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Exercise Prehabilitation in Operable Colorectal Cancer: A Focus on Physiological Resilience and Functional & Clinical Outcomes

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

February 2026

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Statement of Authenticity

I hereby declare that the work contained within this thesis is my own. Where applicable, others who have contributed have been credited in the text or referenced. Statistical support for chapter 2 (systematic review and meta-analysis) was provided by Dr Brett Doleman, with Miss Melanie Paul and Dr Luke Matupi providing independent reviews on study selection. Miss Melanie Paul also co-authored the paper that makes up a large part of chapter 3.

Joshua JS Wall

Acknowledgements

'It takes a village to raise a child' and though I cannot individually thank everyone who helped me progress and grow in the last three years, there are some who deserve a special mention.

Firstly, I'd like to thank my supervisors, Mr Jon Lund and Professor Beth Phillips for the guidance, patience, nurturing and general support in the lead up to, and during (and possibly post) my PhD. Their *Yin and Yang* advice, ability to see the bigger picture and practical and unwavering support has been crucial in shaping this work.

I would like to thank Dr Brett Doleman for his statistical support with the systematic review and meta-analysis that make up chapter 2 and Miss Melanie Paul and Dr Luke Matupi who acted as independent reviewers. I would also like to thank Lindsay Snell (Librarian, University Hospitals of Derby & Burton NHS Foundation Trust) for her help with the search strategy.

Miss Amanda Gates has been invaluable running the *EPiC* study. She is wonderful with participants, and, on the rare occasion she doesn't know the answer to a question, she certainly knows who to ask. Dr Eleanor Jones too has been a superb research partner and has been instrumental in the day-to-day running of *EPiC* but has also been very helpful advising me on analytical techniques and help with publications. Towards the end of my time on *EPiC*, we would know instinctively what the other would be doing, who would take responsibility for any issues and how to squeeze *another* participant into an already over-booked schedule.

A special mention goes to my girlfriend, Emma, for her patience, acceptance, love and support. Extending my clinical training to complete a PhD impacts both our lives and not once has she been anything other than my rock, not wavering, even for a second. Not many couples end their 20s with professional careers and start their 30s as full-time students; but we did.

I’d like to thank the everchanging members of the 5032 office for their help and companionship. Countless coffees, chats, moans, memes, (dis)agreements and general camaraderie made these three years go by so quickly. I’d also like to mention the support and buy-in from the consultant body at RDH, and the wider colorectal and general surgical team for mentoring me whilst on-call and thinking of me when referring patients to *EPiC*.

Finally, I’d like to thank the participants involved in the *EPiC* study for their precious time in the run up to a life changing operation. I have learnt so much, enjoyed our time together, and been humbled by each and every one of you.

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List of Abbreviations

%BF	Percentage Body Fat
1-RM	One-Repetition Maximum
2ww	Two Week Wait
6MWT	Six-Minute Walk Test
A1	Assessment 1- Baseline Period
A2	Assessment 2- Intra-Exercise Period
A3	Assessment 3- Immediately Postoperative Period
A4	Assessment 4- Recovery Period
ACCP	American College of Chest Physicians
ACSO	American Society of Clinical Oncology
ADL	Activity of Daily Living
AET	Aerobic Exercise Training
ALS	Advanced Life Support
ANF	Autonomic Nervous Function
ANOVA	Analysis of Variance
ASA	American Society of Anaesthesiologists
AT	Anaerobic Threshold (see Gas Exchange Threshold)
ATS	American Thoracic Society
BBC	British Broadcasting Corporation
BLS	Basic Life Support
BPM	Beats per Minute
BM	Body Weight
CENTRAL	Cochrane Central Register of Controlled Trials
CI	95% Confidence Intervals
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMJ	Countermovement Jumps
CoV	Coefficient of Variance
CPET	Cardiopulmonary Exercise Testing
CRC	Colorectal Cancer
CRF	Cardiorespiratory Fitness
CSa	Cross-sectional area
D2O	Deuterium Oxide
D3-Cr	D3-Creatine
D3-MH	D3-Methyl Histidine
DASI	Duke Activity Status Index
DTT	Decision-to-Treat
DVT	Deep Vein Thrombosis
DXA	Dual-Energy X-Ray Absorptiometry
ECG	Electrocardiogram
EORTC	European Organisation for Research and Treatment of Cancer
EPiC	Exercise Prehabilitation in Colorectal Cancer
ERAS	Enhanced Recovery After Surgery
FFM	Fat-Free Mass
FIT	Faecal Immunochemical Test
GET	Gas Exchange Threshold (see Anaerobic Threshold)
GI	Gastrointestinal
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HGS	Handgrip Strength

HIIT	High-Intensity Interval Training
HR	Heart Rate
HRA	Health Research Authority
HR-QoL	Health-Related Quality-of-Life
HRR	Heart Rate Recovery
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive Care Unit
ILS	Immediate Life Support
IQR	Interquartile Range
IRAS	Integrated Research Application System
Lat	Latissimus dorsi
LM	Lean Mass
LOS	Length-of-Stay
MCID	Minimal Clinically Important Difference
MD	Mean Difference
MDT	Multidisciplinary Team
MeSH	Medical Subject Headings
MET	Metabolic Equivalent
MET.h	Metabolic Equivalent Hours
MPB	Muscle Protein Breakdown
MPE	Medical Physical Expert
MPS	Muscle Protein Synthesis
MVC	Maximal Isometric Voluntary Contraction
NHS	National Health Service
NS	Non-Significant
ONS	Oral Nutritional Supplementation
OR	Odds Ratio
PERSiST	implementing Prisma in Exercise, Rehabilitation, Sport medicine and SporTs science
PIS	Participant Information Sheet
PNS	Parenteral Nutritional Support
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROSPERO	The International Prospective Register of Systematic Reviews
QLQ-C30	Core Quality of Life Questionnaire
QoL	Quality-of-Life
RCT	Randomised Controlled Trial
RDH	Royal Derby Hospital
REC	Research Ethics Committee
ReHIIT	High-Intensity Interval Training and Resistance Exercise Training Combined
RET	Resistance Exercise Training
ROB-2	Risk-of-Bias 2
ROBINS-I	Risk Of Bias In Non-Randomised Studies of Interventions
SD	Standard Deviation
SOP	Standard Operating Procedure
SPPBT	Short Physical Performance Battery Test
STS	Sit-to-Stand
STS-30	Sit-to-Stand in 30 Seconds
TNM	Tumour Node Metastasis
TOS	Take-Off Speed
TUG	Timed Up & Go
UHDB	University Hospitals of Derby and Burton NHS Trust
UK	United Kingdom

USA	United States of America
V1	Assessment Day 1 (Baseline)
V2	Assessment Day 2 (Preoperative)
V3	Assessment Day 3 (6-Week Postoperative)
VCO2	Pulmonary CO_2 Output
VL	Vastus Lateralis
VO2Max	Maximal Oxygen Uptake
VO2Peak	Oxygen Uptake at Peak exercise
VPAN	Panoramic Capture Setting

Publications & Presentations

Papers

- *Nutritional interventions in prehabilitation for cancer surgery*. **Joshua Wall**, Melanie Paul, Bethan E Phillips. November 2023. *Current Opinion in Clinical Nutrition and Metabolic Care.*
- *Exploring the utility of bedside tests for predicting cardiorespiratory fitness in older adults*. Laura Carrick, Brett Doleman, **Joshua Wall**, Amanda Gates, Jon N. Lund, John P. Williams, Bethan E. Phillips December 2023. Aging Medicine.
- *A call for clarity: a scoping review of predictors of poor outcome after emergency abdominal surgery for inflammatory bowel disease*. J A Bunce, **J J S Wall**, J N Lund, G M Tierney December 2023. Colorectal Disease.
- *Clinical and Functional Effects of Resistance Exercise Prehabilitation in Colorectal Cancer: Systematic Review and Meta-Analysis*. **Joshua J. S. Wall**, Luke Matupi, Melanie Paul, Brett Doleman, Jon N. Lund, Bethan E. Phillips September 2025. *JCSM Communications.*
- *The Effect of Leucine-Enriched Beta-Lactoglobulin Versus an Isonitrogenous Whey Protein Isolate on Skeletal Muscle Protein Anabolism in Young Healthy Males*. Isabel A Ely, Melanie Paul, **Joshua J S Wall**, Jake Cox, Mads S Larsen, Paula J Scaife, Jon N Lund, Leigh Breen, Daniel J Wilkinson, Kenneth Smith, Bethan E Phillips, Philip J Atherton. October 2025. *Nutrients.*
- *Investigating the Digestibility, Bioavailability and Utilization of Protein Blends in Older Adults Using a Dual Stable Isotope Tracer Technique.* Jake Cox, Bethan E Phillips, James

Bunce, Thomas Smart, **Joshua Wall**, Hannah Crossland, Daniel J Wilkinson, Kenneth Smith, Philip J Atherton. October 2025. *Nutrients.*

Presentations

- *Body Composition Measured via DXA versus BIA in a Population with Colorectal Cancer undergoing Pre-Operative Exercise*. **Joshua Wall**, Eleanor Jones, Amanda Gates, Jon Lund, Bethan E Phillips. December 2024. *The Biomedical Basis of Elite Performance 2024.*

1. Introduction

1.1 Cancer

Cancer is common. Global estimates suggest there were 18.1 million new cases of cancer in 2020, leading to an estimated 10 million deaths[1]. Both the incidence and prevalence of cancer is growing, and with it so too are the associated burdens on individuals, support-networks, and healthcare infrastructure[1]. Economically, estimates of the global financial cost of cancer from 2020 to 2050 is $25.2 trillion US accounting for the association of cancer-related morbidity with labour supply; age and sex specific differences of those who are affected by cancer; and the diversion of finances to cancer treatment expenses[2]. In addition to the effects on physical health, cancer has a substantial impact on mental health and wellbeing both for individuals with cancer, and their wider network from family, friends and carers, to employers and dependants[3].

1.1.1 Cancer in the United Kingdom

Cancer disproportionately effects older individuals[4] (Figure 1.1). In the United Kingdom (UK), the incidence of cancer peaks between 85-89 years, with a sharp rise in incidence seen from

age 55-59 onwards[4]. Mirroring global trends[5], the population of England and Wales continues to age, and with it, so does the expectation that more individuals will develop cancer[6].

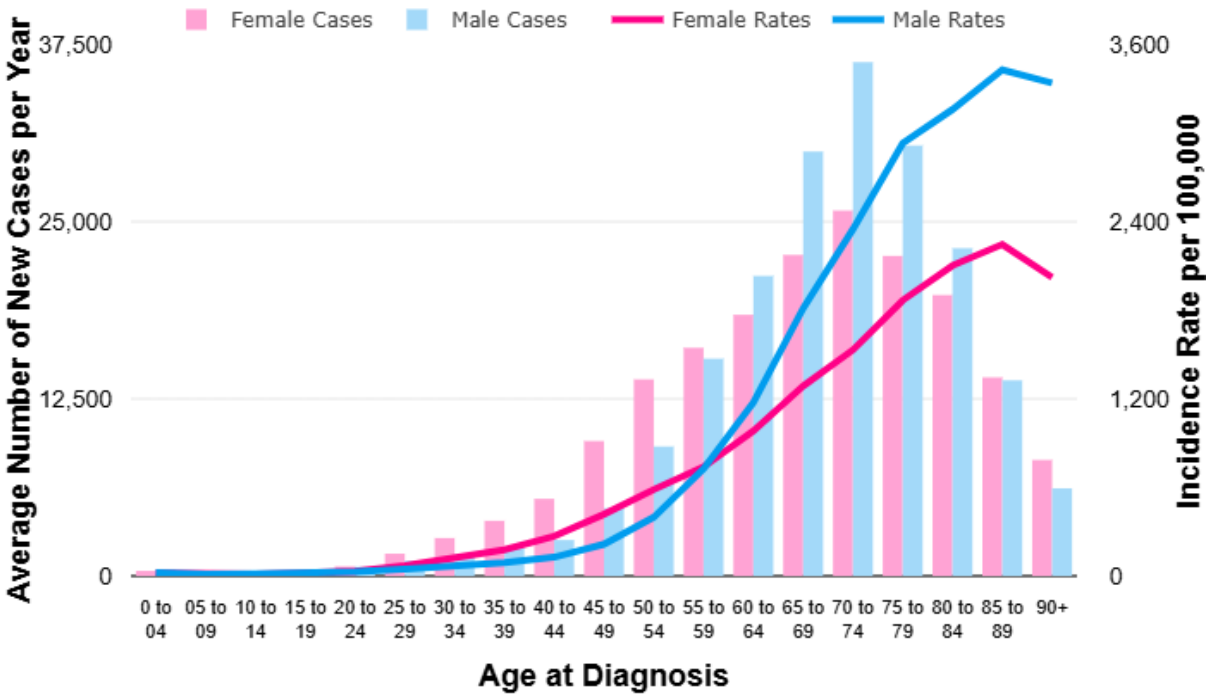


Figure 1.1- Cancer incidence by age (UK). Taken from Cancer Research UK[4]

In the UK alone, 375,000 new cases of cancer are diagnosed each year, with 167,000 individuals dying because of cancer[7]. Owing partially to this, cancer care has been the focus of successive governments who have implemented specific guidance for dealing with cancer on a national level.

