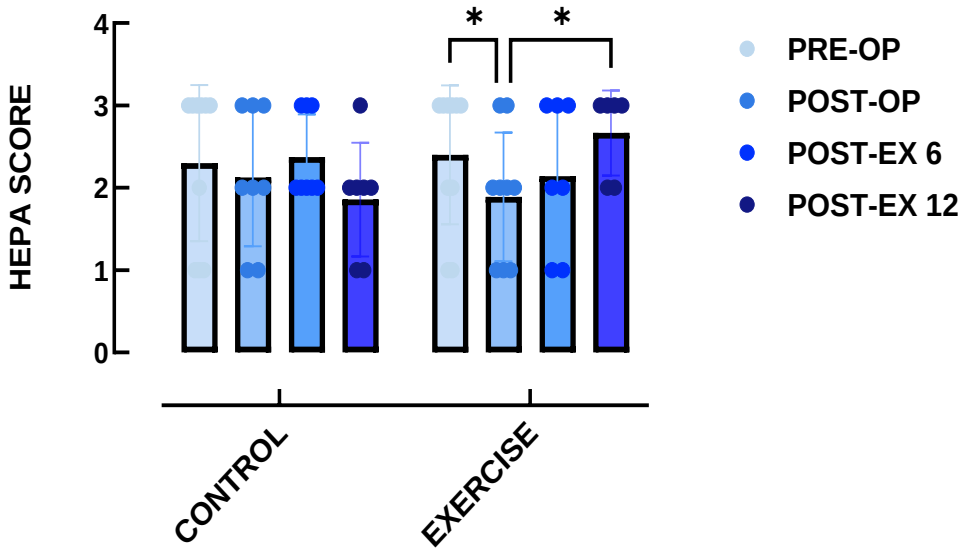


*Figure 4.21. Mean HEPA scores as calculated from completion of the IPAQ questionnaire before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training (exercise) or a no-intervention control group. In the exercise group, there was a significant difference in scores from POSTOP to POSTEX+12 (MD 0.6502, 05% CI -1.264 to -0.03625, p=0.0385). Analysis via mixed effects analysis to account for missing values. *=p<0.05, **=p<0.01, ***=p<0.001. HEPA; health-enhancing physical activity.*

4.3.5.3 EORTC-QLQ C30

The results of the EORTC-QLQ C30 questionnaire are shown below. For QoL and functioning scales, a higher score is associated with increased QoL/higher level of functioning. For symptom scales, a higher score is associated with worse/more severe symptomology.

4.3.5.3.1 Global Health Status/QoL

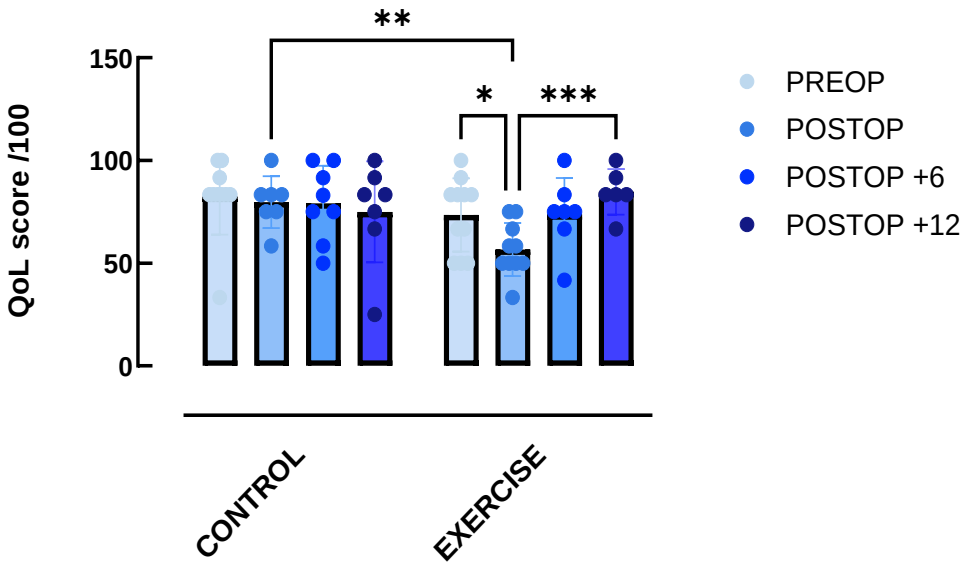


*Figure 4.22. EORTC QLQ-C30 QoL scores before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training (exercise) or a no-intervention control group. A higher score is indicative of a high/healthy level or QoL. Analysis via mixed-effects analysis to allow for missing values. *=p<0.05, **=p<0.01, ***=p<0.001.*

4.3.5.3.2 Functional Scales

Within the EORTC QLQ-C30, there were some significant differences noted in some of the different domains (see Figure 4.23).

Role functioning

In the exercise group there were significant differences seen between PREOP and POSTOP timepoints (MD 65.91, 95% CI 47.62 to 84.21, p<0.0001). There was also a significant difference between the POSTOP scores and both post-intervention timepoints (POSTOP vs POSTEX+6: MD, -60.56 95% CI -81.35 to -39.77, p<0.0001; POSTOP vs POSTEX+12: MD -66.29, 95% CI -88.16 to -44.42, p<0.0001).

Within the control group, there was a significant difference noted between the PREOP and POSTOP timepoints only (MD 24.65, 95% CI 4.720 to 44.58, p=0.0166). At the POSTOP timepoint, there was a significant difference between the two group (MD 45.20, 95% CI 24.10 to 66.30, p<0.0001).

Emotional functioning

In the control group, there was a significant difference between the POSTOP and POSTEX +12 timepoints (MD 6.211; 95% CI, p=0.0357). In the exercise group, there were differences between the start of intervention and both the 6 and 12 weeks timepoints (POSTOP vs POSTEX+6: MD -16.56; 95% CI -29.65 to -3.474, p=0.0146; POSTOP vs POSTEX +12: MD -16.73; 95% CI -30.47 to -2.985, p=0.0184). Both inter-group differences were observed prior to the start of intervention in the exercise group (PREOP- CON vs EX: MD 13.94; 95% CI, p=0.0216; POSTOP- CON VS EX: MD 26.01; 95% CI 12.70 to 39.33, p=0.0003)

Physical functioning

There were no differences seen within the control group with regards to physical function. Within the exercise group, there was a significant decrease in scores between the PREOP and POSTOP timepoints (MD

26.02; 95% CI 16.39 to 35.65, p<0.0001), and increases between the POSTOP and POSTEX+6 (MD -26.65; 95% CI -37.57 to -15.73, p<0.0001) and POSTEX+12 (MD -1.535; 95% CI -13.80 to -16.71, p<0.0001) timepoints.

Social functioning

There were no within-group differences in social functioning seen in the control group. The exercise group demonstrated significant differences between the PREOP and POSTOP (MD 50.27 95% CI 31.15 to 69.39, p<0.0001), POSTOP and POSTEX +6 (MD -59.04 95% CI -80.73 to -37.35, p<0.0001) and POSTOP vs POSTEX+12 (MD -57.46 95% CI -80.26 to -34.66, p>0.0001) timepoints.

Cognitive functioning

There were no group (p=0.3481), time (p=0.4973), nor group x time (p=0.7363) interactions with regards to cognitive functioning.

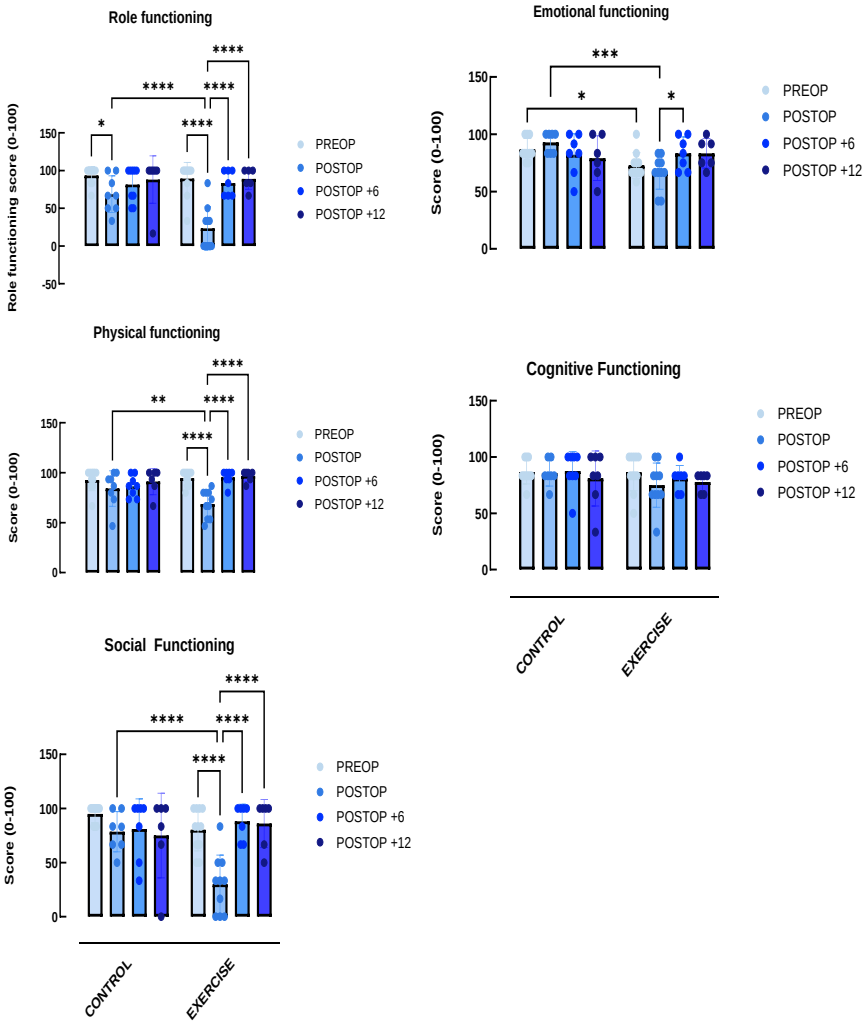


*Figure 4.23. EORTC QLQ-C30 Functional scale scores before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training (exercise) or a no-intervention control group. A higher score is indicative of a high/healthy level of functioning. Analysis via mixed-effects analysis to allow for missing values. *=p<0.05, **=p<0.01, ***=p<0.001.*

4.3.5.3.3 Symptom Scales

Symptom scale scores showed mixed results (see Figure 4.24).

Nausea and vomiting

For nausea and vomiting, the exercise group had a significant PREOP vs POSTOP difference, which was the only significant finding (MD -6.667 95% CI -12.92 to -0.4161, p=0.0372).

Fatigue

There were no significant within-group differences in the control group at any timepoint. In the exercise group, there was a significant difference in scores between the PREOP and POSTOP (MD -33.87 95% CI -51.13 to -16.60, p=0.0003), POSTOP and POSTEX +6 (MD 31.13 95% CI 11.60 to 50.66, p=0.0026) and POSTOP and POSTEX+12 (MD 35.29 95% CI 14.80 to 55.79, p=0.0013) timepoints. There was a significant between-group difference seen at the POSTOP (MD -20.07 95% CI -39.02 to -1.132, p=0.0382) and POSTEX+12 (MD 26.34 95% CI 2.176 to 50.50, p=0.0332) timepoints.

Pain

There were no significant differences for pain scores in group (p=0.7049), time (p=0.1155), nor group x time (p=0.4593).

Dyspnoea

Dyspnoea scores were significantly different within the control group only at a single interval, with a PREOP to POSTOP significant difference observed (MD -12.76; 95% CI -24.38 to -1.138, p=0.0323).

Sleep

Sleep scores were significantly different within the control group only at a single interval, with a POSTOP to POSTEX+12 significant difference observed (MD -40.42; 95% CI -66.96 to -13.88, p=0.0338).

Appetite

There were no significant differences seen in appetite scores in the control group. Within the exercise group, the major difference was seen between the POSTOP and POSTEX+12 timepoints (MD 29.31, 95% CI 8.295 to 50.32, p=0.0075). There was a difference seen between the groups at the POSTOP timepoint only (CON vs EX: MD -25.29, 95% CI -45.16 to -5.414, p=0.0136).

Constipation/Diarrhoea

Constipation scores differed significantly in the exercise group, with a higher score (more constipation) seen in the POSTOP timepoint compared to PREOP (MD -20.81, 95% CI -38.96 to -2.669, p=0.0257). The scores decreased significantly from POSTOP to both POSTEX+6 (MD 21.20, 95% CI 0.6198 to 41.79, p=0.0438) and POSTEX +12 timepoints (MD 3.883 to 47.16, p=0.0220).

With regards to diarrhoea, there was a significant difference in scores between the control and exercise groups at the POSTOP timepoint only (MD -25.33 95% CI -49.73 to -0.9217, p=0.0422).

Financial difficulties

There were no group (p=0.376), time (p=0.4953), nor group x time (p=0.2248) effects seen in the financial difficulties subscale scores.

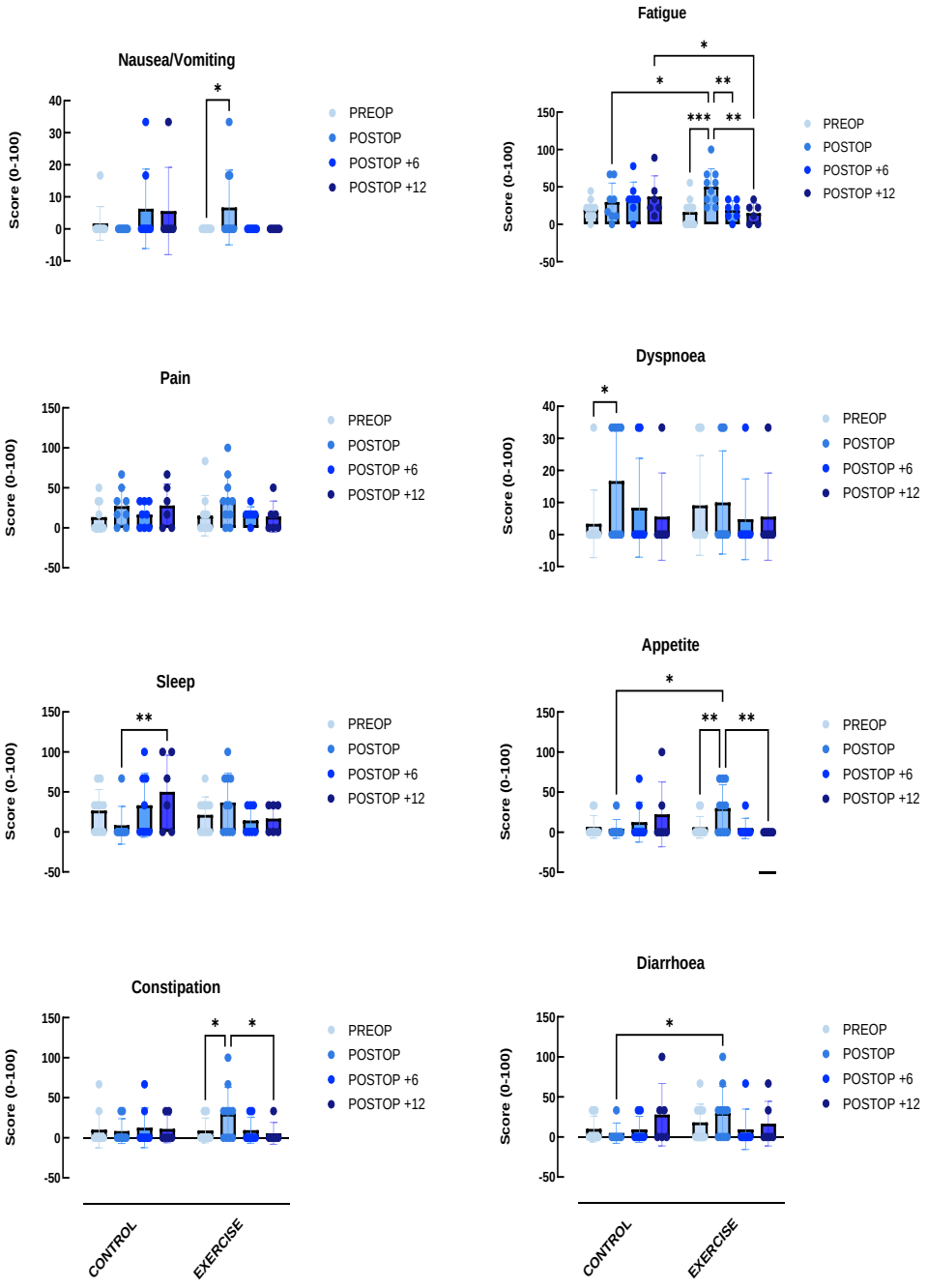


*Figure 4.24. EORTC QLQ-C30 symptom scale scores before (pre-op) and ~6-weeks after (post-op) major abdominal surgery for colorectal cancer, and after a subsequent 6 (post-ex 6) or 12-weeks (post-ex 12) of mixed modality (aerobic and resistance) exercise training (exercise) or a no-intervention control group. A higher score is indicative of more severe symptomology. The symptom scale "Financial difficulties" was removed as there were no differences in values from baseline. Analysis via mixed-effects analysis to allow for missing values. *=p<0.05, **=p<0.01, ***=p<0.001.*

4.3.6 Acceptability and enjoyment of postoperative exercise training

4.3.6.1 Adherence to resistance sessions

Patients were asked to do and perform a minimum of 2 sessions and maximum of 3 sessions a week as detailed in Appendix 7.10.1.

Study ID	***Week***											
	1	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***
KS01	>70	>70	>70	>70	>70	>70	-	-	-	-	-	-
KM04	67	33	67	100	67	67	0*	67	33	0	33	71
CB11	-	-	-	-	-	-	-	-	-	-	-	
PH16	0	100	95	90	86	43	81	100	-	-	-	-
EJ17	>70	>70	>70	>70	>70	>70	-	-	-	-	-	-
MB18	100	100	100	100	100	100	100	100	100	100	100	100
DL20	100	100	67	67	100	67	67	100	67	100	67	100

*Table 4.5. Adherence rates (%) of participants to the resistance sessions in the exercise programme. 100% adherence was the completion of all 7 exercises 3 times in that week. 67% was the completion of the minimum of 2 sessions of all 7 exercises in one week. *KM04 developed pain and bleeding during week 7 which meant she temporarily halted exercise. KS01 & EJ17 did not return their resistance diaries at the end of the programme, but it was checked at A3 to ensure at least 70% compliance. CB11 was excluded due to lack of completion of the resistance exercises.*

4.3.6.2 Adherence to aerobic exercise sessions

Study ID	Week											
	1	2	3	4	5	6	7	8	9	10	11	12
KS01	100	100	100	100	100	87	80	67	100	100	100	100
KM04	100	100	100	100	100	100	100	100	100	100	100	60
TS08	100	100	100	100	100	100	100	100	100	100	100	100
CB11	100	100	100	100	100	100	100	-	-	-	-	-
PH16	100	100	100	100	100	100	100	100	-	-	-	-
EJ17	>70	>70	>70	>70	>70	>70	-	-	-	-	-	-
MB18	100	100	100	100	100	100	100	100	100	100	100	100
DL20	100	100	100	100	100	100	100	100	100	100	100	100

Table 4.6. Adherence rates (%) of participants to the minimum weekly aerobic requirements of the exercise programme. 100% adherence was the completion of all 150 minutes of moderate or 75 minutes of vigorous exercise per week. Excess activity was recorded but not input. EJ17 did not return their aerobic diary at the end of the programme, but it was checked at A3 to ensure at least 70% compliance.

4.3.6.3 End of study Exercise Programme Feedback Questionnaire

6 participants completed an end of exercise programme feedback questionnaire. This was a Likert 5-point scale design that was given to the patient at the final assessment day. The results are seen in Figure 4.25.

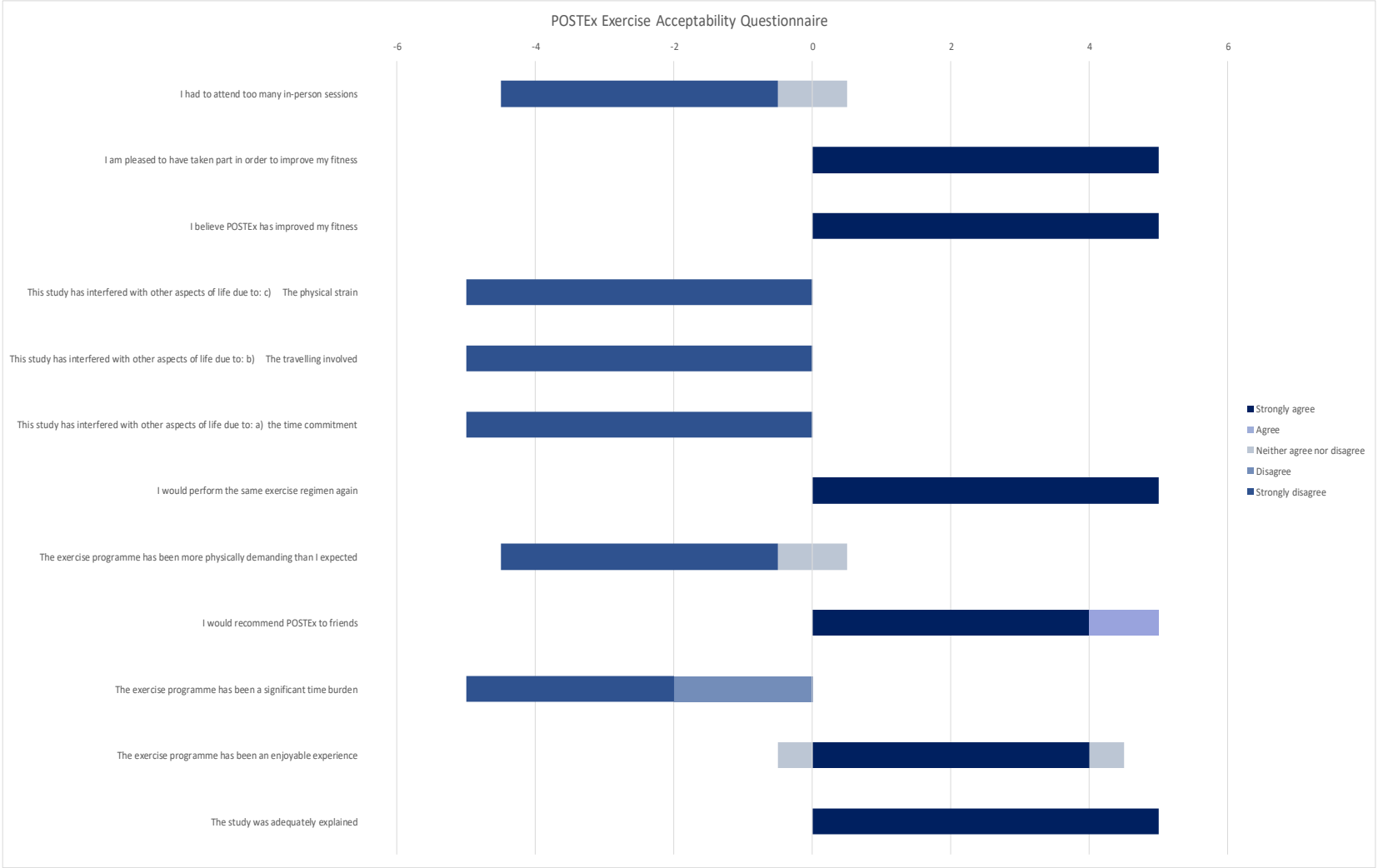


Figure 4.25. Exercise Acceptability Questionnaire. The questions were purely in relation to the exercise component of the study, not feedback on the study as a whole.