In 2000, the *NHS Cancer Plan* mandated the review, that all patients with cancer were reviewed by a multi-disciplinary team (MDT)[8]. The MDT meets to discuss individual cases, and agree on a proposed management plan, that is then offered to the individual with cancer. MDTs consist of professionals from several backgrounds, but commonly amongst them are an MDT coordinator; a consultant surgeon, oncologist and radiologist; and a clinical nurse

specialist. In addition to the MDT, the UK government, via the National Health Service (NHS) has several cancer-related pledges on waiting times in England. These include:

- A maximum two-week wait (2ww) to see a specialist for all people referred with suspected cancer symptoms
- A maximum two month (62-day) wait from urgent referral for suspected cancer to the first definitive treatment
- A maximum one month (31-day) wait from the date a decision-to-treat (DTT) is made to the first definitive treatment[9]

The *NHS Cancer Plan* also discussed screening for various cancers. This included extension of the breast cancer screening programme, improved cervical cancer screening, and continuing colorectal cancer (CRC) screening pilots, with a pledge to introduce screening nationally for CRC if the pilot demonstrated appropriability, feasibility and acceptance to the public[8].

1.1.2 Colorectal Cancer

CRC, also known as *bowel cancer,* is the 4th most common cancer in the UK, accounting for 42,900 new diagnoses each year representing 11% of all new cancers. This number is set to increase to 47,700 by 2038-2040[10]. It is the third most common cancer in males (UK data, after prostate and lung cancer) and females (after breast and lung cancer) and costs the UK approximately £1.6 billion per year[11]. Despite the risk of developing CRC being associated with age, the incidence of CRC is increasing in young adults in high-income countries including the UK[12].

CRC is responsible for the deaths of around 17,000 individuals each year in the UK. However, 53% of those diagnosed with CRC survive for 10 years or more[10] and with advances in screening and treatment, CRC is being transformed from a deadly disease to an illness that is

increasingly curable. Though this is clearly a positive step, CRC survivorship poses its own challenges. Long-term adult survivors have more physical limitations in sustained activities than matched individuals without cancer, with, for example, older female long-term survivors self-report functional limitations such as inability to walk up and down stairs[13]. Furthermore, many long-term survivors do not meet physical activity or dietary recommendations which may lead to a poorer quality-of-life (QoL) and post-cancer functional status[13]. Williams et al., showed that patients with CRC had a lower exercise tolerance than those without cancer, but that this difference disappeared after resection of the tumour. However, despite the normalisation of exercise tolerance, the self-reported measures of maximal physical capacity were significantly lower after resection than preoperatively. The authors concluded that the disparity between subjective and objective measures of exercise capacity may impede functional recovery[14].

1.1.2.1 Colorectal Cancer Screening

The national *bowel cancer screening programme* is available to everyone in England and Wales aged 54 to 74, with ongoing expansion to decrease the entry age to 50. The process involves the use of a home testing kit (faecal immunochemical test- FIT) with the results classifying individuals into either '*no further tests needed*' or '*further tests needed*' cohorts[15]. Individuals who require no further testing are invited to take part in FIT-based screening every two years dependant on their age. Individuals in the '*further tests needed*' groups, where appropriate, should be referred to a specialist on a 2ww basis. The 2022 *National Bowel Cancer Audit Annual Report* concludes that the number of people diagnosed with CRC via screening has increased over time, with an uptake in the screening programme to 70% in 2020/21 representing ~11% of new diagnoses[16].

1.1.2.2 Treatment For Colorectal Cancer

As with many cancers, the treatment for CRC is dependent on multiple factors including site, size and local spread of the tumour; metastatic status; MDT recommendations; fitness of an individual to receive intervention; patient-choice; local expertise/facilities and; financial considerations, both to an individual and to the healthcare system.

Broadly, treatment for CRC can be broken down into five non-mutually exclusive categories:

- 'Conservative' management- ranging from no intervention versus a matched individual without CRC to symptomatic treatment alone
- Chemotherapy-based treatment
- Radiotherapy-based treatment
- Surgical/endoscopic-based treatment
- Multimodal therapy- treatment of CRC with more than one of the aforementioned modalities.

Though theoretically possible, very few individuals with CRC have a single-modality treatment; very few would accept surgery with no symptomatic support, nor would surgery be offered for a tumour with a widespread metastatic burden, except with palliative intent.

As with all cancers, MDT decision making, in addition to patient preference is key in deciding an individual's treatment regime. A diagnosis of CRC is made after reviewing relevant histology, radiology, and symptomology at an MDT meeting. Each individual's cancer is categorised using the *Tumour, Node, Metastasis* (TNM) classification, with the summation of these factors offering a grade which can help guide therapy[17,18]. '*Tumour*' denotes the size of the primary tumour and its invasion into adjacent tissues; 'node' denotes the involvement of

regional lymph notes, and 'metastasis' signifies presence or absence of tumour beyond regional lymph nodes[19](Table 1.1).

Tumour Stage	Description
T1	Invasion into, but not through, the submucosa
T2	Invasion into, but not through, the muscularis propria
T3	Invasion into subserosa or pericolic/ perirectal tissues
T4	Directly invades other organs or structures and/or perforates visceral peritoneum
Nodal Stage	
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
Metastatic Stage	
M0	No distant metastases
M1	Distant metastases

Table 1.1-Description of the TNM Classification System for colorectal cancer[20,21]

Other classification systems exist such as '*number staging*', which is often discussed with patients, and the *Dukes' system*, which is sometimes referred to in the literature[20]. Number staging relates to the degree of local, lymph node and distant spread (Figure 1.2).

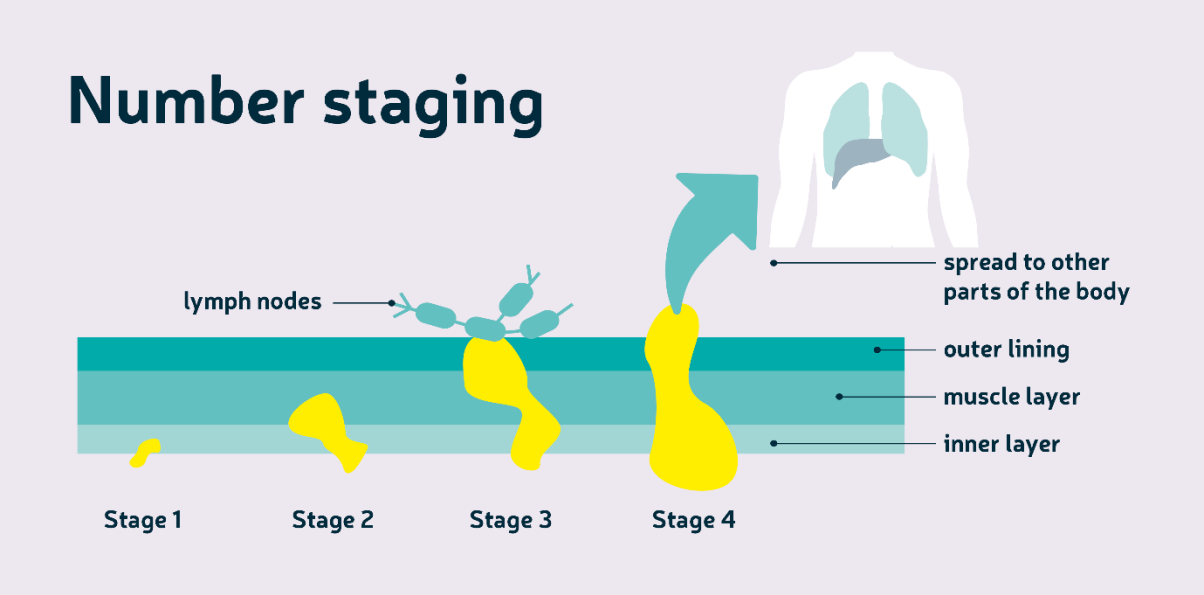


Figure 1.2-Number staging in colorectal cancer. Taken from www.bowelcanceruk.org.uk[20]

Should a cancer be deemed amenable to a selected therapy, and the informed patient is willing to undergo said therapy, this should commence under the 31-day target, with the date of the MDT being the date of DTT.

1.1.2.2.1 Surgery for Colorectal Cancer

Once proposed by the MDT, and agreed by the consenting individual with cancer, surgery may pose as the key, or one of a few key steps in the treatment of cancer with curative intent. Surgery may be undertaken after a period of chemo- or radiotherapy to 'downgrade' a tumour- this is termed *neoadjuvant therapy*; or may be undertaken prior to chemo- or radiotherapy- *adjuvant therapy* (Figure 1.3). Some individuals with a suitably staged cancer, may be cured with surgery alone[22]. For individuals with non-curative disease, surgery may be indicated with palliative intent.

Figure 1.3-Timeline for neo/adjuvant therapy in relation to surgery

Considering the population of individuals who develop CRC, it is important to consider the effects of surgery on an ageing population. A 2004 UK-based study revealed that in individuals aged >80y, survival is disproportionately poor compared with other age groups, despite this being the age group with the highest incidence[23]. Over 10% of older adults who have a resection will not return to their preoperative accommodation[24]. Older adults, however, are more likely to present with later-stage disease, have emergency surgery and are less likely to have curative surgery than their younger counterparts so these discrepancies in outcomes are not necessarily due to age alone[25]. Indeed, although ageing has been described as '*a progressive decline in functional reserve of multiple organ systems*', the process is '*highly individualised and poorly reflected in chronological age*'[26].

Even in individuals who work, a cohort which is naturally younger, return to work after surgery for CRC is limited. Bhalla et al., showed that out of 49 working individuals (median age 68) who had surgery with curative-intent for CRC, only 30 (61.2%) of them returned to work afterwards. Although 11 (22.4%) reported that they retired on a voluntary basis, 8 (16.3%) did not, citing incomplete recovery as the reason. In addition, the mean time to return-to-work ranged from six to 252 days, with those who had laparoscopic surgery having a significantly shorter return-to-work time compared to those who had open surgery (44 vs 71 days; $p<0.05$)[27].

1.2 Surgery

The term *surgery* comes from the Latin *Chirurgia*, derived from the Greek *Cheirourgos*, a compound word formed from *Cheir* "hand" and *Ergon* "work"; i.e. "doing by hand". A more contemporary understanding is '*the branch of medicine concerned with diseases and conditions requiring or amenable to operative or manual procedures'*[28]. Surgery in the 21st century is a complex undertaking, with ever advancing methods and complex MDT working built around a rigorous evidence base.

Surgery can encompass a host of interventions, from complex multi-cavity, multi-organ undertakings such as an *heart-lung transplant*, to simple procedures that can be done in minutes and with little discomfort such as a *skin biopsy*. The context in which surgery takes place is of utmost importance when considering the likely outcomes and the physiological insults. An unplanned, 'emergency' operation is widely accepted on a population level, to have poorer outcomes than the equivalent planned operation[29,30]. This is largely because patients are acutely systemically unwell when surgery is performed as an emergency. In 2020-21, 22,132 patients had an emergency laparotomy in England and Wales, with nearly 10% of these (2,191) having an intraoperative finding of CRC[31]. A planned operation on the contrary, allows for complex decision making to be discussed by an MDT and for a patient to be 'optimised' prior to intervention.