4.3.7 End of study Exercise Semi-Structured Interview

The semi-structured interview was introduced as a late amendment to the original protocol. The three remaining participants in the exercise group at the time of approval were invited to interview, 2 agreed to take part. Excerpts from both interviews are shown below when asked about various aspects of the programme (see Appendix 6.7.7).

The overall feedback was excellent from both participants, with one participant calling the exercise programme "*phenomenal. Genuinely*". Both participants reported an adequate level of information about the exercise programme prior to starting. One participant stated *"I knew what I was going to do. Yes. So it was sufficient",* and the other said *"It was very clear.*" With regards to the frequency and setup of the check-ins, both were again happy with how they had been conducted. One participant said that they acted as "*a good nudge*". Both were happy with remote contact, not preferring face-to-face and that the video was "*quite well illustrated actually".* The other participant did acknowledge the social advantage to in-person sessions, saying, *"It would have been nice from a sociability or encouragement perspective, but it wouldn't have changed the training I was doing or how much training it probably just might have might have made it slightly easier to stick with it".* When exploring the idea of a purely virtual programme, one said, "*So I think it was the interaction bit which was probably the key differentiator. As I said, if it's just been do this exercise and then log it on an app. I'd have done it, but it would have felt extremely different and much less good."*

Positive aspects of the programme given as examples from both participants. One participant stated *"if I hadn't had to do this programme with you, I wouldn't be at the fitness levels I am now*," and the other said, *"I think the exercise themselves are quick, easy….probably the biggest positive for me was the fact it was something to focus on"*. In terms of negative aspects, one participant talked about maintaining motivation between the check-ins, *"I think the periods between the check ins were probably the slightly harder to stay motivated and actually towards the end. Weirdly it got a little bit harder to stay motivated."* From a more

practical aspect as well, they remarked on the resistance bands, saying "*the bands themselves sometimes are quite hard on the hand."* Both participants stated that they would recommend the programme when asked, with one saying *"I've told all my mates up at the up at the football and the rugby club said if you ever want, you know, an incentive after an operation, this is it"*, and the other saying "*Absolutely yes*.

4.4 Discussion

The POSTEX study has shown, despite lack of power due to recruitment (which will be discussed later), some positive associations between postoperative exercise and functional, physiological and qualitative improvements. The lack of significant difference in $VO2_{AT}$ is unsurprising, as, during the various time points, some patients struggled to achieve their anaerobic threshold due to existing co-morbidities (e.g. knee osteoarthritis) which limited comparison. Adjuvant chemotherapy in both groups likely further reduced the ability to exceed baseline. This does not represent the whole picture, however, when looking at individual improvements, there are some patients who have clearly made significant improvements on their baseline. For example, four participants in the exercise group had an absolute VO_2 max increase at POSTEX+12 compared to their PREOP VO_2 max values. With regards to VO_2 peak, there is an enhanced postoperative effort seen only in the exercise group (p=0.0013). This may be explained by a perceived subjective effort increase, which is supported by the improvement seen in max wattage at the same timepoints. Participation in regular exercise may increase the confidence of participants, empowering them to feel more able to exert themselves more to reach their perceived maximum, hence the significant improvement in VO_2 peak seen between POSTOP and POSTEX+6 in the exercise group (MD 3.075ml/min/kg; 95% CI -5.442 to -0.7074, p=0.0123), despite there not being a significant overall effect between the two cohorts (p=0.3283). During the end of study interview, one participant who did regular exercise prior to study enrolment said the following:

Me: *"Knowing that you were coming into this study, did it change the exercise that you did before your operation or not?"*
POSTEXMB18: *Yeah. Yes.*
Me: *In what way?*

POSTEXMB18*: More intense, more what you've done was more intense than what I've been doing before.*

Another potential benefit of the programme was that some participants increased their activity levels even above baseline, as it helped them to see how they could really push themselves, even outside of a rehabilitation model, and may account for the VO_2 peak changes.

The effect on MVC in both group (p=0.0093) and time (p=0.0438) and good adherence rates to the resistance component of the programme infer a beneficial effect of regular resistance training in the postoperative period. In a cohort of middle-aged and older healthy previously inactive adults who performed twice weekly resistance training sessions over the course of 8 weeks, Marcos-Pardo *et. al* found an improvement in bilateral MVC (p<0.001) (Marcos-Pardo et al., 2024.) It should also be noted that although the group versus time interaction did not reach statistical significance (p=0.057), there was an absolute value difference that was notable. As with the rest of the study, increased recruitment is key in investigating this potential difference further. Force steadiness improvements seen at 25% of MVC (which is roughly equivalent to the amount of force required for many activities of daily living) are encouraging, as benefits seen at that level may better translate to an increased ability to perform normal ADLs for patients.

The effect of training on muscle fatiguability is encouraging. Muscle fatigue is seen in the post-cancer state (Prinsen et al., 2015) as well as a result of ageing itself (Merletti et al., 2002), so whether it is possible to attenuate its effect through physical activity is an important factor to consider. Time to fatigue was preserved in the exercise group throughout both post-intervention timepoints, whereas in the control group there was a significant difference from PREOP to POSTEX +6 (MD 167.7s; 95% CI 25.09-310.3s, p=0.0224). The significant difference between the two groups at baseline (p=0.0255) is likely due to a single participant in the control group who was able to contract for nearly twenty minutes at 30% of his MVC, which was considerably lower than expected. His

strength/endurance mismatch was attenuated slightly at the subsequent assessment points, hence the significant effect seen at the first timepoint only.

The functional results seen in the POSTEX study also seem to support a positive effect of postoperative exercise. When looking at the 6MWT, within the exercise group there was a clear increase in time between the PRE-OP and POST-OP timepoints in the exercise group ($p=0.0014$) which improved at both post-intervention timepoints (POSTEX +6 $p=0.0001$, POSTEX+12 $p<0.001$) and showed a non-significant change from baseline (PRE-OP to POSTEX+12, $p=0.4069$) by the end of the study. A similar pattern was also seen in the short performance physical battery test results (see Figure 4.18) but was in both cases not seen in the control group. A previous study by Boereboom *et. al* showed a significant negative correlation between TUG time and anaerobic threshold derived via CPET ($r=-0.317$, $p<0.0001$) and TUG and VO_2 peak ($r=-0.4247$, $p<0.0001$) (C. L. Boereboom et al., 2021). The significant changes seen in TUG times between the groups at both post-intervention timepoints with no significant POST-OP difference (POSTEX +6: MD 0.898s; 95% CI 0.3837 to 3.411s, $p=0.0149$; POSTEX +12: MD 2.054s, 95% CI 0.4428 to 3.665s, $p=0.0133$) infer that the programme has had some benefit in improving patients' performance, which may relate to a cardiorespiratory as well as functional improvement. For handgrip strength, non-dominant outcomes showed a significant group versus time interaction ($p=0.0344$) which was not replicated for dominant HGS scores ($p=0.2320$). The reasons for this are not immediately clear, but a possibility may be that by doing regular exercise, there is an increased training effect of the non-dominant side that may have previously not been targeted, even in participants who did regular exercise prior to joining the programme.

The within-group improvements in QOL in the exercise cohort are encouraging, but they have a significantly worse post discharge quality of life perception. There is a previously recognised need for identifying not just symptom burdens in patients with CRC, but more nuanced

psychological concerns such as problems in cognitive and functional roles (Miniotti et al., 2019). The reason(s) for this are not clear, but in knowing intervention is about to start, there may be some unconscious perception of worse quality of life to justify a future difference. For role functioning, physical and sole functioning, the exercise group results follow a trend showing a possible role of the intervention improving these scores over time, that is not seen in the control group. However, the other (unintended) intervention aside from exercise in the POSTEX group was the regular check-ins. Although the control group had access to any advice if they required, the active monitoring of the exercise group added a psychosocial intervention. This makes direct assumptions of the role of exercise on the QoL outcomes difficult, although the differences seen between the control and exercise groups mean it is less likely that they are attributable to being in the study itself.

The major limiting factor of the study restraining the significance of the results was the inability to achieve full recruitment numbers. Two patients withdrew from the study before attending the postoperative baseline visit (A2), 3 withdrew prior to the 6-week assessment (A3) and a further 3 withdrew prior to the final study visit (A4). Table 4.4 gives the reasons for withdrawal. This pattern is also seen in the role functioning, physical function, and to A3, in the emotional functioning scales, but not seen in the physical symptom domains. The low overall numbers limit the concrete messages from the results, but do give an idea of why.

Engagement was generally good for those who opted to take part, with only a few issues with non-responses. One participant however did respond but at the A3 assessment day it became evident that the exercise stated was not in line with the programme (no resistance component documented) despite prior check-ins and so he was excluded at that point. Mandatory single visits to observe a training session within the first few weeks of the programme is a potential way to combat this, although all participants were offered the option to attend/have an in-person assessment if anything needed clarification that could not be resolved over the phone. It was also encouraging to see that no patients

withdrew **during** their adjuvant chemotherapy because of the treatment itself; the assessment visits were altered to allow the assessment visits to take place as close to their next infusion date as possible (i.e. to allow them to recover symptomatically as much as possible).

The aerobic component of the programme was based on time and a participant's ability to distinguish the difference between moderate and vigorous activity. On review of the aerobic exercise diaries they were generally appropriately recording activities at the correct intensity, but some participants continued to do moderate exercise only throughout the whole of the programme length, reducing the potential for aerobic improvements as time progressed by increasing the frequency of intensive exercise. This may help explain the lack of difference in the aerobic physical activity parameters and the CPET results between the exercise and control groups. On reflection, introducing a minimum amount of vigorous activity per week, increasing stepwise throughout the programme would help to ensure that participants are continuing to push themselves to improve. This would also improve adherence to the aerobic component of the study.

It is difficult to attribute a single aspect of the programme to the significant differences in reported functional outcomes, however the resistance aspect appeared to be more feasible. This showed a relatively good adherence rate (see Table 4.5) and was easy to initiate with the video demonstrations that patients could refer to. The low cost of the bands, even when patients moved up through the different strengths, made this a cost-effective method of providing resistance training that could be used by patients within the normal NHS pathway; given at any point from clinic to discharge with the link to the video.

The use of telemedicine would be another potential way to improve both monitoring and data acquisition. Previous studies have used apps for post-operative participants to upload data as well as for monitoring (Patel & Thind, 2020). Real-time feedback may help to reduce the rate of withdrawal rather than waiting until the next assessment to assess

compliance. In-hospital exercise visits were also considered but given the difficulties around logistical issues such as parking and transport, home-based exercise was preferred. When speaking to potential participants in the recruitment phase, they often asked re: the location of exercise, saying that reduced hospital visits would be preferable to in-hospital supervised sessions.

The major disappointments of this study were lack of recruitment and retention of patients after approximately 6 weeks. If looking to modify this programme to make it more successful as a study, another possibility for recruitment into a postoperative rehabilitation programme would be in the postoperative period. This could be whilst still an inpatient or in the early days post discharge. It can be difficult for potential participants to face having to take on another potential burden during the stressful preoperative period, especially when coming to terms with a difficult diagnosis. At 6 weeks, significant improvements were seen in many of the functional parameters as well as in EMG, so a reduction in the length of the regimen could be another possibility. There was also a lack of diversity in recruitment, with 100% of participants identifying as Caucasian. This is a widespread problem in trial recruitment, with multifactorial reasons (Nouvini et al., 2022). The study participants were not reflective of the local population's ethnic diversity and more does need to be done in order to remedy this, perhaps by recruiting a more diverse PPIE group to collate ideas to improve this (Oyer et al., 2022). Specialist physiotherapy input in study design could have potentially helped to improve the aerobic exercise regimen; both to incorporate an increase in intensity, and to perhaps make it more stimulating in later weeks to keep the interest of the participants. Also, recruitment at the start of a healthcare professional to embed the qualitative interviews into the study more effectively would have been useful, although this was a late amendment to the original study plan. Considering this as an option during the original study design process would have ultimately made it more successful.

In summary, patients have found it beneficial to undergo a structured postoperative exercise rehabilitation regime, not only in helping to regain their fitness but to give them a sense of confidence in restarting physically exertive movements earlier than they may have done otherwise. With the reduction in face to face postoperative follow up and a move away from routine in-person clinic check-ups after discharge, it can be difficult for patients to accurately gauge when they can (re)start more moderate and vigorous activity. This can potentially further decondition them at a time when they have had a significant physiological insult. Although there is a lack of clear conclusions that can be drawn from the study itself due to insufficient numbers to power the study, those who did complete the study in both groups reported extremely positive feedback and felt it was a useful adjunct to their postoperative rehabilitation. There would be value in continuing the study to full recruitment numbers to see if the effects outlined here are seen at full power. The POSTEX study shows that a 12-week exercise programme is feasible and can be run without the need for significant cost outlay and even if adjuvant chemotherapy is required, but does need regular and sustained support for patients, as well as a main point of contact for any potential problems.

5 Thesis Discussion

5.1 Summary of findings

Overall colorectal cancer incidence is rising and is also increasing in slightly younger age groups (Morgan et al., 2023). The focus historically has been (quite appropriately) on reducing the perioperative risks associated with surgery by modifying both systemic and surgery associated factors. For example, minimally invasive approaches have been developed and implemented (Kolarsick et al., 2020), and optimisation of patient-related factors, via comprehensive preoperative assessments, improvement of existing conditions, and prehabilitation to improve cardiorespiratory function prior to surgery, have come to the fore (Souwer et al., 2018). However, to look solely at reduced complications, morbidity and mortality which has largely been the focus to date, generates an incomplete picture. Patients report struggling to achieve their baseline level of function up to 2 years after surgery (Reudink et al., 2022), and in some cases, cannot return to work for a prolonged time, if ever (Zhang et al., 2022). During the postoperative follow-up period, there are potential opportunities to give good quality evidence-based advice to patients. Therefore, it is vitally important as holistic clinicians that we drive more research into post discharge exercise rehabilitation, not least because some patients may also require adjuvant treatment, and exercise has been shown to help with chemotherapy-related symptom burden (Adamsen et al., 2003; Andersen et al., 2006; Nakano et al., 2018), reduce hospitalisation rates (Mijwel et al., 2020) and to a lesser extent improve completion rates (Courneya et al., 2007).

Via a systematic review, **chapter 2** of this thesis sought to clarify the previous evidence for postoperative exercise rehabilitation in patients with intra-abdominal cancers. Generally, the overall evidence showed that it is both feasible and safe, but the paucity of good quality RCT's limited the amount and certainty of conclusions that could be drawn with regards to the improvements made over normal care. The heterogeneity

of the studies included also limited multi-variate analyses. Using structured, consistent guidance to design and report on (postoperative exercise) interventions in studies going forward (such as that recommended by the TiDIER template (Template for Intervention Description and Replication)) (Hoffmann et al., 2014) will help to generate evidence that can be critiqued in a more robust manner. The primary finding of this systematic review, that postoperative exercise is both feasible and safe for patients with intra-abdominal cancers (Paul et al., 2023), informed the decision as to why the subsequent intervention study (POSTEx) was designed as a RCT rather than another feasibility trial.

Prior to exploring the impact of a postoperative exercise intervention study, **chapter 3** of this thesis sought characterise the baseline physical activity patterns of intra-abdominal cancer patients prior to their perioperative period. This observational research exercise showed that there is a significant heterogeneity in levels and profiles of physical activity across this patient cohort, seemingly due to multiple factors such as comorbidities, disease symptomology (i.e., positive screening results in asymptomatic versus first presentation of symptomatic patients), and patients' usual habitual physical activity levels.

A decline in physical fitness postoperatively is to be expected (Jakobsson et al. 2014), attributed to both the physiological impact of surgery (Shibata et al., 2015) and the associated period of inactivity (Hamaker et al., 2014); however, as with physical activity profiles, there is significant variation in the magnitude of this decline between patients (Cuijpers et al., 2022; Malietzis et al., 2016) and also in how they self-perceive their decline/recovery relationship (Allvin et al., 2007). Clinically, collection of baseline physical activity data is easy to achieve and may be useful to help establish a potential goal to return to and strategy to achieve this. For example, in a resource-limited setting, patients could be asked to gain an idea of their preoperative activity levels with simple fitness tracking/pedometers and use that as their postoperative goal. In addition, if preoperative physical activity levels are seen to be associated with

poorer clinical and patient-centred post-operative outcomes, those who do very little could be identified early in the preoperative period and highlighted for more intensive input (i.e. exercise prehabilitation (Van Rooijen et al., 2019) and/or structured rehabilitation (Silver et al., 2013)) running throughout the perioperative period, rather than being seen postoperatively in an already deconditioned state.

The PHYSPAL study reported in **chapter 3** of this thesis explored physical activity profiles in the immediate postoperative period while patients were in hospital. The importance of this period is highlighted by work showing that during a period of immobilisation or inactivity (such as during hospitalisation), muscle mass and functional losses occur rapidly (with <5d), and that these losses are greater in those with injury or illness (E. J. O. Hardy et al., 2022; Wall et al., 2014). Despite this study being conducted at a single clinical centre, there was great variability in the amount of physical movement during this in-hospital period. This is largely unsurprising given the differing postoperative courses of the enrolled patients; LoHS ranged from 4 to 30 days.

The majority of patients in the PHYSPAL study did follow all major points of the colorectal ERAS pathway at the clinical site and given the average LoHS of 8.24 days it is in keeping with other clinical sites in the UK (National Bowel Cancer Audit Project Team., 2024). That there is a correlation between the amount of movement and the day of surgery, given the resource limitation of physiotherapy input, especially at the weekend, needs to be afforded attention. This potentially acts as a limitation to in-hospital rehabilitation and is also a major barrier to the effective input of inpatient rehabilitation programmes requiring daily specialist input. This is important to realise as provision of equitable care is vital in order to ensure optimal outcomes. Patients who are at higher risk could potentially be considered for surgery earlier in the week to ensure that they have as much opportunity for expert rehabilitation in-hospital as possible.

A follow-on to the PHYSPAL study would be to use goal-setting and real-time feedback to enable patients to achieve target-driven step counts and time spent out of bed, sitting and moving. This does require in certain circumstances healthcare professional input, for example, with early postoperative mobilisation if patients have catheterisation or intravenous infusions. However, for those on the ERAS pathway, removal of extraneous accoutrements as soon as viable should allow patients to be independently mobile as early as possible and to take ownership of their own activity where possible.

The original aim of the POSTEX study reported in **chapter 4** of this thesis was to explore the impact of a semi-supervised postoperative exercise training regime on functional and psychological recovery. Although this study did not show a significant difference in change between the exercise and control groups with regards to the primary outcome (mean difference in VO_2 max via CPET), this may be due, in at least some part, to failure to achieve full recruitment. This failure to achieve recruitment was in itself surprising. Initially, the idea of a study that provided a structured programme for exercise after surgery with clinician oversight would seem to be a premise that would be attractive to most patients, but there were a host of different reasons why patients declined. Some had no capacity to attend the preoperative visits due to existing commitments; mainly work, holidays/trips taken in the run-up to surgery, or because they were the main carer for another family member. Early on in study recruitment, some patients were reluctant to attend any unnecessary visits due to the risk of contracting COVID-19 and the chance that it would postpone their operation date. A conversation with one patient resulted in an unfavourable outcome as they stated that they did not want to engage with the idea of having cancer until it came to it being removed. However, despite the lack of difference in change for VO_2 max, the findings of this study do suggest that postoperative exercise training may have a positive role to play in maintaining muscle strength and as an added benefit, with the setup of POSTEx, participants valued the

extended physician contact and opportunity to voice any concerns/questions whilst in the immediate few months post discharge.

To continue this study to full recruitment and follow-through would potentially provide additional information as to whether the programme has significant benefits in relation to cardiorespiratory fitness - a known measure of physical fitness (Myers et al. 2015) -, which has been shown to be associated with a quicker return to normal activities, morbidity and even premature mortality (Mann et al., 2020).

In addition, it would be useful to conduct some semi-structured interviews in those who did not take part in the exercise programme (i.e. the control group), to see if they felt as though their own recovery was as expected without formal instruction, as well as give more in depth review of their attitudes towards their activity levels just by virtue of inclusion in the study, and whether there was any change by having an increased awareness of the potential for benefits in doing early regular activity. This part of the study could also be served as a future standalone project to further explore the biopsychosocial factors around engagement and attitudes to exercise rehabilitation after colorectal cancer surgery, as it is still poorly understood in this particular cohort as discussed in **chapter 1**. This may help to further refine the exercise prescription aspect of further rehabilitation interventions in future, bespoke to UHDB.

Finally, a review at 6 or 12 months to assess for longer-term sequelae that could potentially be attributed to postoperative exercise, such as incisional hernia rates, would also be of note, to ensure that the advice given is not contributing towards delayed complications. Incisional hernias have a significant morbidity (Shao et al., 2020; Van Ramshorst et al., 2012), but there is little evidence to show that early exercise interventions increase the risk of incisional hernias (Weir et al., 2006), hence its lack of inclusion in this study. A review by Güsgen et. al demonstrated that most incisional hernias most develop >18 months post-surgery and in patients with other risk factors and lower physical activity profiles (Güsgen et al., 2020).

5.2 Retrospection

Considering this thesis as a single body of work, it has not only highlighted the need for more consistency in interventions and outcomes in work exploring the potential benefits of postoperative exercise for intra-abdominal cancer patients but has also characterised the physical activity levels of this patient cohort at different stages of their perioperative journey. Finally, building on both of these aspects, the impact of postoperative home-based structured exercise was explored, yielding suggestions of potential benefit in maintaining or improving muscle strength and empowering patients to start active exercise earlier than they may have considered safe/feasible, but was likely underpowered to determine changes in our primary endpoint of VO2 max.

Already published in Techniques in Coloproctology and with a comprehensive search strategy (see Appendix 7.1, few changes would strengthen the systematic review chapter of this thesis, with the exception of comparing different modalities of exercise in the postoperative period. Similarly, the observational collection of inpatient whole-group physical activity using accelerometry was relatively simple in design, and as such comes with few limitations save for the scope of the monitors' capabilities. However, in retrospect the addition of patient interviews to gather their experiences along their journey throughout their postoperative inpatient course would have added a stronger patient voice. This data set may have been richer also had more specific information regarding the degree and perceived intensity of physiotherapy input and time spent with nursing assistance/encouragement to mobilise had also been collected and should be considered for future work in this space. Considering the failure to reach full recruitment, the POSTEx study offers the greatest opportunity for retrospection. Firstly, in terms of study design, reducing the exercise period to 8 weeks is an option. The idea of continuing in a cancer-related study for 3 months after surgery in patients who want to

improve and move on with their lives can serve as an unwelcome reminder as to what they have been through. However, previous studies have previously shown in cancer that at least 12 weeks of exercise training elicits benefit in key physiological (Luo et al., 2021) and psychosocial (Li et al., 2023; Mardani et al., 2021) parameters associated with health such as CRF, hence the initial intervention design.

Despite the disappointment of not reaching the recruitment target, this study can be considered a success for other reasons. Firstly, the uptake and feedback showed that patients found it worthwhile and helpful. One participant stated it gave them “the confidence to do exercise” and allowed them to realise that although they were postoperatively recovering, their ability to exercise and engage in a rigorous training programme was at a higher level than they may have otherwise dared to attempt. That many participants found study involvement helpful and beneficial is evidenced through the cards, gifts of appreciation and expressions of thanks gratefully received from patients in both the control and exercise group (see Appendix 7.11 for examples). Even for the control group, their assessment days gave them a good evaluation of their postoperative progress, and they also valued having contact with a clinician for an extended period of time, as most patients did not see a member of the surgery team again after discharge (as is common practice). The simple thought of signing up to the study made even the control patients think more about their activity levels, and one participant in the control group even bought her first pair of trainers for the trial.

5.3 Conclusions

Despite the challenges with recruitment, there is good evidence for patient-centric activity/exercise support that can be delivered throughout the cancer treatment pathway (Avancini et al., 2020; Campbell et al., 2019; Gao et al., 2020; Ligibel et al., 2022; Maddocks, 2020). Preoperative conditioning has been shown to be effective at reducing

complications (Barberan-Garcia et al., 2018), but in-hospital exercise rehabilitation that continues post-discharge is vital in order to make patients feel not only more able to return to or better their preoperative physical state but feel as though they can take ownership of their own recovery whilst feeling reassured that what they are doing is safe and appropriate. For those unable to perform dynamic activity whilst in hospital, recent work has highlighted the promise of alternative contractile based strategies (e.g., neuromuscular stimulation (NMES)) in this cohort (Hardy et al. 2022), which may also give patients the confidence and ability to engage with postoperative exercise rehabilitation after hospital discharge. Patient-centred goals and approaches are paramount to future research in this area, not looking exclusively at traditional outcomes such as morbidity and mortality, but also aspects such as the ability to reintegrate back into normal life, which varies depending on the in-dividual (i.e., working/caring responsibilities, previous physical activity). Multi-disciplinary health professional input into a larger scale multi-centre trial of postoperative rehabilitation, with a combination of both quantitative and qualitative outcomes will help ensure the production of robust, translatable results that can be applied directly to the clinical setting.

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7 Appendices

7.1 Systematic Review Search Strategy

Search Strategy – Ovid Medline

Search Terms
("post op*" or "post-op*" or "postop*" or "post operative" or "post-operative" or "postoperative" or (after ADJ4 surg*) or (post ADJ4 surg*) or (follow* ADJ4 surg*) or

inpatient* or "after care" or "after-care" or "aftercare" or "after discharge" or "post discharge" or outpatient*).mp. OR exp AFTERCARE/ OR exp INPATIENTS/ OR exp OUTPATIENTS/ OR exp "POSTOPERATIVE CARE"/ OR exp "POSTOPERATIVE PERIOD"/

AND

(aerobic OR (muscle ADJ4 train*) OR "enhanced recovery" OR exercise* OR "strength training" OR sport* OR weightlifting OR "weight* training" OR "weight* bearing strengthening" OR (resistance ADJ4 train*) OR (weight* ADJ4 lift)).mp OR exp EXERCISE/ OR exp "EXERCISE THERAPY"/ OR exp "WEIGHT LIFTING"/ OR exp "RESISTANCE TRAINING"/ OR exp RUNNING/ OR exp SWIMMING/ OR exp WALKING/ OR exp SPORTS/

AND

((abdo* or anal or bladder or bowel or cervi* or colon or colorectal or endometr* or gastr* or gynae* or intestin* or liver or ovar* or prostat* or rectal or stomach or urolog* or uter* or pancrea*) ADJ4 (neoplasm* or tumor* or tumour* or cancer*)).mp OR exp "ABDOMINAL NEOPLASMS"/ OR exp "COLONIC NEOPLASMS"/ OR exp "COLORECTAL NEOPLASMS"/ OR exp "ENDOMETRIAL NEOPLASMS"/ OR exp "GASTROINTESTINAL NEOPLASMS"/ OR "GASTROINTESTINAL STROMAL TUMORS"/ OR "LIVER NEOPLASMS" OR exp "INTESTINAL NEOPLASMS"/ OR exp NEOPLASMS/ OR exp "OVARIAN NEOPLASMS"/ OR exp "PERITONEAL NEOPLASMS"/ OR exp "PROSTATIC NEOPLASMS"/ OR exp "STOMACH NEOPLASMS"/ OR exp "URINARY BLADDER NEOPLASMS"/ OR exp "UROLOGIC NEOPLASMS"/ OR exp "UTERINE NEOPLASMS"/ OR exp "UTERINE CERVICAL NEOPLASMS"/ OR exp "PANCREATIC NEOPLASMS"/

AND

(laparotom* OR laparoscop* OR keyhole OR "robotic surg*" OR tumour ADJ4 excis* OR tumor ADJ4 excis* OR surg*).mp OR exp SURGICAL PROCEDURES, OPERATIVE/ OR exp "HAND-ASSISTED LAPAROSCOPY"/ OR exp "LAPAROTOMY"/ OR exp "LAPAROSCOPY"/ OR exp "MINIMALLY INVASIVE SURGICAL PROCEDURES"/ OR exp "ROBOTIC SURGICAL PROCEDURES"/

Search Strategy – Ovid Embase

Search Terms
("post op*" or "post-op*" or "postop*" or "post operative" or "post-operative" or "postoperative" or (after adj2 surg*) or (post adj2 surg*) or (follow* adj2 surg*) or inpatient* or "after care" or "after-care" or "aftercare" or "after discharge" or "post discharge" or outpatient*).mp. OR exp AFTERCARE/ OR exp "HOSPITAL PATIENT"/ OR exp OUTPATIENT/ OR exp "OUTPATIENT CARE"/ OR exp "POSTOPERATIVE PERIOD"/ AND (aerobic OR "muscle ADJ3 train*" OR "enhanced recovery" OR exercise* OR "strength training" OR sport* OR weightlifting OR "weight* training" OR "weight* bearing strengthening" OR (resistance adj4 train*) OR "weight* ADJ4 lift").mp OR exp "MUSCLE EXERCISE"/ OR exp "LOW INTENSITY EXERCISE"/ OR exp "MODERATE INTENSITY EXERCISE"/ OR exp "DYNAMIC EXERCISE"/ OR exp "AEROBIC EXERCISE"/ OR exp "ANAEROBIC EXERCISE"/ OR exp "ISOTONIC EXERCISE"/ OR exp "ISOMETRIC EXERCISE"/ OR exp "HIGH INTENSITY EXERCISE"/ OR exp "ISOKINETIC EXERCISE"/ OR exp "SQUATTING (EXERCISE)"/ OR exp EXERCISE/ OR exp "ARM EXERCISE"/ OR exp "AQUATIC EXERCISE"/ OR exp "STRETCHING EXERCISE"/ OR exp "TREADMILL EXERCISE"/ OR exp "EXERCISE INTENSITY"/ OR exp "STATIC EXERCISE"/ OR exp "EXERCISE TOLERANCE"/ OR exp "LEG EXERCISE"/ OR exp KINESIOTHERAPY/ OR exp "WEIGHT LIFTING"/ OR exp "RESISTANCE TRAINING"/ OR exp RUNNING/ OR exp SWIMMING/ OR exp WALKING/ OR exp "NORDIC WALKING"/ OR exp "MUSCLE TRAINING"/ OR "LACROSSE (SPORT)"/ OR exp ENDURANCE SPORT/ OR exp "SQUASH (SPORT)"/ OR BALL SPORT/ OR exp SPORT/ OR exp "CRICKET (SPORT)"/ OR exp AERONAUTICAL SPORT/ OR exp "CROSS TRAINING (SPORT)"/ OR exp "SURFING (WATER SPORT)"/ OR "SPORTS AND SPORT RELATED PHENOMENA"/ OR exp DISABLED SPORT/ OR exp WATER SPORT/ OR exp COLLISION SPORT/ OR exp RACQUET SPORT/ OR exp TEAM SPORT/ OR exp "FENCING (SPORT)"/ OR exp WINTER SPORT/ OR exp NON CONTACT SPORT/ OR exp COMBAT SPORT/ OR exp "SAILING (WATER SPORT)"/ OR exp CONTACT SPORT/ OR exp WHEELCHAIR SPORT/ AND

((abdo* or anal or bladder or bowel or cervi* or colon or colorectal or endometr* or gastr* or gynae* or intestin* or liver or ovar* or prostat* or rectal or stomach or urolog* or uter* or pancrea*) adj3 (neoplasm* or tumor* or tumour* or cancer*)).mp OR exp "ABDOMINAL CANCER"/ OR exp "ABDOMEN METASTASIS CELL LINE"/ OR exp "ABDOMINAL TUMOR"/ OR exp "COLON CANCER"/ OR exp "COLON CARCINOMA"/ OR exp "COLON TUMOR"/ OR exp "COLORECTAL CANCER"/ OR exp "COLORECTAL TUMOR"/ OR exp "DIGESTIVE SYSTEM CANCER"/ OR exp "ENDOMETRIUM CANCER"/ OR exp "ENDOMETRIUM TUMOR"/ OR "GASTROINTESTINAL STROMAL TUMOR"/ OR exp "GASTROINTESTINAL TUMOR"/ OR exp "INTESTINE CANCER"/ OR exp "INTESTINE TUMOR"/ OR exp "LIVER CANCER"/ OR exp "LIVER TUMOR"/ OR "OVARY CANCER"/ OR "OVARY TUMOR"/ OR exp "PERITONEUM CANCER"/ OR exp "PERITONEUM TUMOR"/ OR exp "PROSTATE CANCER"/ OR exp "PROSTATE TUMOR"/ OR exp "STOMACH CANCER"/ OR exp "STOMACH TUMOR"/ OR "BLADDER CANCER"/ OR "BLADDER TUMOR"/ OR "URINARY TRACT CANCER"/ OR "URINARY TRACT TUMOR"/ OR "UTERUS CANCER"/ OR exp "UTERINE CERVIX CANCER"/ OR exp "UTERINE CERVIX TUMOR"/ OR exp "UTERUS CARCINOMA"/ OR exp "RECTUM CANCER"/ OR exp "RECTUM TUMOR"/ OR exp "RECTUM CARCINOMA"/ OR exp COLON CANCER/ OR exp COLON CARCINOMA/ OR exp RECTUM CANCER/ OR exp RECTUM TUMOR/ OR exp COLON TUMOR/ OR exp RECTUM CARCINOMA/ OR exp PANCREAS CANCER/ OR exp PANCREAS TUMOR/

AND

((laparotom* OR laparoscop* OR keyhole OR "robotic surg*" OR (tumour adj3 excis*) OR (tumor adj3 excis*) OR surg*)).mp OR exp SURGERY/ OR exp "LAPAROSCOPY"/ OR exp "GASLESS LAPAROSCOPY"/ OR exp "HAND-ASSISTED LAPAROSCOPY"/ OR exp SURGERY/ OR exp LAPAROSCOPIC SURGERY/ or exp LAPAROENDOSCOPIC SINGLE SITE SURGERY/ OR exp "LAPAROTOMY"/ OR exp "MINIMALLY INVASIVE SURGERY"/ OR exp "ROBOT ASSISTED SURGERY"/ OR exp STOMACH SURGERY/ OR exp BLADDER SURGERY/ OR exp PANCREAS SURGERY/ OR exp RECTUM SURGERY/ OR exp CANCER SURGERY/ OR exp UROLOGIC SURGERY/ OR exp ABDOMINAL SURGERY/ OR exp UTERINE TUBE SURGERY/ OR exp ANUS SURGERY/ OR

exp PROSTATE SURGERY/ OR exp URINARY TRACT SURGERY/ OR exp GYNECOLOGIC SURGERY/ OR exp COLORECTAL SURGERY/ OR exp GENERAL SURGERY/ exp COLON SURGERY/ OR exp INTESTINE SURGERY/ OR exp UTERUS SURGERY/ OR exp GASTROINTESTINAL SURGERY/ OR exp LIVER SURGERY/ or exp URETHRA SURGERY/ or exp SPLEEN SURGERY/ OR exp BILIARY TRACT SURGERY/ or exp KIDNEY SURGERY/ OR exp TRANSANAL ENDOSCOPIC SURGERY/ or exp URETER SURGERY/

Search Strategy – Ovid Emcare

Search Terms
("post op*" or "post-op*" or "postop*" or "post operative" or "post-operative" or "postoperative" or (after adj4 surg*) or (post adj4 surg*) or (follow* adj4 surg*) or inpatient* or "after care" or "after-care" or "aftercare" or "after discharge" or "post discharge" or outpatient*).mp. OR exp AFTERCARE/ OR exp "HOSPITAL PATIENT"/ OR exp OUTPATIENT/ OR exp "OUTPATIENT CARE"/ OR exp "POSTOPERATIVE PERIOD"/ AND (aerobic OR "muscle adj4 train*" OR "enhanced recovery" OR exercise* OR "strength training" OR sport* OR weightlifting OR "weight* training" OR "weight* bearing strengthening" OR (resistance adj4 train*) OR "weight* adj4 lift").mp OR exp "MUSCLE EXERCISE"/ OR exp "LOW INTENSITY EXERCISE"/ OR exp "MODERATE INTENSITY EXERCISE"/ OR exp "DYNAMIC EXERCISE"/ OR exp "AEROBIC EXERCISE"/ OR exp "ISOTONIC EXERCISE"/ OR exp "ISOMETRIC EXERCISE"/ OR exp "HIGH INTENSITY EXERCISE"/ OR exp "ISOKINETIC EXERCISE"/ OR exp "SQUATTING (EXERCISE)"/ OR exp EXERCISE/ OR exp "ARM EXERCISE"/ OR exp "AQUATIC EXERCISE"/ OR exp "STRETCHING EXERCISE"/ OR exp "TREADMILL EXERCISE"/ OR exp "EXERCISE INTENSITY"/ OR exp "STATIC EXERCISE"/ OR exp "EXERCISE TOLERANCE"/ OR exp "LEG EXERCISE"/ OR exp KINESIOTHERAPY/ OR exp "WEIGHT LIFTING"/ OR exp "RESISTANCE TRAINING"/ OR exp RUNNING/ OR exp SWIMMING/ OR exp WALKING/ OR exp "NORDIC WALKING"/ OR exp "MUSCLE TRAINING"/ AND

((abdo* or anal or bladder or bowel or cervi* or colon or colorectal or endometr* or gastr* or gynae* or intestin* or liver or ovar* or prostat* or rectal or stomach or urolog* or uter* or pancrea*) adj4 (neoplasm* or tumor* or tumour* or cancer*)).mp OR exp "ABDOMINAL CANCER"/ OR exp "ABDOMEN METASTASIS CELL LINE"/ OR exp "ABDOMINAL TUMOR"/ OR exp "COLON CANCER"/ OR exp "COLON CARCINOMA"/ OR exp "COLON TUMOR"/ OR exp "COLORECTAL CANCER"/ OR exp "COLORECTAL TUMOR"/ OR exp "DIGESTIVE SYSTEM CANCER"/ OR exp "ENDOMETRIUM CANCER"/ OR exp "ENDOMETRIUM TUMOR"/ OR "GASTROINTESTINAL STROMAL TUMOR"/ OR exp "GASTROINTESTINAL TUMOR"/ OR exp "INTESTINE CANCER"/ OR exp "INTESTINE TUMOR"/ OR exp "LIVER CANCER"/ OR exp "LIVER TUMOR"/ OR "OVARY CANCER"/ OR "OVARY TUMOR"/ OR exp "PERITONEUM CANCER"/ OR exp "PERITONEUM TUMOR"/ OR exp "PROSTATE CANCER"/ OR exp "PROSTATE TUMOR"/ OR exp "STOMACH CANCER"/ OR exp "STOMACH TUMOR"/ OR "BLADDER CANCER"/ OR "BLADDER TUMOR"/ OR "URINARY TRACT CANCER"/ OR "URINARY TRACT TUMOR"/ OR "UTERUS CANCER"/ OR exp "UTERINE CERVIX CANCER"/ OR exp "UTERINE CERVIX TUMOR"/ OR exp "UTERUS CARCINOMA"/ OR exp "RECTUM CANCER"/ OR exp "RECTUM TUMOR"/ OR exp "RECTUM CARCINOMA"/ OR exp "PANCREAS CANCER"/ OR exp "PANCREAS TUMOR"/

AND

((laparotom* OR laparoscop* OR keyhole OR "robotic surg*" OR (tumour adj4 excis*) OR (tumor adj4 excis*) OR surg*)).mp OR exp SURGERY/ OR exp "LAPAROSCOPY"/ OR exp "GASLESS LAPAROSCOPY"/ OR exp "HAND-ASSISTED LAPAROSCOPY"/ OR exp SURGERY/ OR exp LAPAROSCOPIC SURGERY/ or exp LAPAROENDOSCOPIC SINGLE SITE SURGERY/ OR exp "LAPAROTOMY"/ OR exp "MINIMALLY INVASIVE SURGERY"/ OR exp "ROBOT ASSISTED SURGERY"/ OR exp STOMACH SURGERY/ OR exp BLADDER SURGERY/ OR exp PANCREAS SURGERY/ OR exp RECTUM SURGERY/ OR exp CANCER SURGERY/ OR exp UROLOGIC SURGERY/ OR exp ABDOMINAL SURGERY/ OR exp UTERINE TUBE SURGERY/ OR exp ANUS SURGERY/ OR exp PROSTATE SURGERY/ OR exp URINARY TRACT SURGERY/ OR exp GYNECOLOGIC SURGERY/ OR exp COLORECTAL SURGERY/ OR exp

GENERAL SURGERY/ exp COLON SURGERY/ OR exp INTESTINE SURGERY/ OR exp UTERUS SURGERY/ OR exp GASTROINTESTINAL SURGERY/ OR exp LIVER SURGERY/ or exp URETHRA SURGERY/ or exp SPLEEN SURGERY/ OR exp BILIARY TRACT SURGERY/ or exp KIDNEY SURGERY/ OR exp TRANSANAL ENDOSCOPIC SURGERY/ or exp URETER SURGERY/

Search Strategy – EBSCOhost CINAHL

Search Terms
("post op*" or "post-op*" or "postop*" or "post operative" or "post-operative" or "postoperative" or (after N4 surg*) or (post N4 surg*) or (follow* N4 surg*) or inpatient* or "after care" or "after-care" or "aftercare" or "after discharge" or "post discharge" or outpatient*) OR (MH "After Care") OR (MH "Inpatients") OR (MH "Outpatients") OR (MH "Postoperative Care+") OR (MH "Postoperative Period") AND (aerobic OR "muscle N4 train*" OR "enhanced recovery" OR exercise* OR "strength training" OR sport* OR weightlifting OR "weight* training" OR "weight* bearing strengthening" OR (resistance N4 train*) OR "weight* N4 lift") OR (MH "Exercise+") OR (MH "Resistance Training") OR (MH "Abdominal Exercises") OR (MH "Therapeutic Exercise") OR (MH "Exercise Intensity") OR (MH "Group Exercise") OR (MH "Extreme Sports") OR (MH "Sport Specific Training") OR (MH "Aquatic Sports+") OR (MH "Aeronautical Sports") OR (MH "Winter Sports+") OR (MH "Wheelchair Sports") OR (MH "Sports+") OR (MH "Athletic Training+") OR (MH "Body Building") OR (MH "Bowling") OR (MH "Contact Sports+") OR (MH "Cycling") OR (MH "Endurance Sports") OR (MH "Fencing") OR (MH "Golf") OR (MH "Gymnastics") OR (MH "Handball") OR (MH "Martial Arts") OR (MH "Mountaineering") OR (MH "Racquet Sports+") OR (MH "Rock Climbing") OR (MH "Running+") OR (MH "Skating+") OR (MH "Skiing+") OR (MH "Sports, Disabled+") OR (MH "Sports Participation") OR (MH "Target Sports+") OR (MH "Team Sports+") OR (MH "Weight Lifting") OR (MH "Archery") OR (MH "Snow Skiing+") OR (MH "Cross Country Skiing") OR (MH "Water Skiing") OR (MH "Ice Skating") OR (MH "Skateboarding") OR (MH "Jogging") OR (MH "Running, Distance") OR (MH "Sprinting") OR (MH "Tennis") OR (MH "Boxing") OR (MH "Football") OR (MH "Rugby") OR (MH "Wrestling") OR (MH "Diving") OR (MH "Scuba Diving") OR (MH

"Snorkeling") OR (MH "Rowing") OR (MH "Swimming") OR (MH "Walking+") OR (MH "Nordic Walking") OR (MH "Dancing+") OR (MH "Exercise+") OR (MH "Abdominal Exercises") OR (MH "Aerobic Exercises+") OR (MH "Aerobic Dancing") OR (MH "Aquatic Exercises") OR (MH "Jumping") OR (MH "Lower Extremity Exercises") OR (MH "High-Intensity Interval Training") OR (MH "Group Exercise") OR (MH "Endurance Training") OR (MH "Anaerobic Exercises") OR (MH "Muscle Strengthening+") OR (MH "Isokinetic Exercises") OR (MH "Isometric Exercises") OR (MH "Isotonic Exercises") OR (MH "Resistance Training") OR (MH "Pilates") OR (MH "Upper Extremity Exercises+") OR (MH "Arm Exercises") OR (MH "Horseback Riding")