Another consideration is operative approach. In intra-abdominal operating, there are broadly three options:

- Open - a 'traditional' approach where an operation takes place through a large incision.

- Laparoscopic ('key-hole') - a widely-accepted approach where an operation takes place through small incisions with the aid of a long, thin camera and laparoscopic instruments.
- Robotic - a technique where the entry to the abdominal cavity is minimally invasive as in laparoscopic surgery, but the instrumentation is aided by a machine controlled by the surgeon/s.

The approach to an operation is the outcome of considerations regarding anatomical variants, a surgeon/unit's preference/skill and the availability of equipment/expertise. In the UK, laparoscopic surgery is the mainstay of CRC surgery and has been shown to lead to less blood loss, reduced length-of-stay in hospital (LOS), fewer postoperative complications, lower postoperative mortality, and decreased hospital costs[32,33]. Laparoscopic operating takes longer per patient than open surgery, but it appears that this does not lead to significant increases in mobility associated outcomes such as deep vein thrombosis (DVT)[32,33]. Compared to open and laparoscopic surgery, robotic surgery for CRC results in decreased blood loss, shorter time to oral feeding and initial flatus, less conversion to open surgery (versus laparoscopic), shortened LOS and longer distal resection margins. However, its implementation requires huge initial financial investment and for CRC surgery, does not appear cost effective, limiting more widespread use[34].

A final consideration when evaluating the outcomes of an operation is operative intent. A palliative operation in a comorbid patient would naturally carry a larger time-specific mortality risk than a potentially curative operation in a physiologically fit patient.

1.2.1 Surgery as an Insult

The stress response to surgery is similar to that triggered by traumatic injuries and although the stress response has evolved to improve chances of survival following injury, the same response can be detrimental after surgical intervention. During and following surgery, levels of plasma cortisol persist in elevated concentrations. This, in turn, leads to an increase in protein breakdown to levels exceeding that of synthesis. The resulting net catabolism of muscle proteins provides substrates for gluconeogenesis in addition to that from fat breakdown, but is also associated with delayed wound healing, compromised immune function, and diminished muscle strength after surgery[35]. Older adults may be at increased risk of these effects owing to a decrease in muscle mass and function with age ('*sarcopenia'*[36]) and often cancer[37], hence a lower baseline muscle mass and functional level from which to decline [35,38].

In major abdominal surgery, *surgery-related muscle loss* occurs in approximately 40% of patients and is associated with a decreased survival at one-year[39]. Abdominal surgery is also associated with significant pain which can have negative effects on postoperative recovery. Patients recovering from abdominal surgery spend a lot of time in bed after surgery and this is directly proportional to their degree of pain[40]. Postoperative complications are increased as mobility falls after surgery and thus adequate pain relief is a key part of *Enhanced Recovery After Surgery* (ERAS) protocols[40,41].

In addition to the loss of muscle mass and function seen as a direct result of surgery, pain-related immobility furthers this decline[42]. This leads to a cycle of worsening immobility, leading to worsening function (Figure 1.4). Insufficient postoperative physical activity, combined with poor nutritional intake, as commonly seen in the postoperative phase leads

to significant muscle loss, which is associated with poor outcomes including one year survival[39].

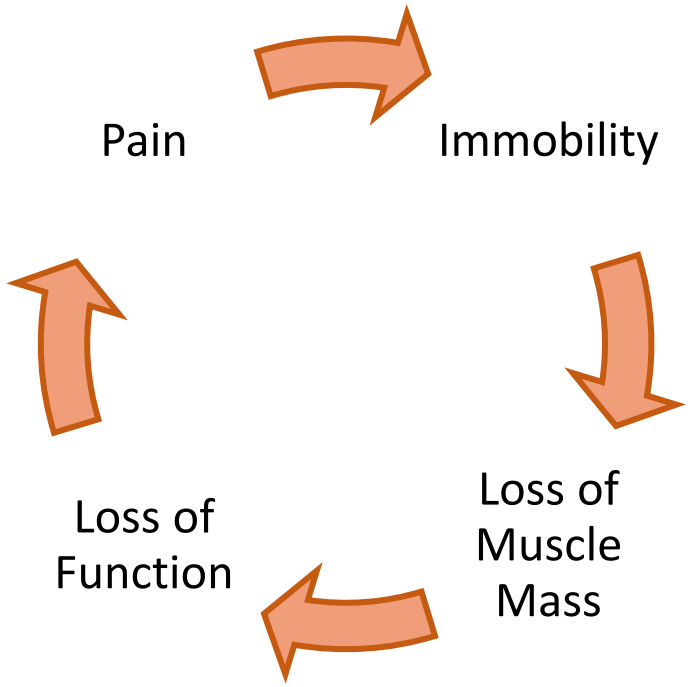


Figure 1.4- Postoperative immobility cycle

1.2.2 Surgery for Cancer

All surgery presents an insult to the body, but there are specific considerations for patients who have operations for cancer. Firstly, due to the time constraints of time-to-intervention from DTT in the UK, individuals who have cancer for whom operative intervention is planned do not have a long for preoperative optimisation (31 days maximum[9]). Individuals with cancer also represent a difficult challenge regarding timing not only from administrative pressures, but also from clinical considerations. Longer surgical waiting time has been associated with poorer long-term survival in individuals with cervical cancer[43] and increased waiting times between diagnosis and surgery have been shown to disproportionately lead to poor patient satisfaction, despite longer waits at other intervals in the diagnosis-treatment-follow-up pathway[44].

As previously mentioned, CRC is predominantly a disease of older adults, who, as a cohort, bring with them their own complexities. Older adults are more likely to have cardiovascular and pulmonary disease in addition to other comorbidities such as *Type II Diabetes Mellitus*[45]. They are also more likely to have an emergency admission for CRC, present with more advanced disease and experience a relatively delayed presentation[45]. Older adults may suffer more postoperative complications such as ileus, peritonitis or septic shock, pelvic abscesses, wound infection and incisional hernias. These complications, regardless of age, have implications for increased LOS and morbidity/mortality[46].

For a certain subgroup of individuals with CRC, outcomes can also be affected by contemporary therapy such as neo/adjuvant chemo- or radiotherapy. Firstly, this group of individuals, almost by definition will have more advanced cancer than individuals who require surgery alone for cure, but in addition to the burden of more advanced disease, they also have a burden of the side-effects associated with the neo/adjuvant treatments. These side effects include bowel and sexual dysfunction, gastrointestinal upset (diarrhoea & emesis), anaemia, neutropenia, thrombopenia, skin disorders, peripheral sensory neuropathy and the associated negative impacts on QoL[47,48]. A more specific sub-group still will only be undergoing surgery after failure of chemo/radiotherapy with curative intent, again placing them in a high-risk group of poor outcomes.

Regardless of the side-effects of any neo/adjuvant therapy, CRC itself causes numerous physiological changes. These include direct inhibition of immune responses, leading to worse postoperative prognoses[49]. In addition to the immunosuppression seen in many due to old age and nutritional status, CRC itself has a direct immunosuppressive effect as evidenced at a molecular and cellular level[49]. Individuals with CRC have reduced levels of inflammatory

cytokines such as TNF-α and IFN-γ, with a negative dose-response based on Dukes stage[50,51]. Levels of these cytokines return to normal within three to six weeks after successful resection suggesting this is a direct effect of CRC[51].

In addition, cancer cachexia, a '*multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment*'[37] is also associated with poorer postoperative outcomes. Individuals with cancer cachexia have reduced oral intake, and systemic inflammatory and metabolic changes that in addition to reducing QoL, also reduce treatment tolerance and survival[52]. Relatively recent work by Carla Prado and colleagues showed that in both male and female individuals with CRC, low muscle mass at the time of operation was associated with a number of postoperative issues including prolonged LOS and more postoperative complications including major complications, and higher overall and 30-day mortality[53].

These effects of cancer (amongst other variables) are considered when defining an individual's American Society of Anaesthesiologists Physical Status Classification System (ASA) grade[54], a common tool in risk stratifying individuals having surgery (Table 1.2). ASA I is defined as '*a normal healthy patient*' and is associated with the best possible outcome at 48 hours post-operation when compared with groups II-V[55]. Of note, an individual with cancer, irrespective of their level of physiological reserve and chronological age, cannot have an ASA of I, representing the heightened operative and anaesthetic risk in these patients over and above physiological parameters alone.

ASA Grade	Description
I	Patient is a completely healthy fit patient
II	Patient has mild systemic disease

III	Patient has severe systemic disease that is not incapacitating.
IV	Patient has incapacitating disease that is a constant threat to life
V	A moribund patient who is not expected to live 24 hour with or without surgery

Table 1.2- ASA Physical Status Classification[54]

Beyond ASA grading, further considerations need to be made regarding the decision to operate. Though operative intervention is an inherently risky strategy, the risk: benefit ratio to the individual is the predominant concern and strategies should be employed to consider this on a case-by-case basis. For those who have a technically operable CRC who do not have surgery, the life expectancy is poor, with the majority not surviving two years[24], yet thirty-day mortality in octogenarians or older with CRC who do have an operation is 13-15% with 60-day mortality possibly even twice that. The same cohort report a deterioration in their ability to perform activities of daily living (ADLs) and 12% of those who survive hospital, do not return to their pre-hospital accommodation. Regardless, most older adults (≥80) deemed 'fit' for an operation benefit at least in terms of mortality; 50% of patients with operatively managed stage I rectal cancer are alive at five years[24]. Clearly the decision to operate in this cohort is a complex one.

Another challenge for individuals with CRC, including those who have surgery is nutritional status. Whilst some issues preventing optimal dietary intake in individuals with cancer may be theoretically simple to understand (e.g. for individuals with gastrointestinal luminal cancer, such as oesophageal cancer, a mechanical obstruction may prevent adequate oral nutrition) other issues may be more complex. These include cancer-related central nervous system alterations that can impact appetite, alterations in food absorption/digestion processes and/or psychological stresses leading to anxiety and depression[56]. As a result, insufficient caloric and micro/macronutrient intake can occur, especially when coupled with the

increased demands associated with tumour metabolism and the associated inflammatory response in an individual with cancer[57]. When considering how nutrition can be difficult to maintain/optimise in individuals with CRC, it must be recognised that malnutrition impacts all forms of treatment outcomes, increases the risk of systemic treatment-related toxicity (i.e., via low muscle mass), leads to poor treatment adherence, and is associated with postoperative morbidity and mortality[56].

1.2.3 Risk Stratification

To ensure informed consent, audit results and make best use of sparse resources, individuals and cohorts are often risk stratified prior to having surgery. At present tools exist for estimating 'risk' in emergency operating[58] and in specific cancers[59,60]. Cardiopulmonary exercise testing (CPET) is commonly used in patients deemed high or intermediate-risk to supplement clinical acumen with regard to surgery, altering perioperative and postoperative care and offering patients an individualised risk estimate which can help inform decisions[61].

Risk stratification is useful in identifying individuals who may not benefit from surgery in terms of quality and length of life, but it can also help identify who have the most to gain from perioperative optimisation. For example, in a 2023 study by Bojesen et al., the introduction of a screening tool to identify those with low functional capacity, malnutrition and anaemia was associated with a 10.9% absolute risk reduction of a complicated postoperative course[62].

1.2.3.1 Modifying risk

Many individuals will have modifiable risk factors that can be optimised prior to surgery such as smoking, alcohol use and obesity[63–66]. In addition, as alluded to in *chapter 1.2.2,* individuals with cancer are also at particular risk of factors associated with malnutrition such as anaemia[67,68]. Further, individuals with cancer are often older, have poor cardiorespiratory

reserve/ poor overall fitness; have concomitant comorbidities; and experience polypharmacy[69,70]. Though interventions can modify some of these risk factors (e.g. via weight loss or smoking cessation), the mandated short period between DTT and first treatment in individuals with cancer brings a significant challenge to both screening for, and optimising, modifiable risk factors. Much work has been done in attempting to quantify and treat such risk factors in individuals with cancer. Interventions to ameliorate modifiable risk factors range from screening for common surgical risk factors[62], to focussed dietary and lifestyle modification[71].