AND

((abdo* or anal or bladder or bowel or cervi* or colon or colorectal or endometr* or gastr* or gynae* or intestin* or liver or ovar* or prostat* or rectal or stomach or urolog* or uter* or pancrea*) N4 (neoplasm* or tumor* or tumour* or cancer*)) OR exp "ABDOMINAL NEOPLASMS"/ OR exp "COLONIC NEOPLASMS"/ OR exp "COLORECTAL NEOPLASMS"/ OR "ENDOMETRIAL NEOPLASMS"/ OR exp "GASTROINTESTINAL NEOPLASMS"/ "/ OR exp "LIVER NEOPLASMS" OR exp "INTESTINAL NEOPLASMS"/ OR exp "OVARIAN NEOPLASMS"/ OR exp "PERITONEAL NEOPLASMS"/ OR exp "PROSTATIC NEOPLASMS"/ OR "STOMACH NEOPLASMS"/ OR "BLADDER NEOPLASMS"/ OR exp "UROLOGIC NEOPLASMS"/ OR exp "UTERINE NEOPLASMS"/ OR exp "CERVIX NEOPLASMS"/ OR exp "PANCREATIC NEOPLASMS"/

AND

((laparotom* OR laparoscop* OR keyhole OR "robotic surg*" OR (tumour N4 excis*) OR (tumor N4 excis*) OR surg*)) OR (MH "Surgery, Operative+") OR "LAPAROTOMY"/ OR "LAPAROSCOPY"/ OR exp "MINIMALLY INVASIVE PROCEDURES"/ OR "ROBOTIC SURGICAL PROCEDURES"/ OR "SURGERY, LAPAROSCOPIC"/

Search Strategy – ProQuest BNI

Search Terms
((NOFT("post op*" or "post-op*" or "postop*" or "post operative" or "post-operative" or "postoperative" or (after NEAR/4 surg*) or (post NEAR/4 surg*) or (follow* NEAR/4 surg*) or inpatient* or "after care" or "after-care" or "aftercare" or "after discharge" or "post discharge" or outpatient*) OR MAINSUBJECT.EXACT("Inpatient care") OR MAINSUBJECT.EXACT("Patients") OR MAINSUBJECT.EXACT("Postoperative period")) AND (NOFT(aerobic OR "muscle NEAR/4 train*" OR "enhanced recovery" OR exercise* OR "strength training" OR sport* OR weightlifting OR "weight* training" OR "weight* bearing strengthening" OR (resistance NEAR/4 train*) OR "weight* NEAR/4 lift") OR MAINSUBJECT.EXACT("Exercise") OR MAINSUBJECT.EXACT("Isometric exercise") OR MAINSUBJECT.EXACT("Strength training") OR MAINSUBJECT.EXACT("Sports") OR MAINSUBJECT.EXACT("Running") OR MAINSUBJECT.EXACT("Swimming") OR MAINSUBJECT.EXACT("Walking") OR MAINSUBJECT.EXACT("Weightlifting")) AND (NOFT((abdo* or anal or bladder or bowel or cervi* or colon or colorectal or endometr* or gastr* or gynae* or intestin* or liver or ovar* or prostat* or rectal or stomach or urolog* or uter* or pancrea*) NEAR/4 (neoplasm* or tumor* or tumour* or cancer*)) OR MAINSUBJECT.EXACT("Colorectal cancer") OR MAINSUBJECT.EXACT("Endometrial cancer") OR MAINSUBJECT.EXACT("Liver cancer") OR MAINSUBJECT.EXACT("Ovarian cancer") OR MAINSUBJECT.EXACT("Prostate cancer") OR MAINSUBJECT.EXACT("Stomach cancer") OR MAINSUBJECT.EXACT("Bladder cancer") OR MAINSUBJECT.EXACT("Uterine cancer") OR MAINSUBJECT.EXACT("Cervical cancer") OR MAINSUBJECT.EXACT("Pancreatic cancer")) AND

(NOFT (laparotom* OR laparoscop* OR keyhole OR "robotic surg*" OR tumour NEAR/4 excis* OR tumor NEAR/4 excis* OR surg*) OR MAINSUBJECT.EXACT("Abdominal surgery") OR MAINSUBJECT.EXACT("Cancer surgery") OR MAINSUBJECT.EXACT("Gastrointestinal surgery") OR MAINSUBJECT.EXACT("Gynaecological surgery") OR MAINSUBJECT.EXACT("Laparoscopic surgery") OR MAINSUBJECT.EXACT("Surgery") OR MAINSUBJECT.EXACT("Laparotomy")))

Search Strategy – PubMed

Search Terms
("post op*" or "post-op*" or "postop*" or "post operative" or "post-operative" or "postoperative" or (after surg*) or (post surg*) or (follow* surg*) or inpatient* or "after care" or "after-care" or "aftercare" or "after discharge" or "post discharge" or outpatient*) [All Fields] OR AFTERCARE OR INPATIENTS OR OUTPATIENTS OR exp "POSTOPERATIVE CARE" OR "POSTOPERATIVE PERIOD" [MeSH Terms] AND (aerobic OR "muscle train*" OR "enhanced recovery" OR exercise* OR "strength training" OR sport* OR weightlifting OR "weight training" OR "weight bearing strengthening" OR (resistance train*) OR "weight lift") [All Fields] OR EXERCISE OR "EXERCISE THERAPY" OR exp "WEIGHT LIFTING" OR "RESISTANCE TRAINING" OR RUNNING OR SWIMMING OR WALKING [MeSH Terms] AND ((abdo* or anal or bladder or bowel or cervi* or colon or colorectal or endometr* or gastr* or gynae* or intestin* or liver or ovar* or prostat* or rectal or stomach or

urolog* or uter* or pancrea*) and (neoplasm* or tumor* or tumour* or cancer*))[All Fields] OR "ABDOMINAL NEOPLASMS" OR "COLONIC NEOPLASMS" OR exp "COLORECTAL NEOPLASMS" OR "ENDOMETRIAL NEOPLASMS" OR "GASTROINTESTINAL NEOPLASMS" OR "GASTROINTESTINAL STROMAL TUMORS" OR "LIVER NEOPLASMS" OR "INTESTINAL NEOPLASMS" OR NEOPLASMS OR "OVARIAN NEOPLASMS" OR "PERITONEAL NEOPLASMS" OR "PROSTATIC NEOPLASMS" OR "STOMACH NEOPLASMS" OR "URINARY BLADDER NEOPLASMS" OR "UROLOGIC NEOPLASMS" OR "UTERINE NEOPLASMS" OR "UTERINE CERVICAL NEOPLASMS" OR "PANCREATIC NEOPLASMS" [MeSH Terms]

AND

(laparotom* OR laparoscop* OR keyhole OR "robotic surg*" OR tumour excis* OR tumor excis* OR surg*) [All Fields] OR "HAND-ASSISTED LAPAROSCOPY" OR "LAPAROTOMY" OR "LAPAROSCOPY" OR "MINIMALLY INVASIVE SURGICAL PROCEDURES" OR "ROBOTIC SURGICAL PROCEDURES" [MeSH Terms]

Auto-translated by PubMed into:

("post op*"[All Fields] OR "post op*"[All Fields] OR "postop*"[All Fields] OR "post-operative"[All Fields] OR "post-operative"[All Fields] OR "postoperative"[All Fields] OR ("after"[All Fields] AND "surg*"[All Fields]) OR ("post"[All Fields] AND "surg*"[All Fields]) OR ("follow*"[All Fields] AND "surg*"[All Fields]) OR "inpatient*"[All Fields] OR "after-care"[All Fields] OR "after-care"[All Fields] OR "aftercare"[All Fields] OR "after discharge"[All Fields] OR "post discharge"[All Fields] OR "outpatient*"[All Fields] OR ((("aftercare"[MeSH Terms] OR "aftercare"[All Fields] OR ("inpatient s"[All Fields] OR "inpatients"[MeSH Terms] OR "inpatients"[All Fields] OR "inpatient"[All Fields]) OR ("outpatient s"[All Fields] OR "outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields]) OR "exp"[All Fields]) AND "POSTOPERATIVE CARE"[All Fields]) OR "POSTOPERATIVE PERIOD"[All Fields])) AND ("aerobic"[All Fields] OR "aerobically"[All Fields] OR "bacteria,

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7.2 Study Protocols

7.2.1 PHYSPAL Study Protocol

7.2.2 POSTEx Study Protocol

University of Nottingham
UK | CHINA | MALAYSIA

A randomised controlled trial to assess the efficacy of a postoperative supervised exercise program in patients who have undergone elective curative surgery for colorectal cancer.

Final Version 2.0

18.03.22

Short title: Supervised exercise for post-surgery colorectal cancer patients

Acronym: **POSTEx**

Trial Registration: NCT05090215 (www.clinicaltrials.gov)

IRAS Project ID: *281681*

Trial Sponsor: University of Nottingham

Sponsor reference: *21058*

Funding Source: Private funds of Mr J Lund

TRIAL / STUDY PERSONNEL AND CONTACT DETAILS

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Research and Innovation

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Chief investigator: Mr. Jon Lund, DM FRCS, Clinical Associate Professor, University of Nottingham, Division of Graduate Entry Medicine and Health, School of Medicine and Consultant Colorectal Surgeon, Royal Derby Hospital.

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Add the name and contact details of the medical expert if different to the CI.

Co-investigators: Dr Bethan Phillips, PhD, AFHEA, Associate Professor, Division of Graduate Entry Medicine and Health, School of Medicine, University of Nottingham.

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Email: dr.doleman@gmail.com

Trial / Study Coordinating Centre: Royal Derby Hospital – School of Graduate Entry Medicine, University of Nottingham, Uttoxeter Road, Derby, DE22 3NE

SYNOPSIS

Title	A randomised controlled trial to assess the effect of a postoperative supervised exercise program in patients who have undergone elective curative surgery for colorectal cancer
Acronym	POSTEx
Short title	Supervised exercise for post-surgery colorectal cancer patients
Chief Investigator	Mr. Jon Lund
Objectives	Primary objective: To assess whether a structured 12 week postoperative exercise program can improve the physical recovery of abdominal cancer patients compared to normal postoperative care Secondary objectives: To assess the feasibility of a period of supervised exercise with a home-based component in this cohort of patients after surgery for colorectal cancer
Study Configuration	Single centre randomised controlled trial
Setting	Centre Of Metabolism, Ageing & Physiology (COMAP) Research Group, University of Nottingham, Royal Derby Hospital Centre Recruitment will take place at Royal Derby Hospital (NHS), Uttoxeter Rd, DE22 3NE
Sample size estimate	Using data from a previous study we have looked for a mean difference of 2.26ml/kg/min in VO_2AT (oxygen consumption at anaerobic threshold) as significant. With a power of 0.95, 5% level of significance and an effect size of 0.42 (derived from previous work within a cohort of cancer patients undergoing

	exercise) a sample size of 23 is necessary. Given previous national audit data on outcomes following colorectal cancer surgery, a 3% death rate and 11% readmission rate postoperatively has been used to factor in for any participants following recruitment who may then subsequently become ineligible during the postoperative period. With a 30% dropout rate (increased from 20% as seen in previous work given the increased length of the exercise program) we will require a total of 34 patients.
Number of participants	34 patients n= 17 participants receiving normal postoperative care n=17 participants allocated to the exercise intervention group
Eligibility criteria	Aged 18+ Patients undergoing colorectal cancer surgery with curative intent
Description of interventions	Participants will undergo preoperative baseline screening and will be randomised to either normal postoperative care or a 12-week supervised exercise programme comprising of both an aerobic and resistance component They will be assessed prior to surgery which will include cardiopulmonary exercise testing (CPET). This is a well-established method of assessing aerobic exercise response and is widely used in the perioperative period for assessment of cancer patients with co-morbidity. The assessment days will also include: muscle ultrasound (vastus lateralis) to ascertain muscle structure (thickness, pennation angle and fascicle length), blood tests, functional composite scores,

	quality of life questionnaires, The assessment days will be carried out at four time points during the study; prior to surgery, before commencement of the exercise program, halfway through the intervention (6 weeks post commencement of exercise) and at the end of the study. In the week before the assessment days patients will wear a physical activity monitor to characterise their daily movements. The control group will also be assessed at the same time points and wear the activity monitors but will not take part in the exercise program. All participants will have a physical activity monitor placed onto the right thigh in the midline at postoperative day 1 until discharge or day 7, whichever is sooner. This is a non-invasive measure of activity and can discriminate between whether a patient is lying, sitting, standing or walking. Once participants self-report feeling able to start exercising again post-discharge, they will commence the 12 week programme. The intervention will consist of 2 resistance training (RET) sessions per week and 75 minutes of vigorous or 150 minutes of moderate aerobic exercise per week (can be split according to patient preference). They will receive a diary to log their sessions and will be monitored via twice weekly virtual follow-up (either telephone or video calling) and for the first 6 weeks weekly visits to ensure that they are adherent to the exercise protocol and provide any support/advice. Satisfactory compliance with the programme will be considered to be the completion of at least 27 sessions over the 12 week period, with a minimum of 13 out of

	18 and 14 out of 18 sessions completed in the first and last 6 weeks, respectively.
Duration of study	3 years Patients will be involved in the study from the date of acceptance until 12 weeks after the start of the exercise program when they attend for their final assessment visit. This will vary considering the length of time it may take to recover from the initial operation prior to starting the exercise program but we anticipate the average participant length of involvement to be 6 months.
Randomisation and blinding	Matched controls will be used so patients will be stratified according to baseline characteristics where possible. Randomization will occur using www.sealedenvelope.com. This will be performed by a member of the research team on the patient's first visit. Patients will not be blinded due to the active nature of the intervention. Any independent review performed of data will be done by a researcher who has been blinded to group allocation. All possible analysis will be done in a single blinded manner (e.g., analysis of ultrasound scans, CPET, blood samples etc).
Outcome measures	Primary outcome: To achieve a significant increase in anaerobic threshold (AT) on CPET (above 2.26ml/kg/min) in a cohort of colorectal cancer patients who have undergone surgery with curative intent following a 12-week combined aerobic and resistance exercise program compared to control. Secondary outcomes: Good compliance/adherence to the exercise program (as defined within this protocol). Changes in muscle mass as assessed using USS between the two groups,

	Changes in blood parameters, especially in inflammatory markers between the two groups and pre and post exercise; Ascertain whether there is any improvement in time to return to baseline and functional composite scores in the exercise group compared to control, Subjective questionnaire data with regards to the practical application of a supervised postoperative exercise program and patient opinion with regards to feasibility and utility.
Statistical methods	Upon study completion data will be analysed using GraphPad Prism, v8.0, (La Jolla, Calif. US) and SPSS version 27 (IBM, US), Data will be analysed in house by members of the research team with statistical oversight provided by the study statistician. After testing for normality, data will be analysed using appropriate post-hoc tests to determine differences between the control and intervention groups (one-way ANOVA) and group x time interactions in the exercise groups (i.e. baseline versus 6- and 12-week assessments).

ABBREVIATIONS

AE	Adverse event
COMAP	Centre Of Metabolism, Ageing & Physiology
CPET	Cardiopulmonary exercise testing
CI	Chief investigator overall
CRF	Case report form
CRP	C-reactive protein
DAP	Data analysis plan
DASI	Dukes Activity Score Index
ERAS	Enhanced Recovery after Surgery
ERP	Enhanced Recovery Programme

EORTC-QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients
FBC	Full blood count
GCP	Good Clinical Practice
HBA1c	Glycosolated haemoglobin
ICF	Informed consent form
iEMG	Intramuscular Electromyography
LFT	Liver function tests
NHS	National health service
PI	Principal investigator at a local centre
PIS	Participant information sheet
REC	Research ethics committee

RET	Resistance exercise training
R&D	Research and Development department
SAE	Serious adverse event
SPPBT	Short physical performance battery test
TUG	Timed up and go test
U&E	Urea and electrolytes
UoN	University of Nottingham
USS	Ultrasound

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Surgery is usually the gold standard treatment option to achieve a curative outcome in colorectal cancer patients and forms a large part of the scope of practice for colorectal surgeons(1). Cancer is still primarily a disease associated with advancing age; therefore patients often present with a pre-existing burden of disease which can affect their overall fitness for surgery(2). There are guidelines which are enacted via the use of multi-disciplinary teams (MDT) who determine those who are eligible for potential resection, which can be for both curative and palliative intent (3). Those who are staged appropriately for surgery must be physiologically capable of withstanding the surgery involved, whether that comes in open, laparoscopic or robotic format (4). This decision both should and usually does involve other disciplines beyond surgeons, such as anaesthetists and geriatricians. There has been a plethora of research into preoperative scoring systems to help define the appropriate population to have surgery, and, as cancer is primarily a disease of ageing, this is ever more important in an older multi-morbid patient group that have other pathologies that may preclude them from surgery(5). As progression of these scores, there has also been work into preoperative optimization of patients to help them better withstand the rigors of surgery, largely known as “prehabilitation”(6,7). This has shown some encouraging results, even within the limited timescale of urgent surgery for malignancy.(8)

Postoperatively, programs such as enhanced recovery after surgery (ERAS), also known as enhanced recovery programmes (ERP), have put the spotlight on trying to improve morbidity and mortality postoperatively, by providing goal-directed targets to enable the patient to be ambulatory, well and discharged safely as quickly as possible(9). The effects of these programs are usually measured by the parameters of 30 and 90-day outcomes, with limited conclusions with regards to patient-related quality of life (10). Longer term post-discharge exercise programs in cancer patients after surgery are less well-studied, with little advice given during routine follow-up appointments outside

of the population level government guidelines for physical activity. The onus shifts to self-directed recovery, with little or no structured guidance on how to rebuild strength and fitness in order to attempt to return to either preoperative or ideally pre-disease levels of activity and quality of life. Patients are often not back to their previous quality of life within 12 months and can also suffer long-term emotional effects that are also addressed with variable frequency(11). In addition, a considerable number of patients with colorectal cancer will also have adjuvant chemotherapy, which can further lead to issues such as fatigue and deconditioning and prolong or prevent any return to the premorbid state(12). (9) The effects of these programs are usually measured within the parameters of 30 and 90-day outcomes, with limited conclusions with regards to patient-related quality of life measures.(10) Longer term post-discharge exercise programs in cancer patients after surgery are less well-studied, with little advice given during routine follow-up appointments outside of the government guidelines. The onus shifts to self-directed recovery, with little to no structured guidance on how to rebuild strength and fitness in order to attempt to return to either preoperative or pre-disease levels of activity. Patients are often not back to their previous quality of life within 12 months and can also suffer long-term emotional effects that are also addressed with variable frequency.(11) A considerable number of patients with colorectal cancer will also have adjuvant chemotherapy, which can further lead to issues such as fatigue and deconditioning and prolong or prevent any return to the premorbid state.(12)

It has been shown that even with cancer, patients can start or continue to exercise with few ill effects(8,13). This can improve both physical and mental health, and this exercise can be taken in multiple different formats. The UK government guidelines on exercise recommend either 75 minutes of vigorous/very vigorous or 150 minutes of moderate intensity exercise per week, which can be split up into any format and number of sessions one so chooses. This should also be accompanied by at least two days a week of muscle strengthening exercises for all the major muscle groups(14).(8) (13)This can improve both physical and mental health, and this exercise can be taken in multiple different formats. The UK government guidelines on exercise

recommend either 75 minutes of vigorous or 150 minutes of moderate intensity exercise per week, which can be split up into any format and number of sessions one so chooses. This should also be accompanied by at least two days a week of muscle strengthening exercises.(14)

Our proposed study aims to fill this gap by providing a structured exercise program that participants commence when they self-report an ability to start after post-surgical discharge. The main advantage over preoperative exercise is the lack of time restrictions in a cancer cohort. They will undergo a 12-week program with regular visits or contacts for supervised sessions to ensure they are completing the exercise appropriately and to provide guidance/reassurance. Baseline (preoperative), beginning, mid-point and end of intervention assessments will be performed in order to measure changes in aspects pertaining to physical fitness and quality of life, which seek to show an improvement compared to postoperative status and hopefully and arguably more importantly from a patient-centred approach, compared to initial baseline preoperative measures.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

To determine whether a 12-week supervised exercise program which follows government guidance with regards to physical activity targets, can improve the rate of rehabilitation back to or above baseline in a group of colorectal cancer patients who have had recent surgery.

PRIMARY OBJECTIVE

To achieve a significant increase in anaerobic threshold (AT) on CPET (above 2.26ml/kg/min) in a cohort of colorectal cancer patients who have undergone surgery with curative intent following a 12-week combined aerobic and resistance exercise program.

SECONDARY OBJECTIVES

To assess the feasibility of a twelve-week period of supervised exercise with a home-based component in this cohort of patients after surgery for colorectal cancer.

To assess whether patients feel any emotional/qualitative benefit from a period of supervised exercise in order to help them return to their normal activities of daily living more quickly/at all.

Using muscle ultrasound, blood tests and functional composite scores, measure any changes seen during the study with the application of a supervised postoperative exercise program compared to control (normal postoperative care).

DETAILS OF PRODUCT(S)

No product will be administered as part of this trial.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

This will be a single centre randomised controlled trial.

Primary endpoint

To achieve a significant increase in anaerobic threshold (AT) on CPET (above 2.26ml/kg/min) in a cohort of colorectal cancer patients who have undergone surgery with curative intent following a 12-week combined aerobic and resistance exercise program compared to control.

Secondary endpoint

Changes in muscle mass as assessed using USS between the two groups,

Changes in blood parameters, especially in inflammatory markers between the two groups and pre and post exercise;

Ascertain whether there is any improvement in time to return to baseline and functional composite scores in the exercise group compared to control,

Subjective questionnaire data with regards to the practical application of a supervised postoperative exercise program and patient opinion with regards to feasibility and utility.

Safety endpoints

Initial screening visit and examination will be performed by a qualified doctor. This will include a medical examination of the cardiovascular and respiratory systems and will include a 12 lead ECG.

Abnormal blood results reported and interpreted by a clinical member of the research team.

Any adverse events reported at any point throughout the study

Cardiovascular instability during CPET training as listed below in exclusion criteria or during any of the exercise training sessions.

Stopping rules and discontinuation

Any participant may withdraw from the study at any time without giving reason(s). If at screening any previously unknown abnormality is discovered, the patient and their medical team will be informed, and their eligibility may be revoked. If the screening ECG shows any abnormal arrhythmia, 2nd or 3rd degree heart block or BP >160/100mmHg would warrant exclusion.

RANDOMIZATION AND BLINDING

Matched controls will be used so patients will be stratified according to baseline characteristics where possible. Randomization will occur using www.sealedenvelope.com. This will be performed by a member of the research team on the patient's first visit. Patients will not be blinded due to the active nature of the intervention. Any independent review performed of data will be done by a researcher who has been blinded to group allocation.

All possible analysis will be done in a single blinded manner (e.g., analysis of ultrasound scans, CPET, blood samples etc.).

Maintenance of randomisation codes and procedures for breaking code

There should not be any breaking of the code as both participants and the research team will be aware of allocation by nature of the intervention.