Traditionally, there has been a focus on rehabilitation of patients in the postoperative period, starting immediately after an operation with implementation of ERAS protocols[72], to protracted rehabilitation regimes of exercise over months[73]. One advantage of such regimes is that it allows for a long window of intervention, with cancer patients not limited by short pre-cancer intervention windows in which to effect change. Although rehabilitation does have many positive effects[74], including for individuals with CRC, where it has been shown to improve physical and functional status, faecal incontinence and QoL[75], it cannot influence the preoperative period or help optimise individuals to withstand the physiological insult of surgery; an offering only afforded by prehabilitation.

1.3 Prehabilitation

Prehabilitation is the term used to describe '*personalised, multimodal, needs-based intervention, designed to improve the physiological, metabolic and psychological resilience of an individual prior to an expected major stressor'* such as surgery[76]. It aims to enhance functional capacity[77], improve postoperative outcomes[78] and, specifically in cancer, do so in the time between cancer diagnosis and the beginning of treatment[79] in what is argued to be

the most effective period for intervention[80]. The aim of prehabilitation is to improve the baseline of an individual, whether that be physiological, functional, nutritional, psychological and/or metabolic, so that an expected insult to said domain can be prophylactically counteracted[81] (Figure 1.5).

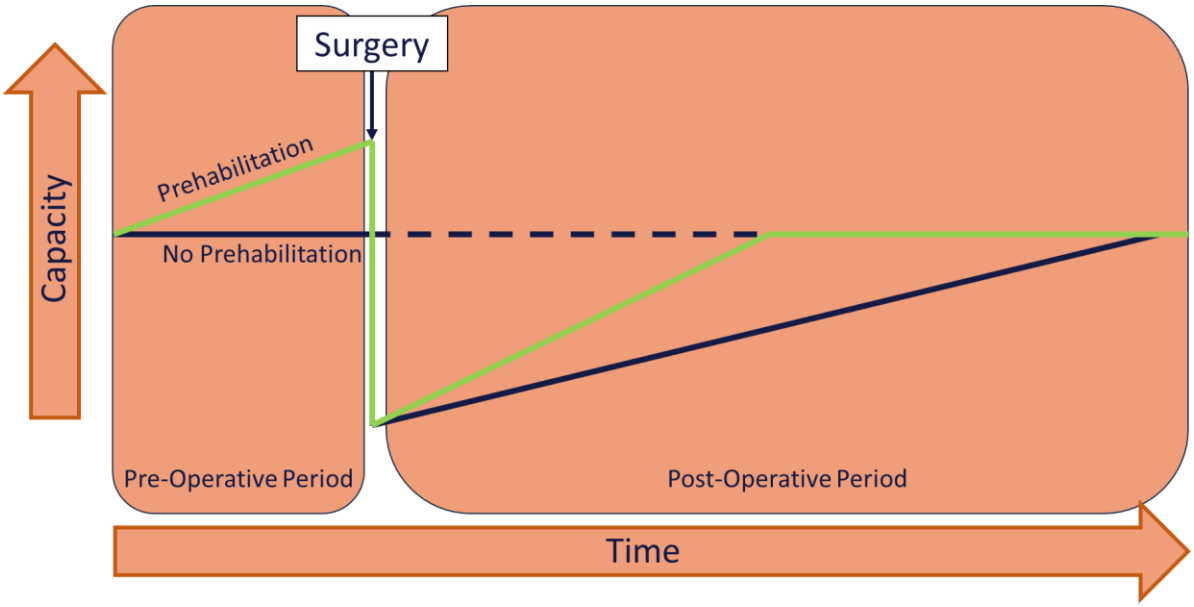


Figure 1.5- A schematic displaying the effects of prehabilitation on 'capcity' over time. The dark line represents the expected course of a non-prehabilitated patient with a baseline capacity which is reduced at surgery and then slowly recovers. In contrast, the green line, representing a prehabilitated patient shows an increase in capacity between baseline and surgery. Though the decline at surgery is equal for both, the rate of recovering back to baseline capacity is higher for the prehabilitated patient. Recreated based on Lundberg et al.[81]

Though the concept of prehabilitation has been considered for at least 75 years, it became common practice and parlance amongst physical therapists in the 1980's[81] with prehabilitation in CRC only robustly studied since the early- to mid-2000's[77]. Prehabilitation can take several forms, but the majority of prehabilitation programmes in individuals with cancer focus on exercise, either alone or in conjunction with other modalities.

In the 1990s. Older et al., determined that anaerobic threshold (AT) is an excellent predictor of cardiovascular mortality in patients who had major intra-abdominal surgery and suggested that those with an AT of <11ml/kg/min be considered for a higher level of care postoperatively[82,83]. The natural progression of this finding was that improving AT prior to surgery may benefit patients postoperatively and a body of literature grew around the idea of prehabilitation[84].

1.3.1 Prehabilitation in Cancer

As already described, the cohort of individuals with cancer represent a challenge in terms of expediency of intervention, and comorbid and functional status. Nonetheless, there is a wealth of literature focussing on prehabilitating individuals with cancer, and a breadth of interventions studied. The Macmillan *Prehabilitation for people with cancer Clinical and implementation guidelines* published in October 2025 suggests that prehabilitation has the ability to benefit patients, '*not only in preparation and recovery from cancer treatment*' but also in their '*experience of care and sense of control'* and that 'preh*abilitation should be integrated into existing cancer pathways'*[85]. In addition to exercise/physical activity and nutritional advice/supplementation[86], prehabilitation regimes have been tested that include psychological support[87–92], alcohol reduction and smoking cessation interventions[71,88], relaxation techniques[93] and 'medical optimisation' of varying degrees[88,92,94,95]. Collating the evidence from individual studies, a 2020 systematic review and meta-analysis by Daniels *et al.*, concluded that exercise, nutritional and multimodal prehabilitation may each reduce morbidity in elective abdominal cancer surgery in older patients[78]. This review supported the results of an earlier (2016) systematic review which concluded that preoperative exercise improves both functional and cardiorespiratory fitness (CRF) prior to CRC resection[96]. Despite

this, Boereboom et al., showed that despite a 31-day compliant exercise training programme improving oxygen consumption at peak exercise (VO_{2Peak}) and oxygen consumption at AT in healthy volunteers, a timeframe in keeping with that of individuals undergoing prehabilitation prior to cancer intervention[97], these effects did not hold true in a population with CRC, with around half of prehabilitated individuals with CRC not showing any improvement in CRF in response to high-intensity interval training (HIIT) prehabilitation[98]. Of promise, but as yet not definitively confirmed in human studies[99], in murine models, exercise has also been shown to reduce the likelihood of dissemination of cancer to distant organs[100].

Prehabilitating individuals with cancer is not without its challenges. Early safety concerns primarily based around exacerbating preexisting conditions have been refuted by a Delphi consensus from 2015 which suggested that surgeons felt exercise prehabilitation in older adults with CRC was safe[101], a conclusion later supported by a 2021 meta-analysis focussing on HIIT in individuals with cancer in which the authors reported HIIT prehabilitation in patients with cancer had a low risk of adverse events[102]. Despite consensus opinion from surgeons agreeing that exercise prehabilitation was safe, this same group of individuals disagreed as to whether implementing such prehabilitation programmes would be possible[101], with a qualitative study published in 2022 suggesting that barriers to doing such included: conflicting scientific evidence on cost-effectiveness of such programmes; the inability to appropriately personalise prehabilitation; and the complex logistic organisation[103]. Further concerns were also raised regarding lack of awareness of the importance of prehabilitation, but with possible solutions highlighted, including appointing programme coordinators and '*involving sceptical colleagues from implementation'*[103]. Separate work highlighted other issues enrolling individuals with cancer in prehabilitation regimes including limited time, misunderstanding relevant information and the emotional impact of a cancer

diagnosis. It was stated that some individuals with cancer, do not want exercise to be too intensive and prefer exercise to be undertaken closer to home which may hamper efforts to roll-out large-scale programmes[104]. There is however a growing body of literature on the effectiveness of home-based exercise regimes, in part due to the restrictions enforced by the COVID-19 pandemic, including in older adults[105], though in cancer patients postoperative and functional outcomes do not seem to be affected after home-based therapy[106,107]. Further, more recent data suggests prehabilitation in CRC may reduce hospital costs which may act to persuade those concerned about cost implications[108].

Regardless of the barriers, exercise is necessary for muscle mass preservation in individuals with cancer[109], and benefits to the individual and the healthcare system on outcomes such as reductions in LOS and complications and their burden, should be sought.

1.3.1.1 Exercise Prehabilitation as Monotherapy

Exercise can be defined as '*activity requiring physical effort, carried out to sustain or improve health and fitness*'[110]. Exercise prehabilitation alone has been shown to reduce pulmonary complications in major abdominal surgery as well as reducing overall morbidity. In cancer cohorts, it has been shown to be safe, acceptable, and feasible, able to improve clinical outcomes such as LOS and fitness parameters such as VO_{2Peak}, and improve functional capacity as determined by, for example, the *six-minute walk Test* (6MWT). Randomised controlled trials (RTC's), large systematic reviews and meta-analyses support these conclusions, though the inclusion of some studies that use multi-modal prehabilitation in the latter make concrete conclusions difficult[96,111–114]. Furthermore, exercise prehabilitation may lead to improvement in oncological measures with a 2019 study concluding that, in individuals

with locally advanced rectal cancer, exercise resulted in significant improvements in fitness and augmented pathological tumour regression[115].

Exercise alone, or the exercise component of multi-modal prehabilitation often represents the largest time and effort commitment for an individual. To combat this, some studies have used home-based workouts whereas others required individuals with cancer to attend supervised sessions. A few studies combined supervised and home-based exercises[116]. Benefits of supervised sessions include monitoring and encouragement of exercise, assurance of safety, and measurement of objective outcomes[117]. Drawbacks include an increased time commitment associated with travelling to and from sessions and time away from home[118]. Should supervised sessions be undertaken in a non-research context, it would also likely be financially expensive, for example employing personal trainers and purchasing appropriate clothing, worsening the financial burden associated with cancer and its treatment to both the individual with cancer and the healthcare system.

Exercise is traditionally divided into aerobic and anaerobic exercise training, the latter of which includes HIIT and resistance exercise training (RET). Aerobic training uses large muscle groups, can be continued indefinitely and is rhythmic in nature, examples include jogging and swimming. In contrast, anaerobic exercise requires intense physical activity which cannot be sustained due to the use of oxygen-independent intracellular pathways to release energy. A byproduct of this, lactic acid, leads to a relative acidaemia and ultimately cellular failure[119]. Though both aerobic and anaerobic exercise can improve measures of physiological fitness, anaerobic training can do so with a low total exercise volume and in a shorter time in comparison to aerobic training and this is commonly utilised in cancer prehabilitation[120].

1.3.1.1.1 High-Intensity Interval Training Alone

HIIT is a mode of exercise training characterised by relatively short bouts of high-intensity workloads separated by periods of low-intensity activity or rest[102]. HIIT can, in diseased[121] and healthy older adults[121], improve CRF in a short (four to eight week) timeframe. A 2020 systematic review and meta-analysis found eight studies, including 896 individuals with cancer who had HIIT as prehabilitation[102]. Six of the eight studies compared HIIT-alone with usual care, with the remaining two combining HIIT with other prehabilitation interventions. Three of the six studies, were pilot or feasibility studies which showed that HIIT can i) negate the negative effects on fitness of neoadjuvant chemoradiotherapy in rectal cancer, returning fitness to baseline prior to surgery[122]; ii) improve CRF in individuals with bladder cancer prior to radical cystectomy[123]; and iii) that HIIT is safe, feasible and well tolerated in individuals with non-small cell lung cancer undergoing concomitant chemoradiotherapy[124]. The remaining three studies showed improvements in i) CRF and walking capacity in individuals with lung cancer[125]; ii) CRF and QoL prior to liver resection for CRC metastases[126]; and iii) CRF and health status in individuals with urological cancer[127]. Importantly, these latter three studies had HIIT regimes lasting ≤31 days, in keeping with the NHS targets from DTT to intervention.