TRIAL/STUDY MANAGEMENT

Potential participants will be recruited from the colorectal outpatient clinic, RDH. The Clinical Research Fellow (Miss Paul) will be responsible for recruitment and will organise and plan all assessment days and data collection for the participants. The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: The study will last for approximately three years and will commence once ethical approval has been granted. Recruitment will close once a sufficient number of patients have been enrolled. They will be involved from their initial meeting in the colorectal clinic until their final postoperative visit

twelve weeks after starting the exercise program. Firstly, there will be the time from recruitment until their operation. We are anticipating that in order to comply with the government 31-day target from treatment plan decision to surgery that this should take no longer than one month. We will also need to factor in variable lengths of postoperative in-hospital stay. Only after this will postoperative exercise begin once the patient self-reports being able to start the program, which is in itself dependent on other factors such as the patients' baseline fitness or any postoperative complications. We anticipate this period to be approximately three to six weeks for the vast majority of patients.

The study will conclude once the final patient has attended their 12-week exercise visit for final assessment.

Participant Duration: The overall length of involvement in the study is approximately six months but will vary according to the patient.

End of the Trial

The end of the study will be the last 12-week exercise visit (3rd postoperative assessment visit) of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Participants will be approached at the colorectal cancer clinic at RDH after they have been given a clear plan of management of their cancer which will include surgery. This plan will have been provided in advance by the multi-disciplinary team meeting (MDT), which will provide an outcome for surgery. This is a high-volume centre with an expert team of surgeons and Nurse Specialists who support patients who have been diagnosed with colorectal cancer. These clinic

sessions are usually face-to-face due to the sensitivity of the discussions. The clinical team will discuss the study briefly with any eligible participant during the clinic, and if patients are interested in further information, their details will be shared with the research team to introduce themselves and discuss the trial in further detail. They will then be provided with the participant information sheet, giving them the chance to read about the study in more detail. If patients are not being offered surgery, or decline a surgical intervention, they will not be eligible for inclusion in the study. This will include both men and women aged 18 and above. No pregnant people will be included.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

The principal inclusion criteria for initial enrollment into the study is as follows:

Aged 18 years and over

MDT outcome of proven or high clinical suspicion of colorectal cancer

Due to undergo either laparoscopic, robotic or open resection with curative intent

Ability to exercise on a static bike (in order to complete the CPET, not required for the exercise programme)

Ability to give informed consent

Must be able to their organize own transport to RDH for the duration of the study in order to complete the supervised exercise sessions

Availability for the period of study inclusion

Exclusion criteria

Participants who lack capacity to consent

Participants with a new diagnosis undergoing emergency surgery

Participants with a past medical history including the following:

Recent myocardial infarction (MI) in the last 6 months or unstable angina

Heart failure (New York Heart Association Class III/IV)

Uncontrolled hypertension (BP>160/100mmHg)

Previous stroke/TIA

Cerebral or abdominal aortic aneurysm

Severe respiratory disease including known pulmonary hypertension (>25mmHg)

Exercise induced asthma or brittle asthma

Abnormal blood and/or ECG results

Patients who are unable to undergo CPET according to the Perioperative Exercise Testing and Training Society (POETTS) published consensus guidelines on performing CPET(15) (see CPET Safety and Adverse Events)

Expected duration of participant participation

Study participants will be participating in the study for approximately 6 months.

Removal of participants from therapy or assessments/Participant Withdrawal

Patients reserve the right to withdraw from the study at any point for any reason, and this will be highlighted to them during the recruitment process. The participants will be made aware that this will not affect their future care. Any data that has been collected up to the point of withdrawal cannot be erased and may still be used in final analysis, if appropriate. Participants may also be withdrawn at the discretion of the research team. The most likely reason for this is a new clinical development resulting in a volunteer becoming ineligible. If this occurs, the participant will be informed, the reason for withdrawal will be documented and it will be re-explained that data collected up to this point cannot be erased and may still be used in the final analysis (as per the patient information sheet and informed consent form). Withdrawn patients may be replaced where feasible and this will apply at all stages of the study.

Informed consent

A member of the research team (principally the Lead Investigator) will discuss the study with a potential patient recruit, after it has been introduced by a member of the patients clinical care team.I If they are interested in being recruited, they will be given a copy of the patient information sheet.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

Recruited patients from the colorectal clinic at the Royal Derby Hospital will be invited to attend the University of Nottingham, Centre Of Metabolism, Ageing & Physiology (COMAP) research group unit at the Royal Derby Hospital Centre.

They will have a screening questionnaire which will review their past medical history, recent results, ECG and BP assessment and determine eligibility into the study. If deemed eligible they will have their consent recorded and be randomised into either the exercise group or control (normal postoperative care). Figure 1 outlines the study design. If they are not eligible for inclusion they will be withdrawn and recorded as screen failures.

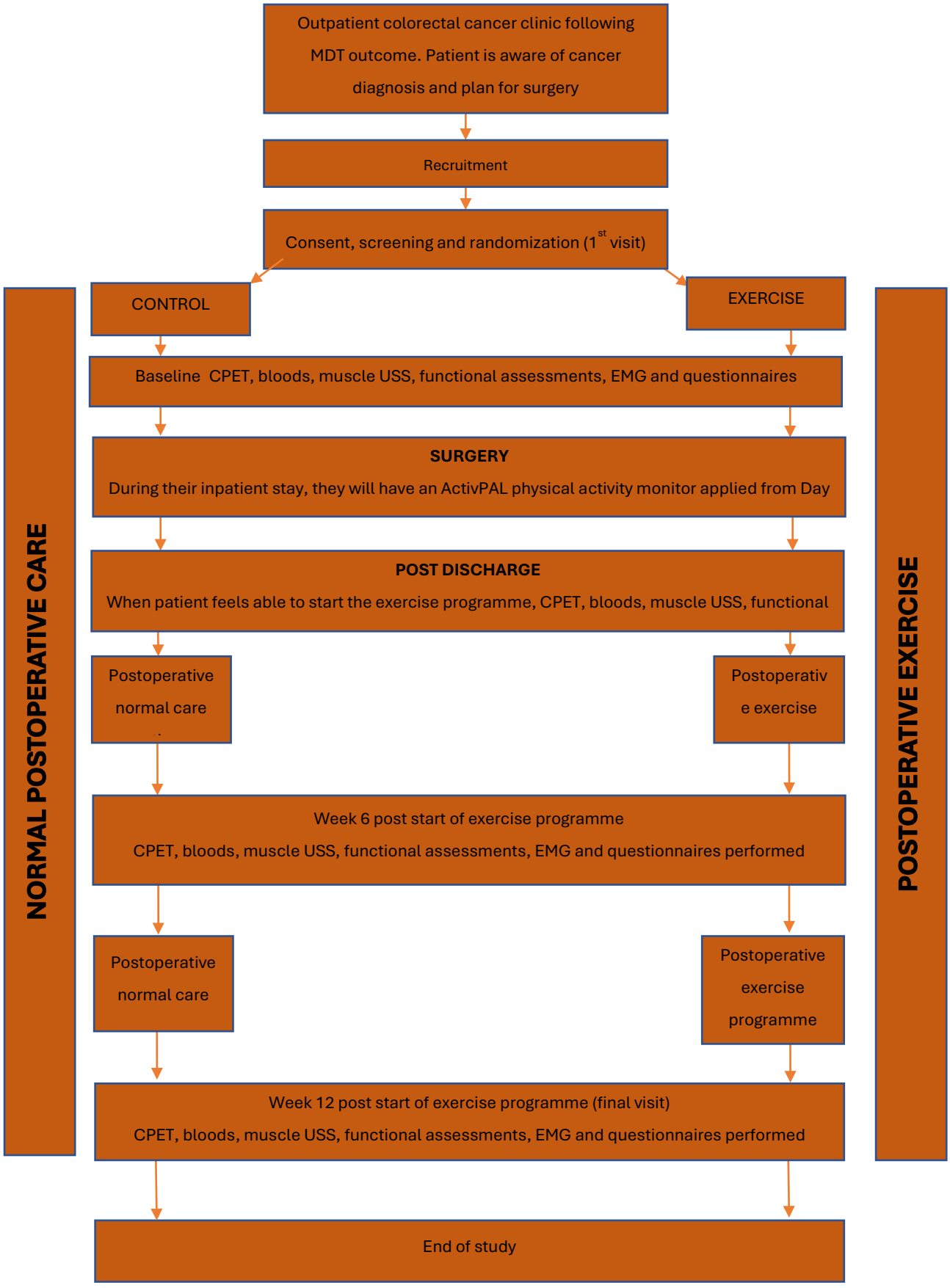

Figure 7.1. Outline of the proposed study.

Baseline assessment

This will take place at the COMAP unit, UoN, RDH 5-7 days prior to surgery. Participants will have a small (~9mL) blood sample taken via venepuncture of a forearm vein (for full blood count, urea & electrolytes, liver function tests, C-reactive protein and inflammatory cytokine analysis) and a muscle ultrasound of the thigh will be performed to determine muscle structure using vastus lateralis to ascertain muscle thickness, pennation angle and fascicle length. The muscle USS is non-invasive and painless. Participants will also have an ECG to assess autonomic nervous system function, which involves cardiovascular measures during a short, prescribed breathing pattern and in response to postural changes.

Participants will also complete a CPET test at this visit. The CPET will be conducted in accordance with POETTS guidelines using a Lode Corival cycle ergometer (Lode Corival, Lode, Groningen) and gas analysis system (ZAN 680, nSpire Health, Colorado, US) and will last for 8-12 minutes (15). A modified Bruce-Ramp CPET protocol will be used as is common practice for the research group hosting this project, with ramp start point and incremental level determined based on participants body weight and self-reported level of physical activity. During all CPET sessions, participants will be monitored with a 12 lead ECG, non-invasive blood pressure monitoring and pulse oximetry with supervision by a clinician trained in advanced life support.

Measures of physical function will include a timed up and go test (TUG), a short physical performance battery (SPPBT) and determination of muscle strength, power, balance and motor control using standard assessment methods as previously used within this research group (IRAS project ID 275264).

During the functional assessment in the COMAP exercise suite we will also perform intramuscular electromyography (iEMG). This will involve the placement of electrodes onto the lateral thigh of the participant whilst they are

sat on a chair. Their leg will be immobilized temporarily and they will be asked to attempt to straighten their leg at the knee. We will place a small electrode intramuscularly using a small needle. This needle is smaller than that used to perform venepuncture, and is similar in size to an acupuncture needle. We will then capture nervous function within the muscle during various movement exercises. The test will take approximately 20 minutes.

The iEMG will be performed using Natus concentric needle electrodes, a CED 1401 data acquisition unit and a Digitimer D440 amplifier. The 1401 and D440 are not medical devices and are designed and sold as research instrumentation only.

All iEMG assessments will be undertaken in the neurophysiology lab, located in the School of Medicine, University of Nottingham, Royal Derby Hospital.

Finally, they will be asked to complete two quality of life questionnaires (Dukes Activity Score Index – DASI and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients, EORTC-QLQ30). They will be provided with light refreshments at this time as well. This will conclude the assessment day.

Post operative period

The day after their surgery, all recruits will have an ActivPAL physical activity monitor applied to their leg. This is a non-invasive physical monitor that records periods spent, lying, walking and engaging in more strenuous activity. This will remain in situ for up to 7 days, or until the patient is discharged, whichever is the shorter length of time. After removal – the data is uploaded (it does not include any person-identifiable data) for analysis using software on a local computer in the COMAP unit. After discharge, they will have telephone follow up from the research team to monitor progress.

2nd assessment

Once the participants feel able to attend and start the exercise program, they will reattend for a second assessment. All of the baseline measurements detailed above will be repeated. They will then be shown the resistance training exercises to be performed and given an intervention pack to record their exercise training (see Appendix 1.). Detailed information regarding their intended aerobic exercise will be documented and they will be given the ActivPAL physical activity monitors and diet diaries to record their habitual physical activity and dietary intake, respectively. Up to three, four-day diet diaries will be provided, with detailed instructions for completion, with patients asked to complete these immediately after their 2nd and 3rd assessments, and in the week prior to their 4th and final assessment.

For participants in the control group, they will be assessed in the same manner as above including the physical activity monitoring and diaries, but then advised to carry on with normal postoperative care advice as given by their medical team.

Participants in the exercise group will be invited to return once a week for the first four weeks in order to check on their progress, answer any questions and if necessary, evaluate their technique and adherence to the exercise program. Participants will also be contacted by telephone once a week, approximately three days after their in-person visit of that week to provide support as needed. After 4 weeks, if they are happy to continue in a self-directed manner, they will not need to attend for in-person visits but instead will receive 2 virtual follow-up sessions a week for the remainder of the intervention. This may be either by telephone or video call. However, if participants feel that they would prefer in person follow up this can be accommodated as well for as long as it is their preference.

Exercise intervention

All exercises are designed to be performed at home with minimal equipment. An information pack will be provided to participants which will outline the exercises and provide space for them to log their activities. They will be asked to do the UK government guidelines of 75 minutes of vigorous or 150 minutes of moderate intensity aerobic exercise per week plus two resistance training sessions per week. If patients take part in any pre-existing regular aerobic exercise (for example, swimming, cycling, etc.) we would encourage them to continue this to complete the required amount of time. Otherwise, at the second assessment day, we will demonstrate with them an aerobic exercise n such as brisk walking, a treadmill run (can be performed with an at home treadmill if they already have one; failing that, an outdoor run) or a cycle session, giving them an idea of what level of exertion they need to be at. When at home, they can split the aerobic component into as many smaller sessions as they like as long as they reach either 75 or 150 minutes as per above. We anticipate that as the programme continues, they may opt for vigorous sessions over moderate sessions, but there will be no requirement to do one or the other at any point.

The resistance training session will be demonstrated and the participant will complete it at the second assessment day under supervision (see Appendix 1).

The exercises include:

Squats

Hip flexion

Hip extension

Hip abduction

Seated row

Bench press

Lateral raises

There are seven exercises which should be completed as 12-15 repetitions for 2 sets. There is a 60 second rest in between each exercise. It will total thirty minutes including a 2 minute warm up and cool down at the beginning and end of each session.

Each exercise will be demonstrated for the participant and then they will perform it under supervision to ensure correct form and technique. These exercises are designed to be performed at home with a resistance band which we will provide. The bands provide varying levels of resistance, and if required can be swapped for a higher resistance after observation of the participant/participant request during the follow-up visits.

The participants will be contacted twice weekly to provide support, help ensure compliance and troubleshoot any potential difficulties, including any adverse symptoms. If required, patients can attend for any face-to-face reassurance or repeat demonstration. They will also be provided with a video of a member of the research team performing the exercises that they can refer to at home. For the first four weeks they will attend weekly to complete one of their sessions in a supervised manner by one of the members of the research team. This will be to ensure correct technique and provide any further support.

Our research group has conducted exercise regimens of this type in both healthy volunteers and cancer patients with similar demographics to our study without incident. We would recommend patients terminate the exercise programme immediately if they experience any of the following symptoms:

Chest pain suggestive of ischaemia

Ischemic ECG changes

Complex ectopy

Second or third degree heart block

Fall in systolic pressure 20 mm Hg from the highest value during the test

Hypertension (250 mm Hg systolic; 120 mm Hg diastolic)

Severe desaturation: SpO2 ≤ 80% when accompanied by symptoms and signs of severe hypoxemia

Sudden pallor

Loss of coordination

Mental confusion

Dizziness or faintness

Signs of respiratory failure

Should any of the other occur, we will advise them to seek immediate emergency medical attention and they will be withdrawn from any further participation in the study on the grounds of safety.

3rd assessment

At week 6 all baseline measurements will be repeated for both groups, with this mid-point visit essential to help us determine the temporal nature of any benefit elicited by the exercise intervention. The exercise group can use this visit as their in-person session for that week if they wish. In the week prior to their attendance, both groups will have the ActivPAL activity monitor reapplied and their physical activity monitored. These will be returned at their 3rd assessment day.

4th assessment (final visit)

Both groups will attend for a final visit 12 weeks after the 2nd assessment. This end of study assessment will mirror the previous assessments. Again, in the week prior to their attendance, both groups will have the ActivPAL activity monitor reapplied and their physical activity monitored. All participants will also

have the opportunity to deliver any verbal and written feedback they may have as to how they have felt the study has run at this session, with anonymous feedback also facilitated by a study specific “post-box” in the COMAP unit.

Semi-structured Interview

Within 4 weeks of completion of the exercise programme, all participants who have consented to future contact in the exercise group will be asked to participate in a semi-structured interview of approximately 30-60 minutes. It will assess participant views and perceptions regarding the setup and running of the exercise programme, exercise in the postoperative period and during chemotherapy, if applicable and anything that they found particularly difficult, as well as suggestions for improvements. All interviews will take place either at the School of Medicine, University of Nottingham, Royal Derby Hospital (transport can be provided at no cost to the participant) or via Microsoft Teams. The audio from the interviews will be recorded in order to analyse the themes emerging from the content, but no identifiable data will be shared or processed.

Compliance

As part of the weekly visits, the participants will be continuously assessed for their compliance to the exercise program.

1 session is defined as either 150 minutes of moderate or 75 minutes of vigorous aerobic exercise per week, or 1 resistance training (RET) session. The programme is designed to provide 2 RET sessions and one aerobic session per week.

Given the nature of their surgery, we do not expect all the participants to be able to complete a full 3 sessions in the first 2-3 weeks; we will explain to them that they should do as much as they feel comfortable. We would anticipate 70% compliance within the first 6 weeks (at least 13 out of 18 sessions completed), increasing to 80% for the final 6 weeks of the programme (14 out of 18 sessions completed). If participants do not achieve the 70% compliance target during the first 6 weeks they will not complete the 6 week assessment. If they do not complete the final 6 weeks, their 6-week data will still be included in the final analysis but they will not complete the final assessment.

Completion of the exercise programme as a whole will be defined as self-reported completion of a minimum of 27 sessions.

Criteria for terminating trial

If there are no recruits that are willing to be recruited to the study, it will be terminated. Given the good uptake of similar studies previously from this department, we do not anticipate that this will be the case.

If there are any major safety concerns that arise, or previously unknown information is made available that may significantly impact the trial then it may also be terminated. If this is the case, any data already collected may be stored and analysed.

TRANSPORT AND STORAGE OF THE TISSUES

Samples will be stored in a linked anonymised format and labelled using a combination of study reference, unique study identifier and cross referenced with location code numbers to permit accurate linkage to study data and the consent form.

Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

Blood samples will be centrifuged to separate plasma and stored at -80C in an on-site freezer. Any samples taken for NHS pathology analysis will be collected and stored in accordance with local protocol. They will be sent to the Clinical Chemistry department at RDH to be analysed for routine clinical chemistry analysis.

Volunteers will be asked to consent for their samples to be stored for future research. If they agree, samples will be stored at COMAP unit under the University's HTA licence (DI William Dunn- Licence Number 12265). If participants do not agree to the future use of samples they will be destroyed at the end of this study in accordance with the Human Tissue Act, 2004.

The master database will be held by M Paul in a password encrypted file.

LABORATORY ANALYSES

The chemical pathology department at RDH will analyse all screening blood samples which assess routine markers for health (FBC, U&E, LFT, coagulation screen, TFT, lipid profile).

STATISTICS

Methods

Upon study completion all data will be analysed using GraphPad Prism, v8.0, (La Jolla, Calif. US) and SPSS version 27 (IBM, US),. Data will be analysed in house by members of the research team with statistical oversight provided by the study statistician.

After testing for normality, data will be analysed using appropriate post-hoc tests to determine differences between the control and intervention groups (one-way ANOVA) and group x time interactions in the exercise groups (i.e. baseline versus 6 and 12 week assessments).

Sample size and justification

In a previous cohort of cancer patients from the same centre, a 4 week preoperative intensive HIIT exercise program showed a mean difference in VO2AT of 2.26ml/kg/min between the exercise group and control (normal postoperative care) with a 95% confidence interval of 1.25 to 3.26ml/kg/min and an effect size of 0.42.(8) Using G*Power calculator (Axel Buchner, University of Dusseldorf), to detect a significant increase in VO2AT with 95% confidence and 5% significance we need to study 23 subjects. Previous studies have achieved a dropout rate of 20%. Given the significantly increased length of this study we have assumed a dropout rate of 30%. With a postoperative readmission rate of approximately 11% and mortality rate of 3% based on the National Bowel Cancer Audit data 2020 we would therefore need to recruit 34 volunteers, 17 in each arm.(16)

Assessment of efficacy

Primary efficacy endpoint

Mean increase in AT (measured via CPET) in exercise group versus control.

Secondary efficacy endpoints

Mean increase in AT (measured via CPET) in exercise group compared to baseline

Mean differences in baseline measures such as BP, resting HR, blood tests and functional composite scores between the exercise group and control.

Differences in muscle thickness & pennation angle changes as seen on USS between the exercise group and control.

Assessment of safety

At the current time both the research team and patients will maintain appropriate social distancing and adhere to the current COVID guidance as per the rules of UoN. This includes wearing personal protective equipment where necessary to reduce the risk of transmission between parties. The research team members will also have regular COVID testing as required by UoN. UoN COVID guidelines will be adhered to for the duration of this study. Similarly, during recruitment for this study, which will take place at the RDH, all current NHS COVID requirements will be adhered to in accordance with up-to-date guidance.

Any blood samples that are required will be taken by medically qualified individuals and complications will be dealt with by appropriately trained medical staff in accordance with best medical practice.

The exercise intervention is proven to be safe in cancer patients and postoperatively. There have been previous studies, including within our centre that have shown both aerobic and resistance training to be safe in cancer patients, and previous studies have shown exercise to be safe in postoperative patients, even those undergoing major surgery (7,9).

Procedures for missing, unused and spurious data

If significant amounts of data are missing the participant will be removed from the trial. If appropriate the data will be included in subanalysis but will not be included in the final dataset.

Definition of populations analysed

Safety set: all participants who complete the initial baseline assessment

Full analysis set: all participants who complete the 12 week exercise program and all assessments

Per protocol set: all participants who are part of the full analysis set without any deviations from protocol that could affect the outcome of the study

ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the treatment or intervention that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

CPET Safety & Adverse Events

The Perioperative Exercise Testing and Training Society (POETTS) have published consensus guidelines on performing CPET, including indications for the stopping the test (15):

Angina >2 mm ST depression if symptomatic or 4 mm if asymptomatic or >1 mm ST elevation

Significant arrhythmias causing symptoms or haemodynamic compromise

Fall in systolic blood pressure >20 mm Hg from the highest value during the test Hypertension >250 mm Hg systolic; >120 mm Hg diastolic

Severe desaturation: SpO2 <80% (lower may be accepted in patients with known underlying lung disease)

Loss of coordination

Mental confusion

Dizziness or faintness

The reason(s) for stopping the test should be documented by both the research member and the participant. The list above is not exhaustive and careful monitoring should identify any of these or any other potential issues.