Despite the wealth of literature showing positive effects of HIIT prehabilitation alone, some studies have shown no improvement after intervention. Specific to CRC, a 2019 study showed that HIIT in the 31-day preoperative period did not improve CRF[98]. This was despite the regime being identical to that trialled in age-matched older individuals without cancer in which significant improvements in CRF were shown[97]. Despite the lack of improvement in CRF, CRC patients did improve their exercise capacity (maximum wattage and time to failure on CPET) and cardiovascular parameters (resting systolic blood pressure) via this regime[98]. Of note, this same HIIT regime was able to improve the CRF of urological cancer patients, suggestive of

differences in adaptive capacity between cancer types. Supporting the notion of physiological processes blunting adaptive potential in CRC, Williams and colleagues showed that muscle protein synthetic responses to nutrition were blunted in CRC patients whilst their tumour was in situ, yet restored by 6-weeks after resectional surgery[128]. Recognising that increases in muscle protein synthesis (MPS; as a result of protein nutrition and contractile activity[129]) are the basis for muscle hypertrophy[129] and that muscle mass and CRF are linked[130], this may explain the lack of CRF improvement seen in this cohort. It is not however only improvements in CRF which can benefit patients if improved prior to surgery. HIIT can improve QoL, pain and diastolic blood pressure in cancer cohorts[131], and may suppress CRC cell growth in patients with recently treated CRC[132].

Beyond improving physiological status at the point of surgery, a number of studies have also explored the ability of HIIT prehabilitation to impact postoperative clinical outcomes and/or longer-term physical function. For example, Karenovics *et al.,* showed that in individuals with operable lung cancer, prehabilitation with HIIT did not alter clinical or functional outcomes one year after resection, despite improvements in aerobic parameters prior to surgery[133].

To date, the benefits of HIIT prehabilitation alone in individuals with *cancer* is not clear, though this may stem from the grouping of different cancer types into a single pathological entity. As evidenced by differences in adaptation to exercise[98,134] individuals with cancer represent a heterogeneous assembly and 'cancer' should not be considered a single disease. Another limitation of the prehabilitation literature is the focus on short-term, pre- and perioperative outcomes, whereas studies following up individuals on a longer time scale may show little or no benefit. That said, HIIT prehabilitation may have a role in optimising

individuals with 'borderline' fitness prior to an operation, who might otherwise not have been offered such intervention.

1.3.1.1.2 Resistance Exercise Training Alone

RET, also known as '*strength training*', aims to increase muscular strength and promote hypertrophy[135], but has also been shown to elicit benefits in domains such as functional ability[136,137], CRF[138] and overall wellbeing[139], especially in older adults and/or those with age-associated conditions. RET may take the form of multi or single joint exercises and may use body or free weights, elastic resistance bands, or exercise machines to provide the resistive stimulus[140]. The mechanism behind RET-induced hypertrophy is conceptually relatively simple, with RET able to alter the dynamic equilibrium (in youth and health) between MPS and MPB, such that a positive net protein balance is achieved[141], (Figure 1.6), and the majority of this increase in MPS appears to take place within three weeks, suggesting this might be beneficial in a prehabilitation setting[142].

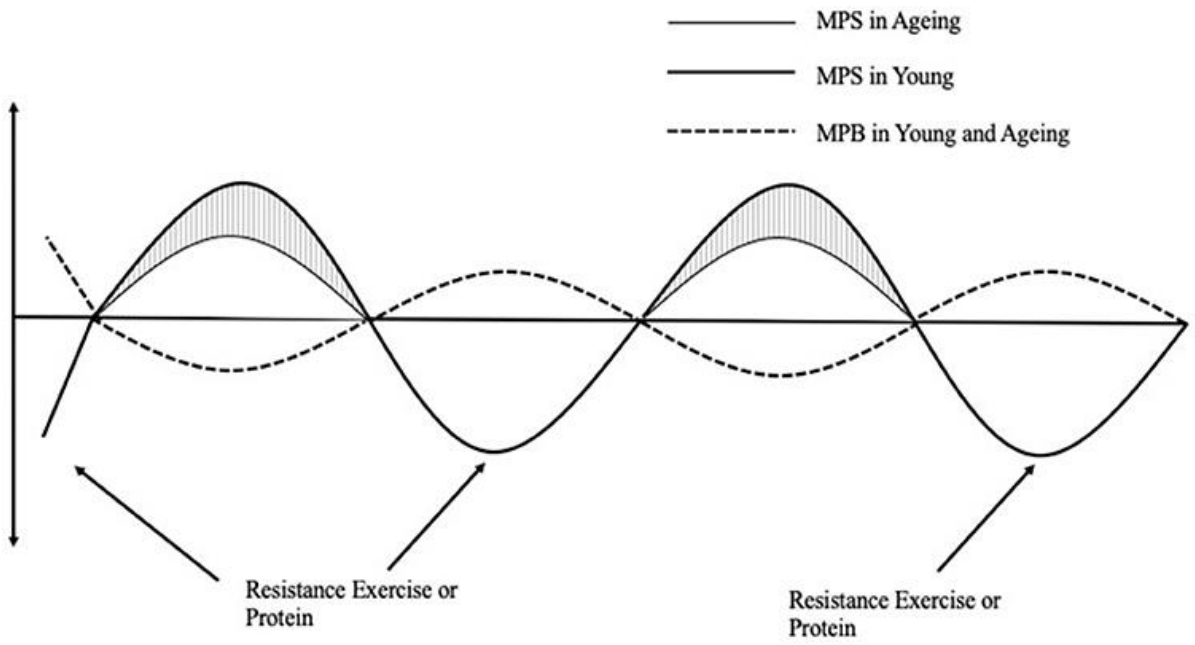


Figure 1.6- The dynamic equilibrium between muscle protein synthesis (MPS) and breakdown (MPB). Taken from Barclay et al.[143]

Functional gains with RET are not only attributable to gains in muscle mass, with clear disparity between mass and function both in terms of losses (i.e., with sarcopenia[144,145]) and gains (e.g., via exercise[146]). Other processes responsible for RET-induced gains in physical function likely include improvements in neuromuscular function[147,148].

As with HIIT-based regimes, RET-based prehabilitation is usually part of multimodal exercise or therapy[149–151], with no prehabilitation randomised controlled studies undertaken in cancer cohorts exploring RET alone[151].

Although not in individuals with cancer, and despite gains in muscle mass and function being the primary physiological adaptations associated with RET, a 2022 systematic review and meta-analysis by Smart *et al*., showed that RET also improved measures of CRF (VO_{2Peak} and AT) and physical function (6MWT) in healthy older adults utilising exercise regimes lasting <24 weeks[152]. Though the effects of RET-alone prehabilitation are not well studied in individuals

with cancer, the findings of RET in combination with other modalities, or in non-cancer cohorts are positive, especially considering the ability to effect change in a short time span.

1.3.1.1.3 Combined High-Intensity Interval Training & Resistance Exercise Training

As alluded to, different modalities of exercise are associated with distinct physiological adaptation. As such, exercise modalities are often combined to try and elicit the most benefit. For example, national guidelines for population level physical activity recommend both aerobic exercise training or HIIT (to improve CRF) and RET (to improve muscle mass and function)[153]. Specific to prehabilitation for cancer patients, HIIT and RET have been combined either as exercise-alone prehabilitation[154], or as part of multimodal prehabilitation encompassing exercise and non-exercise interventions[155], with this literature suggesting that combining exercise modalities can lead to positive effects on functional and physical capacity[154].

Prehabilitation in individuals scheduled for CRC resection has been shown to be superior to rehabilitation in terms of postoperative exercise capacity at eight weeks post-operation[156], with combined HIIT and RET as part of multimodal prehabilitation shown to be a promising strategy by which to improve postoperative physical function[157].

Despite purported benefits of combined HIIT and RET as surgical prehabilitation for cancer patients, the existing literature base is equivocal. For example, McIsaac et al., showed that in older adults living with frailty having cancer surgery, a home-based exercise programme did not improve postoperative outcomes[106].

To date, no studies have focussed on exercise monotherapy prehabilitation with HIIT and RET in individuals with CRC scheduled for therapy with curative intent[158].

1.3.1.2 Exercise Prehabilitation as a Part of Multimodal Therapy

It is widely accepted that preoperative exercise is both safe and efficacious in individuals scheduled for non-cardiac surgery. Recent key recommendations from the *Association of Anaesthetists* suggest that preoperative exercise should be offered as part of a multi-modal prehabilitation programme encompassing further risk factor stratification such as correction of anaemia, smoking cessation and reducing consumption of excess alcohol[159].

Multimodal prehabilitation in individuals with cancer, and cohorts with participants with cancer encompasses a wide range of interventions. The majority of interventions focus, at least partially, on exercise, but other modalities employed include nutritional supplementation/ advice[160,161], nurse-led phone support[162], psychological support[87–90,92,157,163,164], motivational support[71], alcohol reduction and smoking cessation interventions[71,88], 'medical optimisation'[88,92,94,95] and relaxation techniques[93].

As discussed in a recent review[165] there is a large heterogeneity in study design, population, intervention, and outcome, but despite this, multimodal prehabilitation consistently improves clinical metrics such as LOS and complication burden, and functional metrics such as QoL. It is also associated with reduced healthcare costs, though none of the studies comment in detail on the cost of the prehabilitation programme.

Multimodal therapy is still an active area of prehabilitation research. A trial of multimodal prehabilitation, incorporating HIIT and RET in individuals with CRC is ongoing, looking at its effects on functional capacity and postoperative complications[166]. Another, looking at individuals with colorectal and upper gastrointestinal cancer scheduled for surgery has finished recruitment. This study aims to quantify the impact of multimodal prehabilitation, including combined HIIT and RET on functional capacity, nutritional and psychological status,

and surgical outcomes[167]. A study from Xiamen University is also ongoing, looking at the effects of multimodal prehabilitation after surgery for CRC[168].

Exercise prehabilitation then is perhaps most utilised as part of multimodal therapy. It has been speculated that optimising nutrition and other factors such as psychological support may maximise the effects of exercise, allowing for it to have its greatest impact[169].

1.4 Exercise

The UK Chief Medical Officer recommends adults (aged 19-64) and older adults (>64) should undertake activities to develop or maintain strength at least twice a week and should accumulate at least 150 minutes of moderate-intensity; or 75 minutes of vigorous-intensity activity[170]. The term *exercise* can be further sub-divided into differing types, categorised by, amongst other things, levels of muscle activation, subjective exertional effort, and modality of cellular respiration (aerobic or anaerobic).

1.4.1 High-Intensity Interval Training

HIIT is an exercise modality involving alternating short bursts of high-intensity exercise with periods of recovery or light exercise[171] (Figure 1.7) and is performed with maximal or near-maximal effort, corresponding to ≥ 90% of maximal oxygen (VO_{2Max}) uptake or >75% of maximal power[172]. The lack of sufficient time in which to perform exercise is often cited as the most common barrier to adhering to regular exercise, which has, in part, led to the widespread adaption of HIIT which generally takes less time than other methods of exercise whilst inducing similar or even greater physiological adaptions[172].

HIIT has been shown to be safe and effective in older adults[97], and in cancer cohorts [102,173] and crucially, if HIIT is to be used as part of cancer prehabilitation, has been delivered in 31 days with good effect[97].