In addition, our exclusion criteria includes recent MI/unstable angina, heart failure and uncontrolled hypertension. This is to acknowledge the POETTS guidelines re: terminating the test and to reduce the risk of adverse safety events whilst undergoing CPET.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment / intervention administration which makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, but which could also be explained by other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study treatment / intervention is not the cause. The Chief Investigator shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

All treatment related serious adverse events will be recorded and reported to the REC as part of the annual reports. Unexpected serious adverse events will be reported within the timeframes to the REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

Trial Treatment / Intervention Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment or intervention shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

Assess the event for seriousness, expectedness and relatedness to the trial treatment or intervention.

Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.

If the event is deemed related to the trial treatment or intervention shall inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event.

Shall, within a further eight days send any follow-up information and reports to the REC.

Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the

changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise

entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned an identity code number, prefixed with POSTEx for use on all trial-related documents which will be traceable to the electronic database. All hard copies of CRF will be kept in a lockable cupboard in a secured office on site (RDH, University of Nottingham). Back up electronic files will be kept on a password protected computer in a password protected program.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

CRFs will have the participants' unique trial code, as will any other trial documents. This will comprise of the study acronym, two letters, and a sequential study number (e.g POSTExJY01).

All paper forms will be completed using black ballpoint pen. Errors will be struck through but not erased, and any amendments will be initialled and dated. Accuracy of data will be the signed responsibility of the CI which will be recorded in the CRF.

Sample Labelling

Samples will be labelled with the participants' trial identity code as per their CRFs and any other trial documents, such as the consent form. The documents and database will also be labelled with the study acronym and enrolment number. Any samples analysed at the pathology laboratory at RDH will be labelled in accordance with local protocol.

Source documents

The source data will be filed at the investigator's site, which can include but is not limited to the CRF, consent forms and any laboratory results. The CRF may also serve as its own source data. Access shall be restricted to staff listed on the Trial Delegation Log They will be made readily available for review at any time if required.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

DATA PROTECTION

All person identifiable data will be pseudoanonymised at the earliest point possible. All researchers have been trained in data protection and will fully adhere to the principles of GDPR and the Data Protection Act, 2018. The minimal amount of identifiable data required will be collected. Any information in the patients' medical records will be stored and accessed in line with local information governance protocols and will be treated in the same manner as existing hospital records. All ActivPAL data is collected in anonymised format and uploaded to a single computer on site which houses the software for analysis. This will be undertaken by the research team.

Electronic data will be input into an encrypted database which is secure and password protected. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

Access will be restricted to a University of Nottingham password protected computers, which are in a locked office on site (COMAP, School of Medicine, University of Nottingham, Royal Derby Hospital. All consent forms and hard copies of any data (such as questionnaires) will be kept in a lockable filing cupboard in an office that is also locked.

The Chief Investigator will act as both custodian and has overall responsibility for the study and data management.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

The Trial Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

There will be periodic monitoring of trial data to ensure compliance with guidelines for completion and storage. This will include checking consent forms for signatures, ensuring regular back-up and recovery protocols are in place

and validation of data analysis. The Trial Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

All trial data and audit will be made readily available for inspection by the relevant authorities if required. Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Data derived from this study will be published in a peer reviewed journal and may also be presented at national or international meetings. There will be no patient identifiable data included. It will also form a significant part of the research fellow's thesis.

USER AND PUBLIC INVOLVEMENT

The public have been involved in previous work which forms the background to this study. Following previous questionnaires, it has been shown that a supervised preoperative exercise program even within a strict timeframe is feasible, enjoyable and would be recommended to others. This was seen in both healthy volunteers and in a cohort of cancer patients.

An acceptability questionnaire will also form part of this study, so the participants will have the opportunity to give feedback on various aspects of the trial.

STUDY FINANCES

Funding source

This trial is funded by the personal research funds of Mr. Jon Lund.

Participant stipends and payments

There will be no financial payments or reimbursements to the participants for their enrollment in this trial. Travel expenses will be offered for any hospital visits in excess of usual care.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

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7.3 Ethics Approvals and Amendments

7.3.1 PHYSPAL study London (Westminster) research ethics committee approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mr Jon Lund
Clinical Associate Professor, University of Nottingham, Division of Graduate Entry Medicine and Health, School of Medicine and Consultant Colorectal Surgeon, Royal Derby Hospital
University of Nottingham
University of Nottingham Medical School
Royal Derby Hospital
Uttoxeter Road, Derby
DE22 3DT

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

23 June 2023

Dear Mr Jon Lund

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**An observational cohort study to assess the postoperative activity of colorectal cancer patients undergoing elective surgery.**
IRAS project ID:	**313070**
Protocol number:	**23025**
REC reference:	**23/PR/0550**
Sponsor	**N/A**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **313070**. Please quote this on all correspondence.

Yours sincerely,

Abitha Paimpillichalil
Approvals Specialist
Email: approvals@hra.nhs.uk

Copy to: *Angela Shone*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [PHYSPAL Indemnity Insurance]		
IRAS Application Form [IRAS_Form_12052023]		12 May 2023
Letter from sponsor [PHYSPAL Sponsor Letter]		09 May 2023
Non-NHS/HSC Site Assessment Form [PHYSPAL Delegation Log]	Final version 1.0	09 May 2023
Non-validated questionnaire [PHYSPAL Discharge Questionnaire]	2.0	20 June 2023
Organisation Information Document [PHYSPAL OID]	Final version 1.0	09 May 2023
Other [PHYSPAL Insurance Evidence]		09 May 2023
Other [PHYSPAL IRAS 313070 Response to REC Comments 20.06.23]		20 June 2023
Participant consent form [PHYSPAL CONSENT]	2.0	20 June 2023
Participant information sheet (PIS) [PHYSPAL PIS]	2.0	20 June 2023
Research protocol or project proposal [PHYSPAL PROTOCOL]		09 May 2023
Sample diary card/patient card [PHYSPAL Accelerometer Diary]	2.0	20 June 2023
Schedule of Events or SoECAT [PHYSPAL SoE]	Final version 1.0	09 May 2023
Summary CV for Chief Investigator (CI) [PHYSPAL CI CV]		
Summary CV for student [PHYSPAL JB CV (Student)]		09 May 2023
Summary CV for student [PHYSPAL MP CV (Student)]		
Summary CV for supervisor (student research) [PHYSPAL BEP CV (Supervisor)]		
Validated questionnaire [PHYSPAL HADS Questionnaire]		

IRAS project ID	313070

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
Research activities and procedures as per the protocol and other study documents will take place at participating NHS organisations.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study in accordance with the contracting expectations detailed.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other agreement to be used with participating NHS organisations of this type.	Study funding arrangements are detailed in the Organisation Information Document.	In line with HRA/HCRW expectations a Local Collaborator should be appointed at participating NHS organisations of this type. The sponsor has indicated however that they wish to appoint a local Principal Investigator.	Where an external individual will be conducting any of the research activities that will be undertaken at this site type then they would be expected to hold a Letter of Access. This should be issued be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm Occupational Health Clearance. These should confirm standard DBS checks.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

7.3.2 POSTEx study research ethics committee approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mr Jonathon Lund
Consultant colorectal surgeon and Clinical Associate Professor
University of Nottingham
University of Nottingham Medical School
Royal Derby Hospital
Uttoxeter Road, Derby
DE22 3DT

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

09 December 2021

Dear Mr Lund

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A randomised controlled trial to assess the efficacy of a postoperative supervised exercise programme in patients who have undergone elective curative surgery for colorectal cancer.**
IRAS project ID:	**281681**
Protocol number:	**21058**
REC reference:	**21/YH/0264**
Sponsor	**University of Nottingham**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **281681**. Please quote this on all correspondence.

Yours sincerely,
Anna Bannister

Approvals Specialist

Email: approvals@hra.nhs.uk

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template [POSTEx Sponsor/CU agreement]		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
GP/consultant information sheets or letters [POSTEx GP letter]	Final version 1.0	16 September 2021
Interview schedules or topic guides for participants [POSTEx ActivPAL care sheet]	Final version 1.0	02 December 2021
IRAS Application Form [IRAS_Form_28092021]		28 September 2021
IRAS Application Form XML file [IRAS_Form_28092021]		28 September 2021
IRAS Checklist XML [Checklist_28092021]		28 September 2021
Letter from sponsor [POSTEx Sponsor letter]		16 September 2021
Non-validated questionnaire [POSTEx Acceptability Questionnaire]	Final version 1.0	16 September 2021
Organisation Information Document [POSTEx OID]		
Other [POSTEx REC response]	Final version 1.0	02 December 2021
Other [POSTEx Lone Worker Policy]	Final version 1.0	02 December 2021
Participant consent form [POSTEx Consent Form]	Final version 2.0	02 December 2021
Participant information sheet (PIS) [POSTEx PIS]	2.0	02 December 2021
Research protocol or project proposal [POSTEx Protocol]	Final version 1.0	16 September 2021
Sample diary card/patient card	Final version 1.0	16 September 2021
Sample diary card/patient card [POSTEx Exercise Diary]	Final version 1.0	16 September 2021
Schedule of Events or SoECAT [POSTEx IRAS SoE]	Final version 1.0	16 September 2021
Summary CV for Chief Investigator (CI) [POSTEx CI CV]		16 September 2021
Summary CV for student [POSTEx Student CV]		16 September 2021
Summary CV for supervisor (student research) [POSTEx Supervisor CV]		16 September 2021
Validated questionnaire [POSTEx IPAQ Questionnaire]		
Validated questionnaire [POSTEx EORTC QLQC30 Questionnaire]		
Validated questionnaire [POSTEx DASI Questionnaire]		

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one participating NHS organisation therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is intending to use a separate site agreement. The sponsor is using a bespoke agreement. The HRA and HCRW take no position on the acceptability of these changes. Participating NHS organisations should now determine its acceptability and liaise with the sponsor to confirm the content of the agreement.	No external study funding has been sought	A Principal Investigator should be appointed at study sites.	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain an honorary research contract. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio

7.3.3 POSTEx study iEMG amendment approval

NHS
Health Research Authority

Yorkshire & The Humber - South Yorkshire Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

12 April 2022

Miss Melanie Paul
University of Nottingham Medical School
Royal Derby Hospital
Uttoxeter Road, Derby
DE22 3DT

Dear Miss Paul

Study title:	**A randomised controlled trial to assess the efficacy of a postoperative supervised exercise programme in patients who have undergone elective curative surgery for colorectal cancer.**
REC reference:	**21/YH/0264**
Protocol number:	**21058**
Amendment number:	**21058 SA01**
Amendment date:	**22 March 2022**
IRAS project ID:	**281681**

The above amendment was reviewed at the meeting of the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [POSTEx IRAS 281681 Amendment	2.0	22 March 2022

Tool Final Version 2.0 22.03.22]		
Participant information sheet (PIS) [POSTEx_PIS Final version 3.0 date 22.03.22]	3.0	22 March 2022
Participant information sheet (PIS) [Participant Information Sheet]	3.0, highlighted	22 March 2022
Research protocol or project proposal [POSTEx PROTOCOL Amendment Final version 3.0 date 08.04.22]	3.0	08 April 2022

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS Project ID - 281681:	**Please quote this number on all correspondence**

Yours sincerely

pp f. Slade

Dr Louise Taylor
Chair

E-mail: southyorks.rec@hra.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Miss Melanie Paul*

Yorkshire & The Humber - South Yorkshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 05 April 2022

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Simon Baudouin	Retired Medical Doctor	Yes	
Dr Louise Taylor	Registered Nurse	Yes	Chaired the Meeting

Also in attendance:

Name	*Position (or reason for attending)*
Miss Donna Bennett	Approvals Administrator

7.3.4 POSTEx study interview feedback amendment approval

NHS
Health Research Authority

Yorkshire & The Humber - South Yorkshire Research Ethics Committee

NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

15 December 2022

Miss Melanie Paul
University of Nottingham Medical School
Royal Derby Hospital
Uttoxeter Road, Derby
DE22 3DT

Dear Ms Paul

Study title:	**A randomised controlled trial to assess the efficacy of a postoperative supervised exercise programme in patients who have undergone elective curative surgery for colorectal cancer.**
REC reference:	**21/YH/0264**
Protocol number:	**21058**
Amendment number:	**SA02 21058**
Amendment date:	**21 November 2022**
IRAS project ID:	**281681**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [Amendment Tool: Supervised exercise for post-surgery colorectal cancer patients]	v1.6 06 December 2021	21 November 2022
Participant consent form [A randomised controlled trial to assess the efficacy of a postoperative supervised exercise program in patients who have undergone elective curative surgery for colorectal cancer (POSTEx): post stud]	1.0	17 November 2022
Participant consent form [POSTEX_Amendment_ConsentForm_Interviews_Final Version	1.0	17 November 2022

1.0_17.11.22KBcomments]		
Participant information sheet (PIS) [A randomised controlled trial to assess the efficacy of a postoperative supervised exercise programme in patients who have undergone elective curative surgery for colorectal cancer.]	4.0	17 November 2022
Participant information sheet (PIS) [POSTEx_PIS Final version 4.0 date 17.11.22]	4.0	17 November 2022
Research protocol or project proposal [POSTEx PROTOCOL Amendment Final version 3.0 date 31.10.22]	3.0	31 October 2022
Research protocol or project proposal [A randomised controlled trial to assess the efficacy of a postoperative supervised exercise program in patients who have undergone elective curative surgery for colorectal cancer.]	Final version 3.0	31 October 2022

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS Project ID - 281681:	**Please quote this number on all correspondence**

Yours sincerely

pp. Frank Macdonald
Approvals Administrator

Yorkshire & The Humber - South Yorkshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Ruth Clark	Retired CT Senior Project Manager	Yes	
Dr Ian Dumbelton	Retired GP	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Charlotte Miller	Approvals Administrator
Mr Frank Macdonald	Approvals Administrator

7.4 Participant Information Sheets

7.4.1 PHYSPAL study participant information sheet

Local Letterhead to be added

Participant Information Sheet
(Final version 2.0: 20/06/23)

IRAS Project ID: 313070

Title of Study: **An observational study to assess the postoperative physical activity of patients undergoing elective colorectal resection.**

Name of Chief Investigator: Mr Jon Lund
Local Researcher(s): Miss Melanie Paul; Mr James Bunce

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

An accelerometer is a small device that measures how and how often you move non-invasively. We would like to investigate and assess using an accelerometer exactly how much movement, what type of movement and how often you move in the days following your operation. We know that physical activity after surgery is associated with lower rates of

complications such as chest infections but we are less clear on whether this is happening. We would also like to see if your mood and pain levels whilst you are in hospital directly correlates with the amount of activity that you are doing in a significant way.

Why have I been invited?

You have been invited as you are over the age of 18 and are due to have surgery for a colorectal disease. We aim to invite 50 participants like yourself, both male and female. This study also forms part of a PhD study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?

If you agree to take part in the study, you will be required to attend the Centre of Metabolism, Ageing & Physiology (COMAP) research department at the University of Nottingham, Royal Derby Hospital (RDH) site to sign a consent form. If you would rather, we can send the consent form to you by post and you can bring it with you and sign it on the day of your surgery with the researcher.

You will then have your operation as planned, and whilst you are in hospital, we will apply a physical activity monitor to your leg. This will measure the periods of time you spend lying, sitting, standing and walking. This is completely painless and is a small device, around the size of a £2 coin that we affix to your right leg with a clear dressing. We will also give you a questionnaire to complete 3 times during the week

after your operation. When you are discharged, we will remove the monitor prior to you going home and give you a questionnaire to complete. We will upload the data to our computer for analysis, but it will not contain any identifiable data; it is all anonymous. We will contact you after your discharge to see how you are recovering and check for any complications up to 1 month after your surgery.

The entire study will run for roughly 12 months, but you will only be required to be involved from the date of your consent form until 30 days after your surgery. We anticipate this to be around 7 weeks, but it will depend on how quickly you have your operation after the consent has been taken.

Expenses and payments

Participants will not be paid to participate in the study. Travel expenses will be offered for any visits incurred as a result of participation.

What are the possible disadvantages and risks of taking part?

The monitors are completely non-invasive and merely collect information on your position whilst they are on your leg. The only potential issue would be a reaction to the dressing used to apply the monitor. If this is the case, it can be changed for another dressing and moved to the opposite leg.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study may help us to improve the advice we give to patients and how we manage patients after having major colorectal surgery.

What happens when the research study stops?

Once all the participants have finished the final assessment session then we will analyse the data and look for any significant findings. We will then write a series of reports about our results. If you would like to be contacted regarding the results of the study then we will do provided that you have signed the consent form to indicate this.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) within the hospital. PALS contact details: Telephone: 01332785156, Freephone: 08007837691, Email: dhft.contactpals@nhs.net.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you and your medical records during the course of the research. This information will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database at the University of Nottingham. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally – identifiable information possible. Any research data shared with other

institutions or research groups will only be done so anonymously. The use of anonymous data in future research will involve combining your anonymous data with either future studies within the same group or combining your anonymised data with other sites performing similar studies to improve our understanding of the topic.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx.

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Where possible information about you which leaves the site will have your name and address removed and a unique code will be used so that you cannot be recognised from it, however sometimes we need to ensure that we can recognise you to link the research data with your medical records so in these instances we will need to know your name and date of birth.

Your contact information will be kept by the University of Nottingham for 1 year after the end of the study so that we are able to contact you about the findings of the study (unless you advise us that you do not wish to be contacted). This information will be kept separately from the research data collected and only those who need to will have access to it. All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's, and our funders' policies we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified) but if we need to share identifiable information we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

Although what you say to us is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights or clinical care being affected. If you withdraw we will no longer collect any information about you or from you but we will keep the information about you that we have already obtained as we are not allowed to tamper with study records and this information may have already been used in some analyses and may still be used in the final study analyses. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Involvement of the General Practitioner/Family doctor (GP)

We do not need to inform your GP about your agreement to take part in the study.

What will happen to the results of the research study?

We will aim to publish our findings in scientific and medical journals. We may also present the findings at any relevant conferences on the national

and international stage. You will be able to obtain a copy of the final results after the study has ended from the research team.

Who is organising and funding the study?

This study is being organised by the University of Nottingham and funded using the personal research funds of Mr Jon Lund and Dr Bethan Phillips.

Who has reviewed the study?

Before any study involving participants can go ahead, the proposed study must be reviewed by an independent group of people not in any way involved in the study, called a Research Ethics Committee. This study has been reviewed and approved by the London Westminster Research Ethics Committee.

Further information and Contact details

Mr Jon Lund, DM FRCS, Clinical Associate Professor, University of Nottingham, Division of Graduate Entry Medicine and Health, School of Medicine and Consultant Colorectal Surgeon, Royal Derby Hospital.

Email: jon.lund@nottingham.ac.uk

Phone: 01332 724641

Miss Melanie Paul, Clinical Research Fellow, MBChB, MSc, MRCS(Eng). (PhD Student) Division of Graduate Entry Medicine and Health, School of Medicine, University of Nottingham.

Email: melanie.paul@nottingham.ac.uk

Phone: 01332724640

Mr James Bunce, Clinical Research Fellow, BMBS, BMedSci, MRCS(Eng). (PhD Student) Division of Graduate Entry Medicine and Health, School of Medicine, University of Nottingham.

Email: james.bunce@nottingham.ac.uk

Phone: 01332724640

7.4.2 POSTEx study participant information sheet

University of Nottingham
UK | CHINA | MALAYSIA

Participant Information Sheet
(Final Version 5.0 08.12.22)

Title of Study: **A randomised controlled trial to assess the efficacy of a postoperative supervised exercise programme in patients who have undergone elective curative surgery for colorectal cancer.**

Names of Researchers:
Miss Melanie Paul
Dr Beth Phillips
Mr Jon Lund

We would like to invite you to take part in our research study. This information sheet will explain the details of the study, as before you decide whether or not to take part you should understand why it is being performed and what you will have to do. A member of the research team will go through the information sheet with you and answer any questions that you may have. Please feel free to talk to others about the study (i.e. family, friends) and do ask if there is anything that is not clear.

Why are we carrying out this study?

We would like to investigate whether a supervised exercise regime after colorectal cancer surgery can help participants to regain/improve their fitness. We know that especially in older patients, having cancer as well as having a major operation has a significant impact on the body's ability to heal and the ability to get back to previous levels of function. We know patients with cancer can safely take part in moderate and vigorous exercise and a set training programme (that can be tailored slightly to your preferences) based on the government's guidelines should appeal to those who are going to have surgery. This study has been designed for a research doctoral programme and will be included as part of a PhD thesis.

Why have I been invited?

You have been invited as you are over the age of 18 and have been diagnosed with colorectal cancer. Your surgical team feel that you have a good chance of having your cancer removed via surgery. We aim to invite 34 participants like yourself, both male and female.

Do I have to take part?

No. You have the right to decide whether or not to take part. This leaflet is designed to give you as much information as possible before making that decision. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Even after you decide to take part, you can withdraw from the study at any time without having to give a reason. Regardless of whether you agree or not it will not affect your care in any way. This would not affect your legal rights.

What will happen to me if I take part?