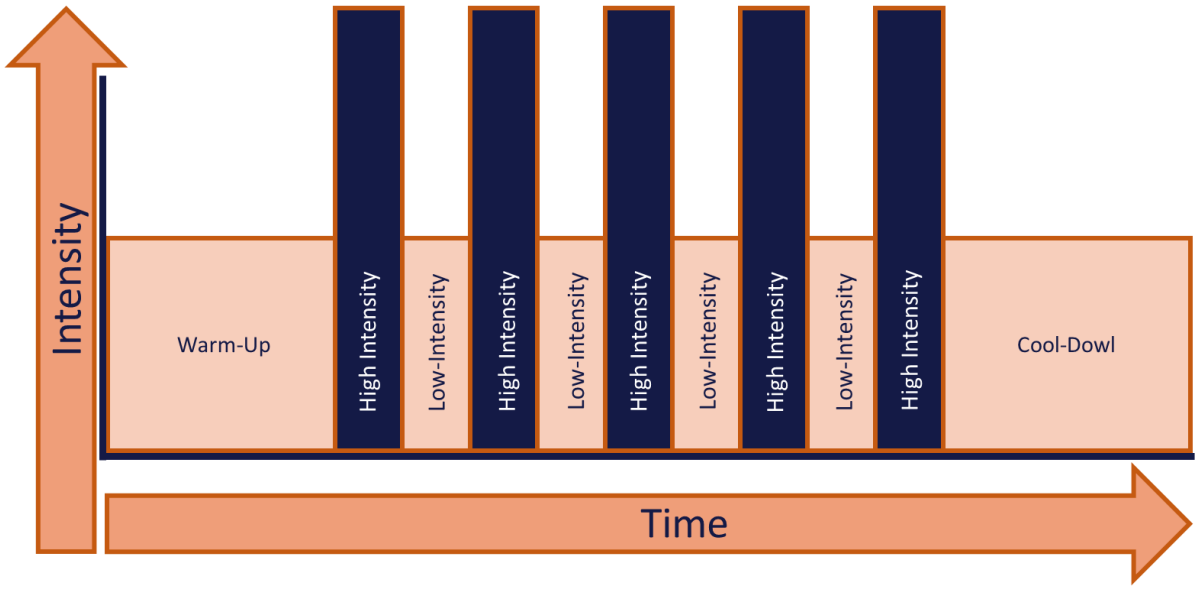


Figure 1.7-An Example of a HIIT protocol

1.4.1.1 Physiological Impacts of HIIT

HIIT can improve muscle mass and CRF in both healthy and diseased cohorts, and specifically in individuals with a history of CRC[102,134,174–176]. Even in the short-term (<12 weeks), moderate intensity HIIT can induce modest body composition improvements, independent of absolute changes to body weight in obese individuals[177,178] and in a near-preoperative timeframe, HIIT can improve VO_{2Peak} and O_2 consumption at AT in older adults[97]. Longer-term (≥12 weeks) HIIT can improve measures of body composition such as % body fat (%BF), and waist circumference in overweight/obese populations[178].

Though HIIT alone has been shown to improve physiological parameters in many populations and over varying timescales, specifically in individuals with CRC awaiting an operation, Boereboom *et al.* showed that HIIT alone did not improve CRF in individual with CRCs in a

preoperative window[98], despite an identical protocol showing improvements in a population with urological cancer[127]. This effect may be related to the specific tumour burden seen in CRC where MPS is significantly hampered[128].

1.4.1.2 Functional Effects of HIIT

Prehabilitation regimes incorporating HIIT in those undergoing operative intervention for gastrointestinal cancers do not appear to effect 6MWT[179] though this may be due to only those who are deemed 'fit' for operative intervention are offered this therapy. This hypothesis is supported as the effects of HIIT on 6MWT is mixed in individuals with cancer who are included in analysis regardless of stage or therapy modality[180].

HIIT can improve QoL in healthy individuals[181] and individuals with cancer, though the effect in those with cancer does not appear to be only associated with HIIT, rather any exercise regime[182]. Preoperative exercise training does not appear to affect health-related QoL (HR-QoL) in individuals who had operative intervention, despite a positive effect being seen in a similar population with lung cancer[182].

1.4.1.3 Clinical Effects of HIIT

HIIT has long been shown to decrease the risk of cardiovascular disease, metabolic syndromes such as diabetes mellitus, all-cause mortality and certain cancers such as breast cancer[183,184] but it's effects on postoperative outcomes are less well documented. Though some studies have investigated the effects of short-term HIIT in major abdominal surgery, most show no or only modest differences in clinical outcomes [176,185].

LOS appears to be unaffected by preoperative HIIT programmes, with a 2023 meta-analysis finding no difference in LOS between those undergoing HIIT and standard care[185]. This may be due to the low absolute value for LOS, with the UK median LOS being 6 days post CRC

major resection, a trend which is decreasing[186]; most studies are also underpowered for this outcome[187]. Similarly, postoperative (90-day) mortality is also relatively rare with a UK national average of 2.4% between April 2021 and April 2022. Unsurprisingly, effects of HIIT on mortality reduction in this cohort are not well documented, but a statistically significant effect is unlikely[185].

Postoperative complications are common in surgery for CRC[188] and therefore could represent a target for improving clinical outcomes. HIIT is associated with a significant reduction in postoperative complications in adults who have major abdominal surgery[185] and at least one actively recruiting trial is attempting to delineate these effects specifically in individuals who have operative intervention for CRC or dysplasia[189].

In a CRC-specific population, HIIT does appear to significantly reduce resting systolic blood pressure and submaximal heart rate (HR), but extrapolating this to tangible clinical outcomes with the numbers of individuals studied is not possible[98].

1.4.2 Resistance Exercise Training

RET is an umbrella term for a variety of exercise regimes that primarily focus on progressive overloading of skeletal muscle with specificity and variation. 'Specificity' applies to the adaption to the applied stimulus e.g. muscle activation, range of movement, energy involved etc; 'variation' applies to the process of altering one of more variables over time to maintain a challenging and effective stimulus. Important principles of RET include a systematic increase in demand placed upon the body via altering exercise intensity, repetitions, speed, rest periods and training volume[190]. RET overloading can be elicited using body weight, free weights or gymnasium equipment[190], though evidence suggests that the method used does not significantly impact the efficacy of the training[191].

Prevention or reversal of sarcopenia is important to ameliorate some of the deleterious effects of ageing, and sarcopenia is common in individuals with CRC with increasing sarcopenia being associated with worsening outcomes in surgical patients[192,193]. A core aim of RET is to increase muscle strength via adaption of muscle mass and function which is inversely correlated with all-cause mortality [194]. This is especially important in individuals with CRC who have an operation. Surgery evokes a stress response similar to that seen in critical illness and trauma and the hypermetabolism and hypercatabolism seen in the postoperative period leads to a wasting of skeletal muscle, which in turn, leads to loss of function and poorer clinical and functional outcomes[35]. One aim of RET-based prehabilitation is to improve muscle mass and function prior to a planned surgical insult. This would optimise the individual through the operative and immediate postoperative period in terms of muscle mass and function versus a matched individual who has not undertaken RET-based prehabilitation.

1.4.2.1 Physiological Impacts of RET

In comparison with aerobic training, RET conveys similar but distinct physiological adaptations. Regarding body composition, RET reduces fat mass whilst simultaneously increasing muscle mass[194] and the fat mass reduction in particular can be enhanced in combination with a caloric restriction in a healthy population[195]. Some of these effects appear to be blunted in older populations however, with increases in muscle mass reducing with advancing age in those performing RET[196]. Further, RET can improve VO_{2Peak} and AT in healthy older adults[152], yet RET participation in this population is very low[197]. Suggesting that many older adults could see improvements in CFR from participation.

1.4.2.2 Functional Effects of RET

RET increases strength and physical endurance and can have a significant impact on functional ability[194]. RET can also increase mobility and cognitive function in older adults and potentially help to reduce falls and their associated comorbidities[198]. In healthy older individuals, short/medium-term (<24 weeks) RET can increase 6MWT distance[152], and RET can improve HR-QoL and physical function in a similar population[199,200]. Other, more specific functional markers such as handgrip strength (HGS) can also be improved via RET[200] and in cancer populations, RET can improve HR-QoL[201].

1.4.2.3 Clinical Effects of RET

RET is associated with a reduction in all-cause, type II diabetes mellitus-related and cancer-related mortality, as well as a decrease in cardiovascular disease[198]. RET can increase insulin sensitivity, improve serum lipid profile and decrease blood pressure[194]. Other clinical measures such as postoperative complications and LOS are more difficult to ascertain as much of the literature fails to differentiate between types of exercise regime, especially in CRC[158].

1.4.3 Combined HIIT & RET

As described, there are many benefits to both HIIT and RET individually, but there is also evidence to suggest that HIIT and RET can act synergistically, with the improved muscle mass and function seen with RET being used to 'unlock' the potential gains predominantly associated with HIIT. Traditionally, the effects of HIIT combined with or immediately after RET were though to reduce the efficacy of RET: '*the interference effect*'[202], but more contemporary data refutes such claims[203]. It is likely that there may be a detrimental effect in some populations, and a positive effect in others, as different populations, duration of intervention, modality and measured outcomes are difficult to compare[204].

In relation to populations specifically, much of the literature about combined HIIT and RET is based on athletes[204], who represent a predominantly younger and less comorbid population than individuals with cancer and as such outcomes, especially in the domains of clinical and functional status, are vastly different. Even in comorbid populations however there is evidence that combined HIIT and RET can promote cardiometabolic gains for example in those with metabolic syndrome[205].

When considering combined HIIT and RET for prehabilitation, a common barrier is a lack of time. In addition to the psychological burden of a cancer diagnosis and a relatively short preoperative period, individuals also must attend multiple hospital appointments and may suffer cancer-related fatigue[206]. Owing partially to this, a combined HIIT and RET programme may allow the benefits of both modalities with the considerable reduction in time commitment. A 2018 clinical guideline recommending preoperative exercise training in adults suggested a combination of RET and aerobic (such as HIIT) training should be offered to patients[159].

Finally, though many prehabilitation regimes in individuals with CRC incorporate some degree of HIIT and RET, much of the literature fails to differentiate between HIIT **and** RET, or, HIIT **or** RET as a homogeneous group, making it difficult to distinguish outcomes from a combined approach (Figure 1.8). Combined approaches also often fail to compare to a single approach making it difficult to draw conclusions specifically about combined therapy[158].

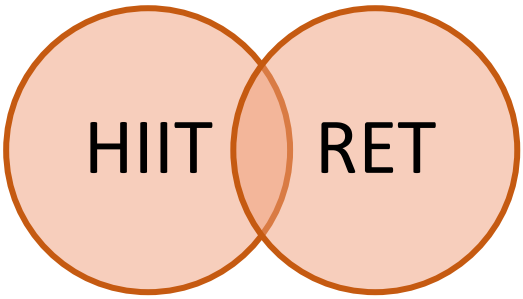


*Figure 1.8- A Venn Diagram of the overlap of HIIT & RET in most prehabilitation regimes. Most studies do not differentiate between HIIT **and** RET, or, HIIT **or** RET*

1.4.3.1 Physiological Impacts of Combined HIIT & RET

For the outcome of muscle strength/ hypertrophy combined HIIT and RET has been shown to have no effect versus RET alone, or a marginal negative effect, depending on specific outcome measures in healthy adults[204]. A 2018 systematic review detailing the response of preoperative cancer patients who had combined HIIT and RET concluded that muscle strength was significantly improved in two out of three studies that reported this outcome, versus the control group[155]. In individuals with breast cancer, a combined HIIT and RET programme increased VO_{2Max} and strength[207].

1.4.3.2 Functional Effects of Combined HIIT & RET

Improvements in 6MWT distances have been seen in cancer cohorts employing combined HIIT and RET prehabilitation, but effects on QoL are either positive or neutral[155]. A 2023 systematic review suggested that HIIT can significantly improve some functional outcome measures, but the addition of strength-orientated body weight exercises (i.e. RET), can improve HGS by up to 100% compared with usual care in individuals with cancer.

1.4.3.3 Clinical Effects of Combined HIIT & RET

Clinical effects of combined HIIT & RET are reported more widely in diseased populations. Though a commonly reported outcome, the majority of studies do not support the conclusion that combined HIIT and RET reduce LOS. A similar mixed conclusion is also true of postoperative complications, and mortality is seemingly unaffected[155].

RET, including in combination with aerobic training is superior to aerobic training alone in reducing all-cause and cancer-specific mortality, but it is unclear if this effect is improved by combining the two approaches[198].

1.5 Exercise Prehabilitation in Colorectal Cancer Surgery with Curative Intent

Exercise-based prehabilitation is well-studied in CRC surgery and can be broadly categorised into single-exercise modality therapy, multi-exercise modality therapy and multimodal therapy, either with a single or a multiple-modality exercise component.