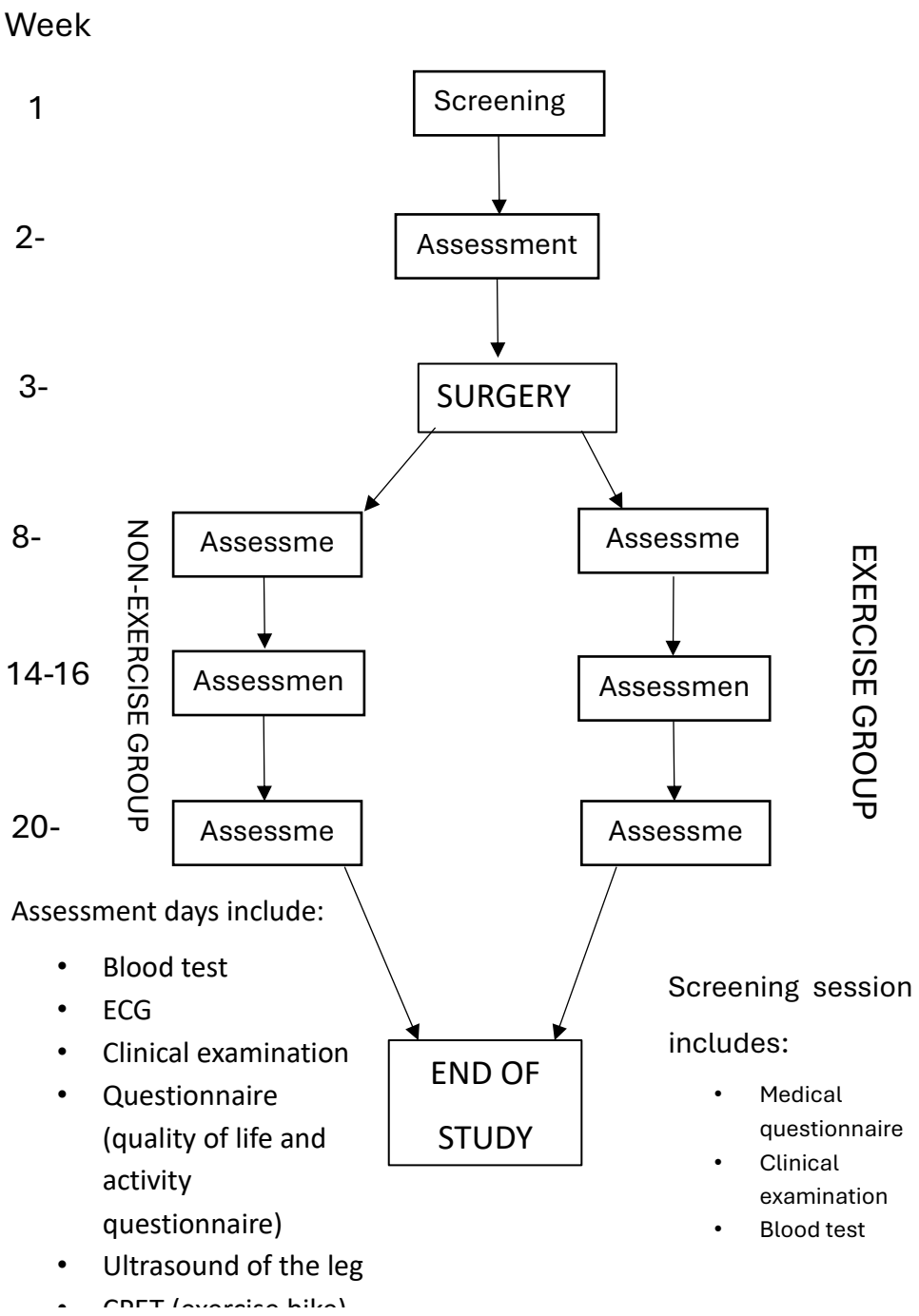
If you agree to take part in the study, you will be required to attend the Centre of Metabolism, Ageing & Physiology (COMAP) research department at the University of Nottingham, Royal Derby Hospital (RDH) site to sign a consent form.

This study is a randomised controlled trial. The study will divide participants randomly into two groups. This is done via a computer and not by the research team. This means that when you sign the consent form to enter the study you must be willing to be in either group. By consenting before randomisation it reduces the chance of bias.

Group 1 will have “standard post-surgical care”. This means that they will be discharged and have a normal postoperative follow up as usual. They will attend the COMAP unit at RDH, for the assessment sessions 4 times, so we can compare them to group 2. Your normal NHS treatment will remain the same as it would be if you were not in the study. Once you feel ready to have the second assessment session, you will attend for us to do so. You will then carry on with your normal post-surgery recovery. We will ask you to come back for another assessment 6 and finally 12 weeks later. At the final session, we will also ask you for feedback on how you think the study has run. The assessment visits will be explained in further detail below.

Group 2 will be required to attend Royal Derby Hospital once a week to be shown and perform the exercises. You will then be asked to perform them at home for a total of 75-150 minutes per week. You will also perform the assessment sessions 4 times but will have to come more often to make sure you are performing the exercises safely and correctly. Again, your NHS treatment will remain the same as it would be if you were not in the study.

At the screening visit, you will complete a questionnaire, which will take some details about your previous history and medical background. A blood test and basic examination will take place, and you will be told if you are eligible to take part in the study. If you are not eligible, you will be told the reason(s) why and your details will be removed from our records. If you consent to be involved, you will be randomised and invited to the first assessment session. The flow chart below outlines how the study will run:



Each assessment session will run in the same way. You will have a blood sample taken (less than 20ml total at each session), an ultrasound of a muscle in your leg (this is painless) and you will be asked to fill out some questionnaires about your quality of life and activity. You will then complete a number of functional assessments to look at factors such as your muscle strength, control, and balance. These will involve you

performing a series of movements such as walking a set distance, performing some jumps if you are able, standing on a board to assess your balance and gait and measuring the time taken to go from sitting to standing. We will also assess how well your nerves send signals to the muscle with a method known as electromyography or EMG. EMG involves small sticky electrodes being placed on the skin, and a very fine needle (much smaller than those used to take blood, similar in size to those used in acupuncture) being placed into the muscle while you move your leg from bent to straight.

Finally, you will perform an exercise test on a static exercise bike. This will give us a baseline level of your fitness to compare with subsequent assessments. Each visit will take approximately 2-3 hours.

You will then have your operation as planned, and whilst you are in hospital, we will apply a physical activity monitor to your leg, regardless of which group you are allocated to. This will measure the periods of time you spend lying, sitting, standing and walking. This is completely painless and is a small device, around the size of a £2 coin that we affix to your right leg with a clear dressing. When you are discharged, we will remove it prior to you going home. We will upload the data to our computer for analysis, but it will not contain any identifiable data; it is all anonymous. We will contact you after your discharge to see how you are recovering; once you are ready to start the exercise programme, we will arrange a repeat assessment session. We will also ask you to have the activity monitor on your leg for up to 7 days at three further points within the 12 weeks, again, regardless of which group you are in.

If you are allocated to the exercise group, we will ask you to do 150 minutes of moderate intensity or 75 minutes of vigorous intensity exercise each week. There are currently no established guidelines on exercise after surgery, so we have based these targets on the government guidelines for exercise in healthy adults. This can be split up into as many sessions as you like throughout the week and can be in any format you so wish. For example, if you enjoy swimming or walking, we

would encourage you to choose this format to fulfil your weekly exercise requirement.

We will also give you a set of resistance exercises to do, which we will demonstrate for you when you attend your sessions. This will involve a resistance band, which we will give to you. It may be that you will require more resistance as the weeks go on, in which case we will give you a different band to use. You will be asked to demonstrate the exercises when you attend for your follow up visits to ensure you are performing them safely and correctly.

We will give you an exercise diary for both the aerobic and the resistance exercises, with instructions on how to complete it. You will be asked to write the date and time of each session, what type of exercise you did, and the time taken to complete it. You will attend each week to see how you are getting on, and we will call you once a week to follow up. These visits will take approximately 60 minutes. After 6 weeks of the exercise programme, you will come back to do another assessment, and then continue with the exercises. We may not require you to come back every week after week 6 if you are happy to continue the exercises at home independently. If that is the case, we will call you twice a week to monitor your progress. After 12 weeks you will come for your final assessment session, where we will also ask you for feedback on how you think the study has run.

The entire study will run for roughly two and a half years, but you will only be required to be involved from the date of your diagnosis until the final assessment session. We anticipate this to be around 5 months, but it will depend on how quickly you feel able to start after your surgery.

Expenses and payments

You will not be paid to take part in this study. Reimbursement of any travel costs incurred will be offered for all visits required as a result of taking part in the study.

What are the possible disadvantages and risks of taking part?

This is understandably a challenging time for you and your family with your diagnosis and upcoming operation, and this study would require further visits to Royal Derby Hospital on top of your NHS appointments. This has been well managed by participants in previous studies without being too burdensome. There is a risk of experiencing a negative side effect whilst participating in this study. If we do discover a new problem, we will inform you of what we have found, inform your clinical team and advise you to seek medical follow-up, where appropriate. We will also inform your GP of any findings. The following is a list of conditions that would exclude you from entering the study as it could put you at undue risk when exercising:

- Participants who lack capacity to consent
- Participants with a new diagnosis undergoing emergency surgery
- Participants with a past medical history including the following:
- Recent myocardial infarction (heart attack) in the last 6 months or unstable angina
- Heart failure (New York Heart Association Class III/IV)
- Uncontrolled hypertension, also known as high blood pressure (BP>160/100)
- Previous stroke/transient ischaemic attack (sometimes referred to as a mini-stroke)
- Cerebral or abdominal aortic aneurysm (a widening of a blood vessel in the brain or abdomen)
- Severe respiratory (lung) disease including known pulmonary hypertension (>25mmHg)
- Exercise induced asthma or brittle (severe) asthma
- Abnormal blood and/or ECG results
-

Cardiopulmonary Exercise testing (also known as CPET)

This is a well-established method of assessing someone's physical fitness, and it is often used in patients who may be considered for surgery as well as for research purposes. The Department of Clinical Physiology, University of Nottingham at Royal Derby Hospital is very experienced in performing these tests, with no adverse events to date. It is performed on a static exercise bike. You will have monitors attached to your chest (like when you have a heart tracing, an electrocardiogram, or ECG) and will wear a tight-fitting face mask. This means that we can safely monitor your heart and lungs whilst you are performing the test. You will also be

supervised through the test by a member of the research team. You will feel quite tired as you complete the exercise and will have the opportunity to rest before going home. You will not be required to use a bike to perform the exercises at home if you are in the exercise group (although if you would like to you can if you wish).

If you experience any of the following symptoms, we will immediately stop the test:

- Angina (chest pain) with relevant ECG changes
- Significant arrhythmias (irregular heart rhythms) causing symptoms or haemodynamic compromise (significant negative changes in your circulation)
- Fall in systolic blood pressure >20 mm Hg from the highest value during the test Hypertension >250 mm Hg systolic; >120 mm Hg diastolic
- Severe desaturation: SpO2 <80% (lower may be accepted in patients with known underlying lung disease)
- Loss of coordination
- Mental confusion
- Dizziness or faintness

This list is not exhaustive and if you feel for any reason that you cannot continue we will immediately stop the test.

Blood samples

Blood samples will be taken during the study. These will be taken in exactly the same manner as you may have had done in the past and will be performed by a trained professional. You may experience a slight temporary discomfort at the puncture site and occasionally a small bruise. We will only take a small sample at each time.

Exercise Programme

During the exercises you may short of breath or develop some muscle fatigue. This should be self-limiting and resolve quickly, but there may be a small chance of developing a muscle strain which would require you to stop exercising. If this happens we would ask you to see your GP or attend Accident and Emergency as you would do for any other acute issue.

What are the possible benefits of taking part?

The data we will collect from your participation in the study may help us to improve the advice we give to patients undergoing surgery in the future. You may also find that your physical fitness may improve and may help you to feel better after your operation.

What happens when the research study stops?

Once all the participants have finished the final assessment session then we will analyse the data and look for any significant findings. We will then write a series of reports about our results.

The questionnaires will have space for any free text responses and you will have the opportunity to give oral as well as written feedback. This may be used as part of the results reporting, but all direct quotes will be anonymised, with no identifiable information published.

We may also contact you to invite you to take part in a single interview within 4 weeks of finishing the exercise programme to discuss how you found taking part in the study, whether you thought it was worthwhile, and your views about doing exercise after having cancer surgery. This will involve you answering some questions but also giving you the chance to talk about your experience more freely. The interview may take place either in person or over video conferencing software and the audio will be recorded. It will take approximately 30 minutes to 1 hour and transport/free car parking and refreshments will be provided if taking place in person. We may take direct quotes from you as part of the analysis of the interviews, all information including the quotes will be anonymised and be in no way traceable to you. The audio recording will be uploaded to a secure network and immediately deleted from the recording device. It will be temporarily stored under your study code; there will be no identifying information on it. As soon as the information from the interview has been transcribed for analysis it will be deleted. The interview is purely optional and declining to take part in the interview study will not affect your ability to participate in the study itself.

What if there is a problem?

If you are concerned about anything at all to do with the study, please speak to the researchers who will try their best to answer any questions you may have. Their contact details are at the bottom of this sheet. If you are unhappy and wish to submit a formal complaint, you can do this by contacting the Patient Advice and Liaison Service (PALS) within the hospital. PALS contact details: Telephone: 01332785156, Freephone: 08007837691, Email: dhft.contactpals@nhs.net.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you during the course of the research. This information will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database at the University of Nottingham. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally – identifiable information possible.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx.

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Where possible information about you which leaves the site will have your name and address removed and a unique code will be used so that you cannot be recognised from it, however sometimes we need to ensure that we can recognise you to link the research data with your medical records so in these instances we will need to know your name and date of birth.

Your contact information will be kept by the University of Nottingham for 1 year after the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted). This information will be kept separately from the research data collected and only those who need to will have access to it. All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's and our funders' policies we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the larger picture in particular areas of

research. Data sharing in this way is anonymised (so that you could not be identified) but if we need to share identifiable information we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

What happens if I don't want to continue in the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw we will no longer collect any information about you or from you but we will keep the information about you that we have already obtained as this information may have already been used in some analyses and may still be used in the final study results. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Involvement of your General Practitioner (GP)

Your GP will receive a letter telling them that you have agreed to take part in the study. They will also receive a copy of this leaflet outlining the study. You will be informed of any abnormal findings or adverse events that occur that may require further investigation and advised to discuss with your GP or clinical team, as appropriate. If any findings have an impact on any further treatment you may require for your cancer we will liaise directly with your cancer specialist team.

What happens to any samples I give?

Any blood samples will be labelled with your unique study number and stored at -80 degrees centigrade in our laboratory freezers. We will then hand deliver them to the pathology lab at Royal Derby Hospital for analysis.

We would also like to ask for your consent to store any remaining samples for use in possible future research. The samples will be stored with a unique identifier code securely at the University of Nottingham under their Human Tissue Research Licence (no. 12265). The future

studies may be carried out by researchers who are not part of the current team and may include those working for commercial companies. Any samples or data would be anonymised and not identifiable to you. Please note that this is optional, and you can indicate separately whether or not you agree to this as part of the study on the consent form. If you do not agree then the remaining samples will be disposed of in accordance with the Human Tissue Authority's code of practice.

Will any genetic tests be done?

If you agree to have your samples used for future research, the blood samples that we take from you will be stored so that future studies may potentially use them to look for any genes that may affect response to exercise.

What will happen to the results of the research study?

We will aim to publish our findings in scientific and medical journals. We may also present the findings at any relevant conferences on the national and international stage. You will be able to obtain a copy of the final results after the study has ended from the research team.

Who is organising and funding the study?

This study is being organised by the University of Nottingham and funded using the personal research funds of Mr Jon Lund and Dr Bethan Phillips.

Who has reviewed the study?

Before any study involving participants can go ahead, the proposed study must be reviewed by an independent group of people not in any way involved in the study, called a Research Ethics Committee. This study has been reviewed and approved by South Yorkshire Research Ethics Committee.

Further information and Contact details

Mr Jon Lund, DM FRCS, Clinical Associate Professor, University of Nottingham, Division of Graduate Entry Medicine and Health, School of Medicine and Consultant Colorectal Surgeon, Royal Derby Hospital.

Email: jon.lund@nottingham.ac.uk

Phone: 01332 724641

Miss Melanie Paul, Clinical Research Fellow, MBChB, MSc, MRCS(Eng). (PhD Student) Division of Graduate Entry Medicine and Health, School of Medicine, University of Nottingham.

Email: melanie.paul@nottingham.ac.uk

Phone: 01332724640

7.4.3 POSTEx GP letter

D

Date:

Dear Dr,

Research Study - **A randomised controlled trial to assess the efficacy of a postoperative supervised exercise programme in patients who have undergone elective curative surgery for colorectal cancer.**

I am writing to inform you that your patient,

Name: XXXXX Date of Birth: XXXXX

has provided informed consent to participate in the above research study that we are conducting within the Centre Of Metabolism, Ageing & Physiology (COMAP), Nottingham University, Royal Derby Hospital. This research study will assess whether a structured 12-week postoperative exercise programme can improve the physical recovery of abdominal cancer patients. **Their usual NHS care will not be affected in any way due to participation within the study.**

This is NOT a drugs trial.

This study has been approved by London-Westminster Research Ethics Committee.

In addition to their usual care, by participating in our trial, your patient will undergo a thorough screening assessment which is likely to be far in excess of their usual screening. This will involve venous blood samples, cardiopulmonary exercise testing (CPET), physical activity monitoring and muscle USS. Depending upon which group they are randomised to they may be required to attend for exercise sessions at least once a week for up to 12 weeks where these tests will be repeated periodically.

If you have any questions about the participation of your patient in the study, then please do not hesitate to contact us using the details below.

A copy of the participant information sheet is included for your information.

Yours Sincerely,

Mr. Jon Lund

Chief investigator, DM, FRCS, Clinical Associate Professor, University of Nottingham, Division of Graduate Entry Medicine and Health, School of Medicine and Consultant Colorectal Surgeon, Royal Derby Hospital.

Email: jon.lund@nottingham.ac.uk

7.5 Consent Forms

7.5.1 PHYSPAL study consent form

CONSENT FORM

(Final version 2.0: 20/06/2023)

Title of Study: **An observational study to assess the postoperative physical activity of patients undergoing elective colorectal resection**

IRAS Project ID: 313070

Name of Researchers: Miss Melanie Paul; Mr James Bunce

Name of Participant:

1. I confirm that I have read and understand the information sheet version number 1.0 dated 09/05/23 for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.

4. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.

5. I agree to take part in the above study.

6. Consent for future contact *(Optional)*
   I agree to being contacted in the future in order to share the findings of the study.

_____ _____

_____

Name of Participant Date Signature

_____ _____

_____

Name of Person taking consent Date Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

7.5.2 POSTEx study consent form

CONSENT FORM

(Final Version 3.0/ Date 08/12/22)

Title of Study: **A randomised controlled trial to assess the efficacy of a postoperative supervised exercise programme in patients who have undergone elective curative surgery for colorectal cancer.**

IRAS Project ID: 281681

REC ref: 21/YH/0264

Name of Researcher: Melanie Paul

Name of Participant:

1. I confirm that I have read and understand the information sheet version number 5.0 dated 08/12//22 for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised

individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.

4. I understand and agree that the following samples will be taken for analysis:

   Blood samples will be taken for analysis of major organ function and markers of chronic health.

5. I agree to any direct quotes I have said or written being used as part of published results of the study and I understand that they will be anonymised so that I cannot be identified from them.

6. I agree to my GP being informed of my participation in this study.

7. I understand that the information collected about me will be used to support
   other research in the future, and may be shared anonymously with other researchers.

8. I agree to take part in the above study.

9. Consent for storage and use in possible future research *(Optional)*

I agree that the samples I have given and the information gathered about me can be stored by the University of Nottingham at the Graduate Entry Medical School building, Royal Derby Hospital, for possible use in future studies. I understand that some of these studies may be carried out by

researchers other than the current team who ran the first study, including researchers working for commercial companies, and this may include genetic analysis. Any samples or data used will be anonymised, and I will not be identified in anyway.

10. I understand that if I take part in the post exercise interview, it will be audio recorded and that anonymous direct quotes from the interview may be used in the study reports. *(Optional)*

11. Consent for future contact *(Optional)*

I agree to being contacted in the future in order to share the findings of the study and/or be invited to participate in future research studies/community events.

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

7.6 ActivPAL™ Monitor Information

7.6.1 ActivPAL™ application instructions

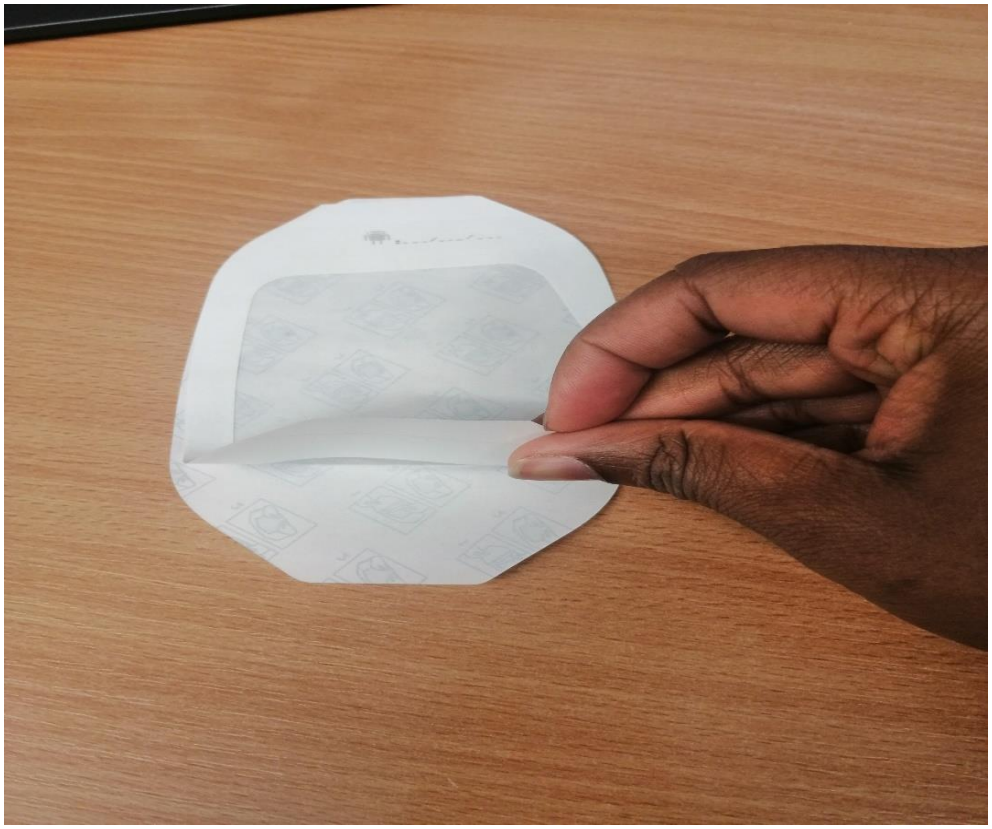
ActivPAL™ – Information and Care Sheet

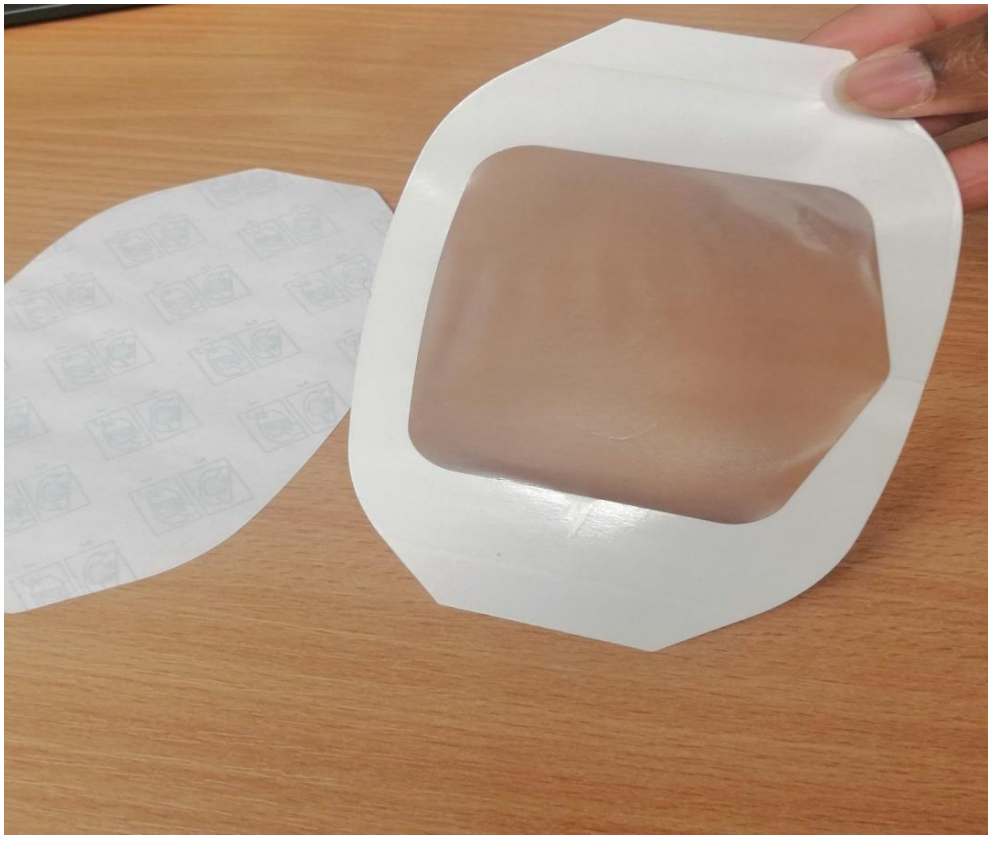
The ActivPAL™ monitor is an accelerometer- they can calculate time spent lying, sitting, standing and walking. It is small and completely non-invasive, and can be applied with a dressing to your bare leg. You will be asked to use this at 4 points during the study. This information sheet will go through some points to help you with this and make sure there are no problems. You will either be told the date and time to first apply the ActivPAL™, or it will be applied for you.

How to apply the ActivPAL™

You will be given a dressing, the ActivPAL™ within a waterproof cover (with spares) in order to apply it to your leg, as seen below. The picture shows the monitor outside of the dressing, you will be provided with the monitor inside the dressing. If you need to change it, it will looks as seen in the picture.

Remove the backing from the dressing and place the dressing sticky side up on a flat dry surface.

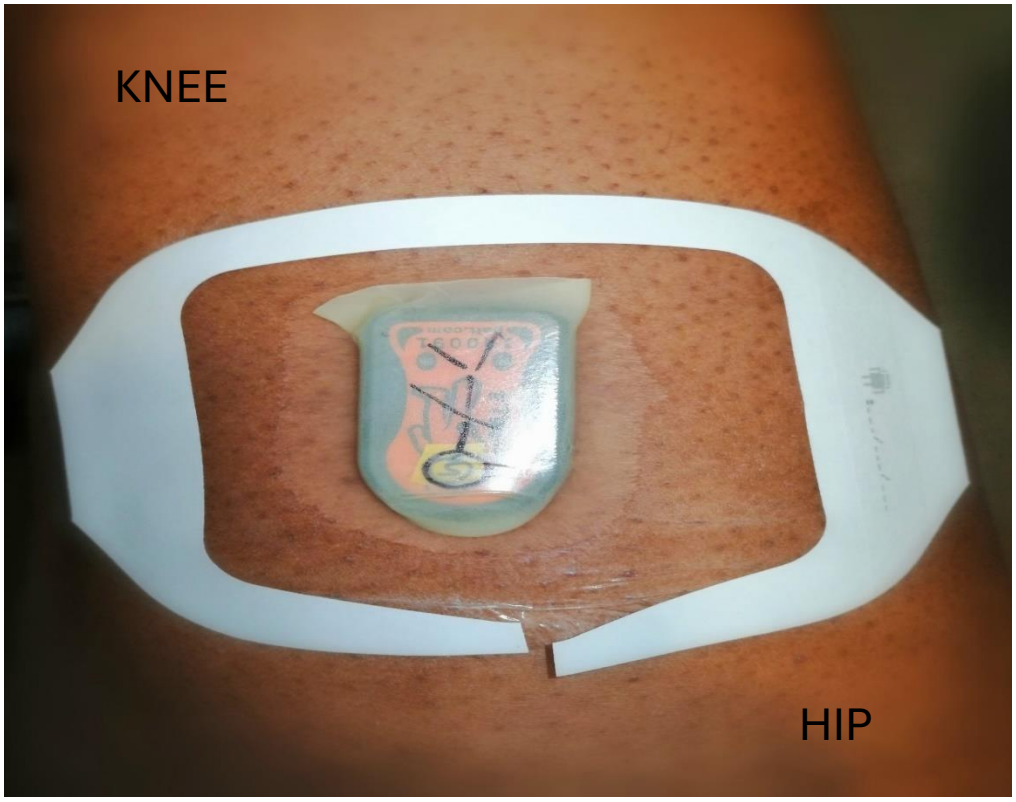




Place the monitor “Stick Man” side down in the middle of the dressing.

The easiest way to apply the ActivPAL is to sit down on a chair in underwear or shorts, with your thighs exposed. You should roughly measure the distance between your hip and your knee, then place the dressing onto the front of your **RIGHT THIGH** under your clothes, with the bottom (straight edge) of the monitor at the midway point. The figure drawn on the waterproof cover should be facing head up when stood up and looking in a mirror.

Press the dressing down onto your thigh ensuring it is stuck down well on all 4 sides. It does not matter in which orientation you place the clear film dressing.



Please note it should be applied to the bare thigh. Once it is stuck firmly, remove the white outer paper. The monitor should now stay comfortably against your thigh.

This link will take you to a video demonstrating the application of the monitor. https://vimeo.com/112874169

During use

Please write down the date and time that you apply the monitor and any time you change/remove it in the table at the end of this sheet. Please note the times you go to bed and wake up as well.

Can I shower?

The dressings are showerproof but we do not recommend soaking them. The best time to replace the dressing is immediately after the shower onto clean, dry skin. The ActivPAL monitor must not get wet.

What if it comes off?

You will be supplied with spare dressings and waterproof covers. If it comes off simply repeat the steps above. If the dressing does not stick, you may need to shave a small patch of your leg. You should avoid any oils or creams to the area as well.

Can it cause any problems?

The monitor itself is completely non-invasive and should not cause any discomfort. The most likely problem that may arise is a reaction to the dressing. If you are known to react to dressings please let us know. If a new reaction should occur please remove the dressing and contact us for any further information using the details below.

Melanie Paul
Email: melanie.paul@nottingham.ac.uk
Phone: 01332724640

Amanda Gates
Email: amanda.gates@nottingham.ac.uk
Phone: 01332724687

Assessment Number	Date	Time	Applied (A), Removed (R), Not applicable (N/A)	Time to bed	Time to out of bed	Other comments

Assessment Number	Date	Time	Applied (A), Removed (R), Not applicable (N/A)	Time to bed	Time to out of bed	Other comments

7.6.2 ActivPAL™ validation protocol

Table for reporting use of ActivPAL 4 monitor. Modified from Edwardson et al.

Item	**Response**
Monitor version	activPAL4
Rationale for selecting ActivPAL 4 monitor	Objective device needed to compare time spent lying, sitting and standing between control and exercise group and pre and post surgery
Which behavioural characteristics are of primary interest	Time spent lying, sitting and standing/stepping
Reliability	ActivPAL 3 interdevice reliability ranged from 0.79-0.99 (Grant et al)

Validity information	
Method and location of monitor attachment	Device covered in a latex sleeve to render waterproof and attached to anterior mid-thigh using clear film dressing. Visual demonstration with written instructions given
Wear period and number of days	24 hours per day for 7 days
ActivPAL software version	PALconnect v8.11.9.100 PALbatch v8.10.12.60 PALanalysis v8.11.6.70
Settings used: • Sampling frequency • Minimum sitting period • Minimum upright period	Default settings 20Hz 10s 10s
Diary data collected	Time woken up, time got up, time went to bed, time went to sleep, and any removal times each day
Type of file used for data processing	Events file
Goal for sampling periods observed	Minimum 10 hours of data per day and 5 days of data
Methods for estimating wearing/time/removing time in bed/sleep	Validation to be determined. Software automatically identifies a period of sleep. Will be checked against the diary entries.
What quality control checks were implemented	To be determined

Specify action taken when data determined to be invalid	Any invalid data will be excluded from analysis (if in worn waking hours)
Compliance criteria to define a valid day of observation	Day has ≥10 h of worn waking hours, <95% of time spent in any one behaviour (i.e., sitting, standing, or stepping) and ≥500 steps
Number and type of days required to be included in final analytic sample	5 consecutive days of data during one assessment period
Definition of a day	Midnight to midnight
Data processing package used and methods used to generate key summary variable	activPAL software PALanalysis version 8.11.6.70

7.7 Quality of Life and Feedback Questionnaires

7.7.1 HADS

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound			**I feel as if I am slowed**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time,	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to			**I get a sort of frightened feeling**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is			**I have lost interest in my appearance:**
	3	Very definitely and quite	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care
	1	A little, but it doesn't	1		I may not take quite as
	0	Not at all	0		I take just as much care
		I can laugh and see the funny side of			**I feel restless as I have to be on the**
0		As much as I always		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used
	1	From time to time, but	2		Definitely less than I
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV**
	0	Definitely	0		Often
	1	Usually	1		Sometimes

	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions, thank you. Should the questionnaire raise any concerns, please speak to your clinical team.

7.7.2 EORTC QLQ-C30 questionnaire

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Today's date (Day, Month, Year):
|_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social	1	2	3	4
28. Has your physical condition or medical treatment caused	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

7.7.3 IPAQ

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

(August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on

the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 1 minute at a time.

During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ **days per week**

☐ No vigorous physical activities → ***Skip to question 3***

1. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

2. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.
_____ **days per week**

☐ No moderate physical activities → ***Skip to question 5***

3. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

7.7.4 DASI

PROVIDENCE Heart and Vascular Institute

[1]**Duke Activity Status Index**

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

		Yes	No
1	Can you take care of yourself (eating, dressing, bathing or using the toilet)?	2.75	0
2	Can you walk indoors, such as around your house?	1.75	0
3	Can you walk a block or two on level ground?	2.75	0
4	Can you climb a flight of stairs or walk up a hill?	5.50	0
5	Can you run a short distance?	8.00	0
6	Can you do light work around the house, such as dusting or washing dishes?	2.70	0
7	Can you do moderate work around the house, such as vacuuming, sweeping floors or carrying in groceries?	3.50	0
8	Can you do heavy work around the house, such as scrubbing floors or lifting and moving heavy furniture?	8.00	0
9	Can you do yard work, such as raking leaves, weeding or pushing a power mower?	4.50	0
10	Can you have sexual relations?	5.25	0
11	Can you participate in moderate recreational activities, such as golf, bowling, dancing, doubles tennis or throwing a baseball or football?	6.00	0
12	Can you participate in strenuous sports, such as swimming, singles tennis, football, basketball or skiing?	7.50	0

Duke Activity Status Index (DASI) = sum of "Yes" replies _____

VO2peak = (0.43 x DASI) + 9.6

VO2peak = _____ ml/kg/min + 3.5 ml/kg/min = _____ METS

The Duke Activity Status Index is a self-administered questionnaire that measures a patient's functional capacity. It can be used to get a rough

estimate of a patient's peak oxygen uptake.

7.8 End of Study Exercise Acceptability Questionnaire

POSTEx Exercise Acceptability Questionnaire

Please rate how strongly you agree with the following statements regarding the exercise training programme.

1 – Strongly disagree

2- Disagree

3- Neither

4- Agree

5- Strongly agree

The study was adequately explained	**1**	**2**	**3**	**4**	**5**
The exercise programme has been an enjoyable experience	**1**	**2**	**3**	**4**	**5**
The exercise programme has been a significant time burden	**1**	**2**	**3**	**4**	**5**
I would recommend POSTEx to friends	**1**	**2**	**3**	**4**	**5**
The exercise programme has been more physically demanding than I expected	**1**	**2**	**3**	**4**	**5**
I would perform the same exercise regimen again	**1**	**2**	**3**	**4**	**5**
This study has interfered with other aspects of life due to:	**1**	**2**	**3**	**4**	**5**
a) The time commitment	**1**	**2**	**3**	**4**	**5**
	1	**2**	**3**	**4**	**5**

b) The travelling involved c) The physical strain					
I believe POSTEx has improved my fitness	**1**	**2**	**3**	**4**	**5**
I am pleased to have taken part in order to improve my fitness	**1**	**2**	**3**	**4**	**5**
I had to attend too many in-person sessions	**1**	**2**	**3**	**4**	**5**

7.9 Semi-structured Interview Supporting Questions

POSTEx End of Exercise Interview

INITIAL IMPRESSION

How much exercise were you doing prior to enrolment?

Information about the exercise before enrolment - adequate

Did it change the exercise you did before your operation?

INPATIENT

Did it make you more aware of how much activity to do whilst in hospital?

START OF EXERCISE PROGRAMME

Were you given enough information prior to starting the exercise programme

Did you understand what was asked of you?

Did you find the check-in useful? Did you find the frequency appropriate? If not how often would you have preferred to be contacted?

Would you have preferred face-toface or happy with remote contact? Would you have preferred any in-person training sessions or was the video sufficient?

Any other comments re: the video? Was it self-explanatory?

SUMMARY

Can you give me an example of a positive aspect of the programme?

Can you tell me a time, about where it could have been better?

To start with, on a scale of 1-10, with 10 being best, how would you rate your experience of the exercise?

Expanding on that can you tell me what would need to change to get you 1 point higher on the scale?

Would you recommend this programme to someone else?

Anything else you'd like to mention?

7.10 Exercise Diaries

7.10.1 Home-Based Resistance Exercise Training (RET) Programme Documentation Pack

Home-Based

Resistance Exercise Training (RET) Programme Documentation Pack

Session Outline

For each exercise perform two sets of 12-15 repetitions. Allow for 60 seconds rest between each set and exercise

Warm up – 2 minutes jogging-on-the-spot

1. Banded chair squats

2. Seated knee pull-ups

3. Standing kick backs

4. Standing kick outs

5. Seated rows

6.Seated bench press

7. Seated lateral raises

Cool down – 2 minutes jogging-on-the-spot

Total training time –30 minutes

Notes

- Your target is to feel mildly fatigued on completion of your final repetition in each set

- If it takes you over the 15 repetitions to achieve fatigue, then increase the band resistance.

    - From minimal to maximal difficulty:
        - Yellow
        - Red
        - Green
        - Blue

    - Black
    - Silver
    - Gold

- The order of exercises can be adjusted to suit your needs, however, try to perform all exercises in one go

- Exercises can be performed anywhere within your home environment

Week		**1**			**2**			**3**			**4**		
Session		1	2	3	1	2	3	1	2	3	1	2	3
Date													
Exercise 1: Squats	Number of repetitions												
	Colour Band												
Exercise 2: Knee pull ups	Number of repetitions												
	Colour Band												
Exercise 3:	Number of repetitions												

Kick backs	Colour Band												
Exercise 4: Kick outs	Number of repetitions												
	Colour Band												
Exercise 5: Seated rows	Number of repetitions												
	Colour Band												
Week		**1**			**2**			**3**			**4**		
Session		1	2	3	1	2	3	1	2	3	1	2	3
Date													

Exercise 6: Bench press	Number of repetitions												
	Colour Band												
Exercise 7: Lateral raises	Number of repetitions												
	Colour Band												
Week		**5**			**6**			**7**			**8**		
Session		1	2	3	1	2	3	1	2	3	1	2	3
Date													
Exercise 1:	Number of repetitions												

Squats	Colour Band												
Exercise 2: Knee pull ups	Number of repetitions												
	Colour Band												
Exercise 3: Kick backs	Number of repetitions												
	Colour Band												
Exercise 4: Kick outs	Number of repetitions												
	Colour Band												

Exercise 5: Seated rows	Number of repetitions												
	Colour Band												
Week		**5**			**6**			**7**			**8**		
Session		1	2	3	1	2	3	1	2	3	1	2	3
Date													
Exercise 6: Bench press	Number of repetitions												
	Colour Band												
Exercise 7:	Number of repetitions												

Lateral raises	Colour Band												
Week		**9**			**10**			**11**			**12**		
Session		1	2	3	1	2	3	1	2	3	1	2	3
Date													
Exercise 1: Squats	Number of repetitions												
	Colour Band												
Exercise 2: Knee pull ups	Number of repetitions												
	Colour Band												

Exercise 3: Kick backs	Number of repetitions												
	Colour Band												
Exercise 4: Kick outs	Number of repetitions												
	Colour Band												
Exercise 5: Seated rows	Number of repetitions												
	Colour Band												
Week		**9**			**10**			**11**			**12**		
Session		1	2	3	1	2	3	1	2	3	1	2	3

Date													
Exercise 6: Bench press	Number of repetitions												
	Colour Band												
Exercise 7: Lateral raises	Number of repetitions												
	Colour Band												

Important

If you develop any of the following symptoms during, or immediately after, an exercise session, seek urgent medical attention (i.e. contact your GP or call 999):

- pain or tightness in your chest
- palpitations (an abnormally fast or irregular heart beat)
- dizziness
- feeling lightheaded
- feeling faint
- feeling disorientated
- sudden paleness
- abnormal levels of breathlessness

Please exercise with someone nearby who can help you if you run into any problems (especially during the first few sessions).

We will contact you weekly to provide encouragement and to answer any questions or difficulties. We will also ask you if you have developed any of the symptoms listed above, or any other symptoms / injuries during the 12-week period.

7.10.2 POSTEx Aerobic Exercise Diary

POSTEx Aerobic Exercise Diary

Please complete the exercise diary as you do your sessions. Feel free to make any other comments if you wish in the free comments box below (e.g. any problems, for example tiredness post chemotherapy, etc.) .

As a reminder, moderate exercise is classed as making your heart beat faster but you should still be able to carry a conversation (e.g. a brisk walk). Vigorous intensity exercise means you would be struggling to carry a conversation and would be breathing much harder (e.g. running).

A session should last for a minimum of 10 minutes and you should be aiming for 75 minutes of vigorous or 150 mins of moderate exercise per week in as many sessions as you wish.

Please bring your diaries with you to your next assessment day.

Please feel free to contact Melanie on melanie.paul@nottingham.ac.uk if you have any further questions or concerns.

Week 1 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 2 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 3 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 4 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 5 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 6 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 7 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 8 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

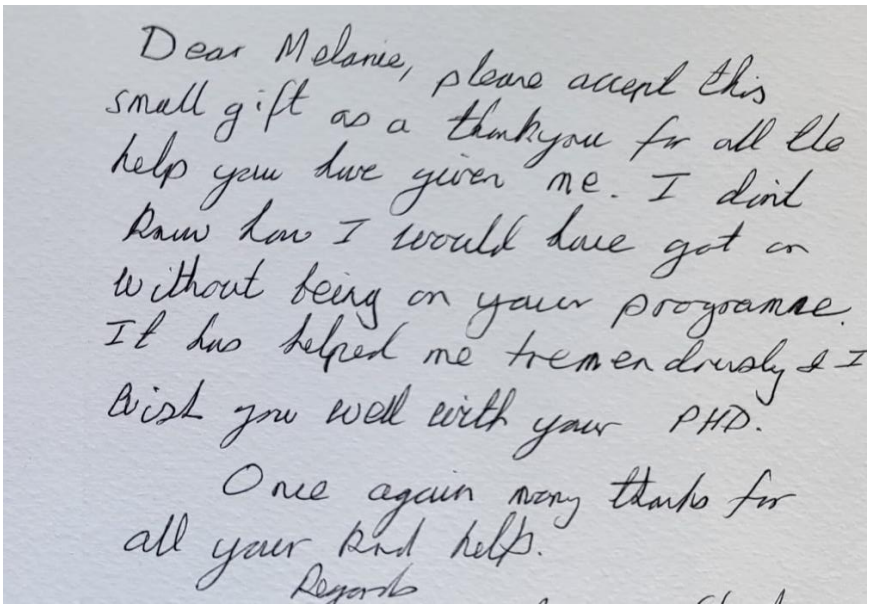
Week 9 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 10 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 11 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

Week 12 Date:	Session number	Exercise type	Duration (mins)	Moderate (M) or Vigorous (V)?	Comments

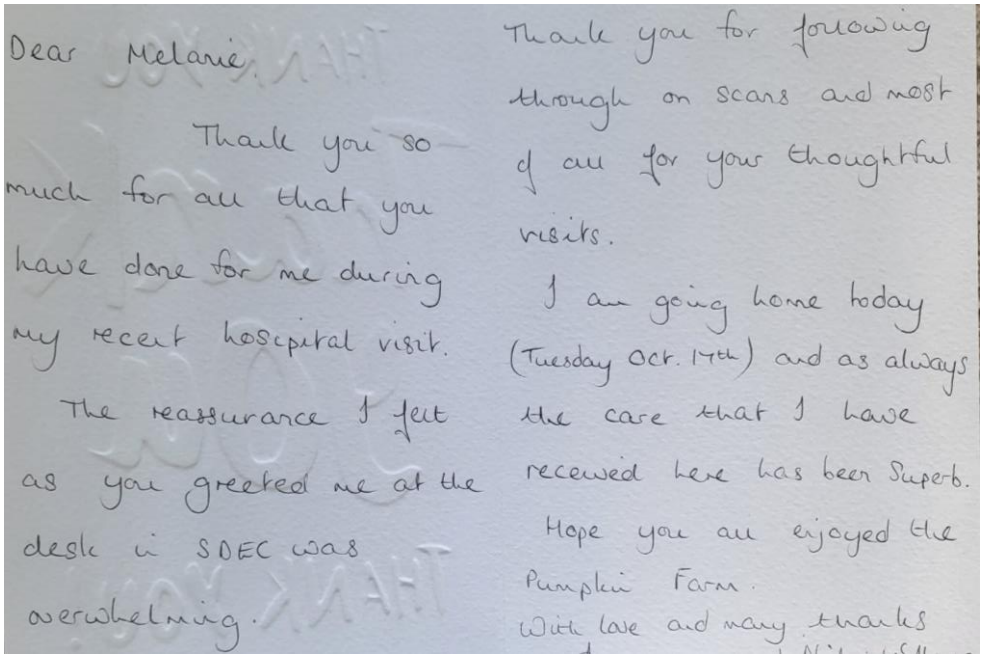
7.11 Evidence of Participant Appreciation



Dear Melanie, please accept this small gift as a thankyou for all the help you have given me. I don't know how I would have got on without being on your programme. It has helped me tremendously & I wish you well with your PHD.

Once again many thanks for all your kind help.

Regards



Dear Melanie,

Thank you so much for all that you have done for me during my recent hospital visit.

The reassurance I felt as you greeted me at the desk in SDEC was overwhelming.

Thank you for following through on scans and most of all for your thoughtful visits.

I am going home today (Tuesday Oct. 14th) and as always the care that I have received here has been Superb.

Hope you all enjoyed the Pumpkin Farm.

With love and many thanks