The concept of exercised-based prehabilitation in a predominantly older, surgical population is not new[208]. But the introduction and adoption of such programmes into CRC cohorts took longer than that seen in other surgery types. In 2015, a Delphi study by Boereboom *et al.* investigated the opinions of consultant colorectal surgeons on exercised-based prehabilitation in CRC. The authors found that most believed exercise-based prehabilitation to be safe and effective, and that they should be based on improving fitness in a 31-day period[101]. In 2019 Boereboom *et al.* furthered their work in showing that a short-term HIIT-based programme was feasible in this population, but also concluded that HIIT-based therapy alone did not improve CRF within the 31-day period, despite positive effects seen in a similar,

but healthy, population[97,98]. A similar protocol did show positive results in individuals with urological cancer[134].

Translational research has shown that MPS is severely hampered in individuals with CRC, on a background of already reduced muscle mass (Figure 1.9). The insult of surgery further exacerbates muscle atrophy, but MPS is normal six weeks post-surgical resection and is inversely correlated with the degree of muscle atrophy when compared with matched healthy controls[128].

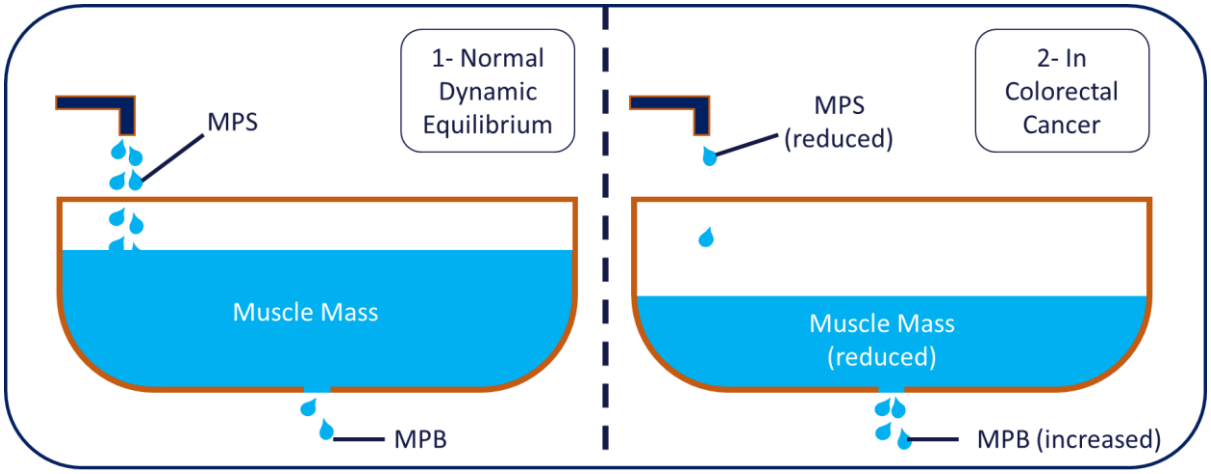


Figure 1.9- The dynamic equilibrium of muscle protein synthesis and breakdown in 1- the healthy state and; 2- colorectal cancer. The interplay can be thought of as a bathtub, with MPS as water coming out of the tap, MPB emptying from the plug, and the water level as muscle mass.

A 2015 meta-analysis concluded that preoperative exercise in individuals with CRC scheduled for surgery can improve functional and CRF prior to resection. The paper includes eight studies but concluded that risk of bias limited the application of the findings, and that *'future research should focus on which type of exercise is most likely to maximise patient adherence and improvements in CRF'*[96].

Patients with CRC have mixed opinions on preoperative exercise. Facilitators of preoperative exercise include patients feeling their healthcare providers should talk about physical fitness and the importance of exercise with patients, as well as the motivational component of exercise programmes. Barriers include a perceived lack of benefit, lack of time and CRC-related symptoms such as fatigue[206].

Though exercise-based prehabilitation is well studied in individuals undergoing surgery with curative intent, to date, there has been no study specifically comparing HIIT to combination HIIT and RET, in those with CRC scheduled for surgery with curative intent. In an attempt to investigate this the *Exercise Prehabilitation in Colorectal Cancer* (EPiC) study was designed.

1.6 An Introduction to the Exercise Prehabilitation in Colorectal Cancer (EPiC) Study and Personal Contributions

The EPiC study is a single-centre, unblinded, interventional, randomised, non-controlled trial to assess the effects of exercise prehabilitation (HIIT vs RET in addition to HIIT) in patients with CRC scheduled for surgery with curative intent. Objectives relevant to this thesis include comparing changes in cardiorespiratory and skeletal muscle function and differences in functional and clinical outcomes between the study arms. Full details of the study can be found in chapter 4.3.1. The study aims to recruit 56 participants.

From a personal perspective, though designing, starting and implementing the EPiC study was a collaborative effort, I played a central role in progressing the study from concept to reality, and in the day-to-day running of the study including generation and collection of the data that makes up the experimental chapters (4 and 5) of this thesis.

The early months of my PhD were dedicated to taking the concept of the Medical Research Council (MRC)- funded study from concept, through practical design, to ethical approval, to

first recruitment. Much of this early work included researching and planning how to practically implement methods of collecting data, much of which required a large practical element. With help from the University sponsor, ethical approval was sought and given from the Research Ethics Committee (REC) after documents detailing the study protocol were reviewed.

After ethical approval, I moved my focus onto broader stakeholder engagement. I presented the study at the local CRC MDT, hearing feedback about the approaches to recruitment and engaging, in particular, the consultant colorectal surgeon and nurse specialist professional body whom I had identified as key partners in recruiting for the study. Owing to my clinical commitments, I felt well positioned to act in both a clinical and research capacity recruiting participants to the study.

Once recruited, I, along with a close team, undertook the *day-to-day* running of the trial. This encompassed supporting and encouraging participants through the complex and intensive intervention period, running exercise sessions and assessment days, collecting and analysing data, ensuring participant safety and reporting appropriate data to the MRC via the trial manager. Further, seemingly trivial matters required a collective large amount of time and organisational skill to perfect, ensuring the study progressed. Examples include organising transport for participants, working exercise sessions around availability of participants and equipment in a busy exercise laboratory with participants with multiple clinical appointments and ensuring welfare by organising food on assessment days etc. Excluding data analysis, administrative tasks and other commitments of running a trial, it is estimated that the average participant required ~30 hours of face-to-face activity with the research team. Formally, I acted as a co-investigator and doctor for the EPiC study, informally, and as might be expected

from running a complex trial, I acted in many more roles to ensure the smooth running of the study, with a goal to make it as ‘easy’ as possible for each participant to progress.

1.7 Aims

The aims of this thesis are to:

1) Review the published literature on RET-based prehabilitation in individuals with CRC with a focus on clinical and functional outcomes (Chapter 2)
2) Explore the recent literature on nutritional interventions in cancer prehabilitation (Chapter 3)
3) To investigate if combined RET and HIIT prehabilitation in individuals with CRC is feasible in a timeframe in keeping with that between diagnosis and intervention (Chapters 4 and 5)
4) To investigate if, and to what extent, the addition of RET to HIIT in a prehabilitation programme for individuals with CRC scheduled for surgery with curative intent impacts physiological adaptation, and clinical and functional outcomes when prescribed in a period in keeping with that between diagnosis and intervention (Chapters 4 and 5)

2. The Effects of Resistance Exercise Prehabilitation in Operable Colorectal Cancer on Clinical & Functional Outcomes: A Systematic Review & Meta-Analysis

2.1 Chapter Introduction

As outlined in Chapter 1, the effects of RET-based prehabilitation in surgical CRC patients remain unclear, with the majority of the literature focussed on aerobic exercise or HIIT. As such, this chapter details a systematic review and meta-analysis of the effects of RET-based prehabilitation in individuals with CRC scheduled for surgery with curative intent, with a focus on clinical and functional outcomes. It has been published in *JCSM Communications*[158]. To date, no study has been performed specifically looking at the addition of RET to HIIT in cancer prehabilitation. As such, the focus of this review is to explore the effects of RET-based exercise prehabilitation in surgical patients with CRC to better understand the potential of this adjuvant regime.

2.2 Introduction

In the 31-day preoperative window, individuals with CRC may benefit from a period of optimisation prior to surgical intervention: '*prehabilitation*' in a similar fashion to how they may benefit from regimens after surgery: *'rehabilitation'*[75]. Prehabilitation can take many forms and often encompasses some combination of exercise therapy, nutritional supplementation, and/or psychological support[165].The effects of prehabilitation in cohorts with cancer must be expeditious to meet government targets and reduce the psychological and physiological burden and progression of the disease. The focus of most exercise-based prehabilitation regimes have been improvements in CRF[209] and though exercise-based prehabilitation has been shown to be safe and achievable in individuals with cancer[116], it can be challenging to elicit changes in CRF in the time-frame available before surgery[98]. Many,

though not all individuals with cancer, may see improvements in measures of CRF via prehabilitation with HIIT regimes [210–212], but there has been less focus on functional and clinical outcomes. Furthermore, despite the importance of muscle mass in individuals with cancer becoming increasingly recognised[213] RET, which is widely accepted as an important driver of muscle adaptation[214], has not been studied as a primary exercise modality in prehabilitation for individuals with CRC scheduled for 'curative' surgery.

A recent meta-analysis by Molenaar et al. studied the effects of multimodal prehabilitation (i.e., those with two or more components) on select functional and clinical outcomes in those undergoing surgery for CRC. The authors found that across the three included reports of studies (n=250; all of which included aerobic and RET), multimodal prehabilitation may improve both functional capacity (as determined via 6MWT) and postoperative complications, although length-of-stay in hospital (LOS) was seemingly unaffected. It should be recognised that owing to inherent bias in exercise studies, the certainty of evidence presented in this review was 'moderate' at best and included 'low' or 'very low' certainty outcomes. It also focussed on postoperative functional capacity and, despite an intention to undertake subgroup analysis on patients who received neoadjuvant therapy, they were included in the main analysis[215]. This limits interpretation as those receiving neoadjuvant therapy, who, by definition, represent a group with more 'advanced' cancer than those with surgery as the primary therapeutic modality. Indeed, neoadjuvant therapy has been shown to reduce physical fitness before rectal cancer surgery[122] and decreases both whole-body physical fitness and muscle mitochondrial function[216]. In addition, neoadjuvant therapies confer significant side-effects, which likely affects both functional and clinical outcomes[217].

Other systematic reviews in this area have included multiple cancer types[218] or multiple exercise intervention types, including non-RET-based exercise, in CRC[96]. Although studies highlighted by these systematic reviews included RET prehabilitation, they did not focus specifically on RET. To date, no systematic review or meta-analysis has defined the impact of RET-based prehabilitation, either alone or as part of multimodal therapy, on clinical and functional outcomes in individuals with CRC scheduled for surgery with curative intent, as is the aim of this systematic review.

2.3 Aim

To determine and delineate the effects of RET-based prehabilitation in individuals with CRC treated primarily with surgery with curative intent on clinical and functional outcomes.

2.4 Methods

This systematic review and meta-analysis was performed in accordance with the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) 2020 statement[219] and *implementing Prisma in Exercise, Rehabilitation, Sport medicine and SporTs science* (PERSiST) guidelines[220], and was registered on the *International Prospective Register of Systematic Reviews* (PROSPERO; CRD42023421372).

2.4.1 Eligibility Criteria

2.4.1.1 Types of Studies

Reports on non-randomised and randomised controlled studies were eligible for inclusion. Non-controlled (single-arm/pilot) study reports were also included providing comparison of outcomes that were measured pre- and post-prehabilitation. Reviews and non-interventional study reports were excluded.

2.4.1.2 Participants

Reports of studies on adults (≥18 years), with histologically confirmed or clinically suspected colorectal neoplasia scheduled for surgery with curative intent were included. Reports were excluded if participants had neoadjuvant chemo- or radiotherapy, unless this was reported separately; or where surgery was undertaken with palliative intent.

2.4.1.3 Intervention

Short-course (<12 weeks) preoperative RET was the studied intervention. Study reports were included regardless of nature of supervision or concomitant prehabilitation modality. Reports on studies which also included postoperative interventions were eligible for inclusion providing outcomes were measured prior to initiation of any postoperative intervention.

2.4.1.4 Control

Reports on studies with control groups of standard care, non-RET prehabilitation (e.g., HIIT/ nutrition-only regimes) or postoperative rehabilitation only were included. Reports on non-controlled studies were also included.

2.4.1.5 Outcome Measures

Reports with measures of clinical outcomes including LOS, mortality, and postoperative complications and/or functional outcomes including 6MWT distance and HGS were included to satisfy the main outcome of the analysis.

2.4.2 Information Sources

2.4.2.1 Electronic Searches

The following databases were searched without restriction from inception to November 2023: i) Cumulative Index to Nursing and Allied Health Literature (CINAHL) database (EBSCO,

CINAHL Ultimate®); ii) Cochrane Central Register of Controlled Trials (CENTRAL); iii) Embase (Ovid SP); iv) Medline (Ovid SP); and v) PubMed.

2.4.2.2 Other Resources

Reference lists from systematic reviews in similar domains were interrogated and relevant reports added to the results from the initial electronic search. In addition, Clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP) were searched for ongoing trials. Where relevant, authors were contacted for unpublished data.

2.4.3 Search Strategy

Searches of the databases were undertaken in a systematic fashion. Individual words and wildcards were supplemented with Medical Subject Headings (MeSH) terms. Words ascertaining to colorectal anatomy were combined using 'OR' e.g. ('Colorectal' OR 'Bowel' OR…) and combined with terms ascertaining to 'cancer' using 'AND'. Further pre-coordinated terms such as 'colorectal cancer' were also included. Boolean logic was applied to the search strategy:

$$[\big((Cr\ AND\ Ca)\ OR\ CrC\big)\ AND\ RET]$$

where: Cr= Colorectal terms ONLY; Ca= Cancer terms ONLY; CrC= Colorectal cancer pre-coordinated terms; and RET= resistance exercise training terms ONLY. Details of full search strategies are available as supplementary material (Appendix A- Full Search Strategies).

2.4.4 Selection Process

Two researchers evaluated duplicates and screened record titles and abstracts of the initial search using Rayyan software[221]. The remaining reports were subjected to full-text review by

two researchers for inclusion in analysis. Disagreements were resolved by consensus with the option of a third reviewer opinion if consensus could not be reached.

2.4.5 Data Collection Process

Two researchers independently extracted data from the included reports using a blinded approach any disagreements resolved by consensus and the option of a third reviewer if required. Unpublished data was sought from the report authors via email.

2.4.6 Data Items

2.4.6.1 Outcomes

Outcomes were categorised into two domains: i) clinical or ii) functional. Measures that were reported in more than one report were eligible for consideration in meta-analysis.

2.4.6.2 Data Management

Where data was reported in formats non-compatible with meta-analysis, authors were contacted for raw data. Where not available, appropriate data were transformed independently by two researchers using a method described by Wan et al.,[222].

2.4.7 Report Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 tool (ROB-2)[223] for reports on randomised controlled studies and the Cochrane Risk of Bias in Non-Randomized Studies of Interventions tool (ROBINS-I)[224] for reports on non-randomised studies. The process was independently undertaken by two reviewers using appropriate assessment tools (ROB-2 Version 9[225] ROBINS-I Version 19[226]) and each report was allocated a low, moderate, serious, or critical risk of bias, where applicable, in each domain, and overall. Disagreements were settled by consensus.

2.4.8 Effect Measures

Continuous effect estimates are reported as difference in means (MD) and binary outcomes as odds ratios (OR) with 95% confidence intervals (CI). Where standard deviations (SD) of change were not reported, these were calculated based on Cochrane methodology[227]. We assumed a correlation coefficient of 0.8 between pre and post values based on our analyses of similar, previous data.

2.4.9 Synthesis Methods

Mean and SD were extracted from reports where available. Where they were not reported, authors were contacted and, for those who responded, the supplementary provided mean and SD values were used. Where no response was received, and the median and IQR was reported, the method described by Wan et al.[222] was used to impute the values for mean and SD.

We used a DerSimonian and Laird random effects model for the analysis. We planned to conduct tests for publication bias based on inverse sample size[228] and conduct meta-regression, but the low number of reports precluded this. We used I^2 to quantify statistical heterogeneity. All analyses were conducted on Stata version 18.

2.4.10 Certainty Assessment

We assessed the quality and certainty of the evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE)[229].

2.5 Results

2.5.1 Report Selection

As illustrated Figure 2.1[219], a total of 5,808 records were identified from the five databases searched. AI-enhanced software (Rayyan[221]) identified 1,910 as duplicates and these were flagged and reviewed by two, independent reviewers. Agreement between the software and researchers was 100% and therefore 1,910 duplicates were removed from further analysis. Of the 3,898 remaining records, 3,874 were removed after initial screening (title and abstract) with the remaining 24 reports retrieved for full-text eligibility screening. A further 18 reports were excluded based on not reaching the analysis inclusion criteria.

In addition to database searching, citation searching of recent systematic reviews and key papers in the field revealed a further nine reports, all of which were retrieved for full-text screening. Seven of these reports were excluded after review with the remaining two added to the six reports found from database searching for inclusion. Searching of clinical trials databases found 17 studies of interest, 15 of these were excluded after initial screening and two progressed to full-text review. Both studies were deemed as potentially having relevant data for meta-analysis. One study was still in recruitment phase so was excluded from further analysis (https://clinicaltrials.gov/study/NCT05854394). The lead author of the other study was contacted but no data was available for sharing at the time (https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12620000409976). In total, eight reports were included in this systematic review and considered for meta-analysis[91,94,95,230–234].

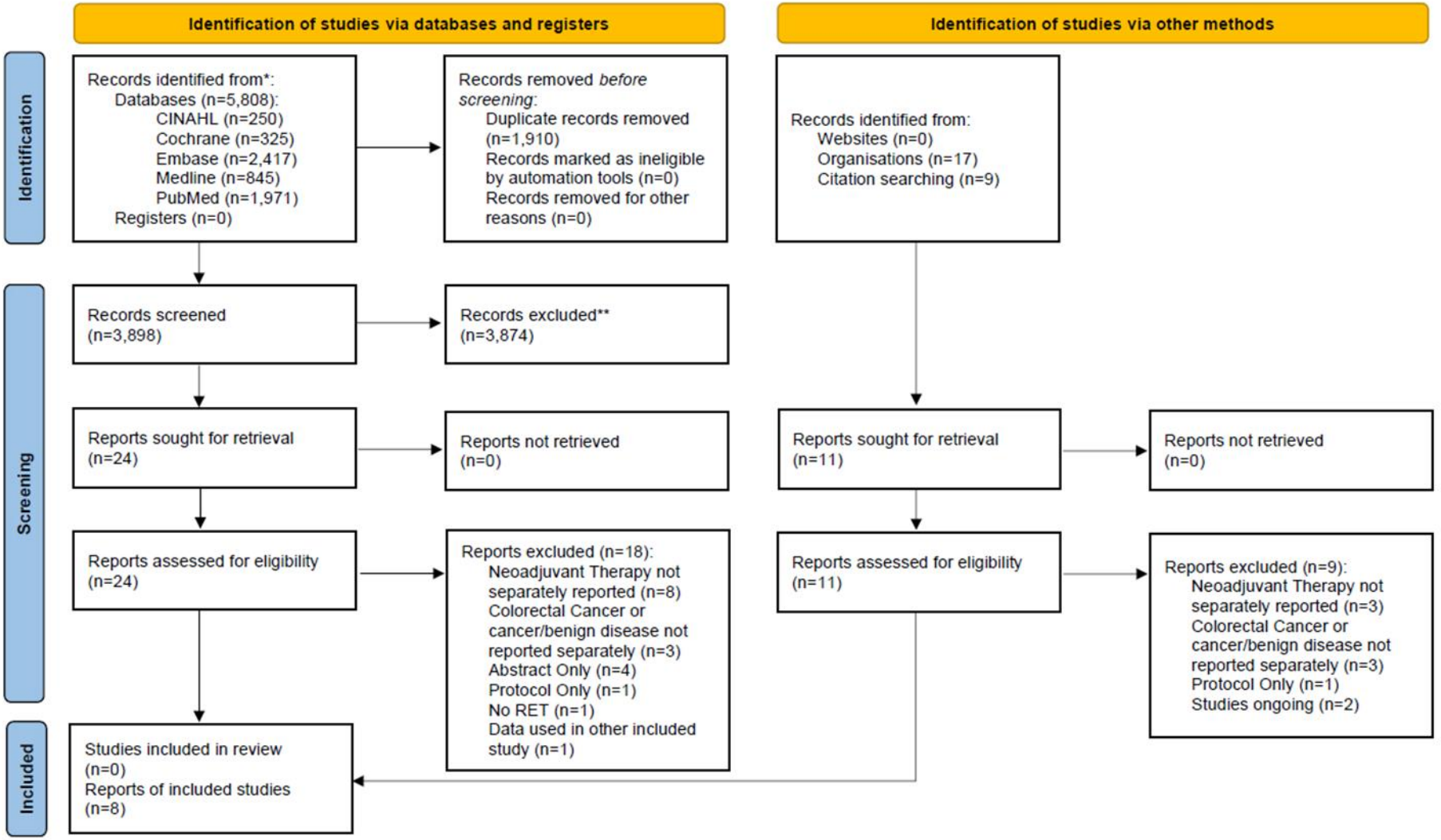

Identification of studies via databases and registers
Identification of studies via other methods
Identification
Screening
Included
Records identified from*:
Databases (n=5,808):
CINAHL (n=250)
Cochrane (n=325)
Embase (n=2,417)
Medline (n=845)
PubMed (n=1,971)
Registers (n=0)
Records removed *before screening*:
Duplicate records removed (n=1,910)
Records marked as ineligible by automation tools (n=0)
Records removed for other reasons (n=0)
Records identified from:
Websites (n=0)
Organisations (n=17)
Citation searching (n=9)
Records screened (n=3,898)
Records excluded** (n=3,874)
Reports sought for retrieval (n=24)
Reports not retrieved (n=0)
Reports sought for retrieval (n=11)
Reports not retrieved (n=0)
Reports assessed for eligibility (n=24)
Reports excluded (n=18):
Neoadjuvant Therapy not separately reported (n=8)
Colorectal Cancer or cancer/benign disease not reported separately (n=3)
Abstract Only (n=4)
Protocol Only (n=1)
No RET (n=1)
Data used in other included study (n=1)
Reports assessed for eligibility (n=11)
Reports excluded (n=9):
Neoadjuvant Therapy not separately reported (n=3)
Colorectal Cancer or cancer/benign disease not reported separately (n=3)
Protocol Only (n=1)
Studies ongoing (n=2)
Studies included in review (n=0)
Reports of included studies (n=8)

Figure 2.1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing study identification, screening and inclusion[219].

2.5.2 Study Characteristics

Study baseline characteristics are detailed in Table 2.1 with details of interventions and outcomes in Table 2.2. Included study reports were published as early as 2010 and as recently as 2022. Four studies were controlled[91,231–233], three were single-arm 'pilot' studies[94,230,234] and one study used mixed methodology (single-arm for some outcomes, partially non-randomised controlled for others)[95]. Seven studies[91,94,95,230,231,233,234] included exercise as part of a multimodal prehabilitation regime and a single study[232] included exercise prehabilitation as monotherapy. Every study included RET in addition to at least one other exercise modality. Outcomes were varied and for the purpose of this review have been divided into clinical and functional outcomes. Non-clinical or functional outcomes, as determined by the authors have not been further reported as they are outside the scope of this review. The most commonly reported clinical outcomes were postoperative complications[91,94,95,231–234] (7/8 reports; 87.5%); LOS[91,94,95,231–234] (7/8; 87.5%); and mortality[95,231,234] (3/8; 37.5%). Commonly reported functional outcomes included HGS[94,95,230,232,234] (5/8; 62.5%) and 6MWT[91,94,95,230,231] (5/8; 62.5%). Further clinical and functional outcomes reported are detailed in Table 2.2.

Study	Study Design	n (Control/Intervention)	Age		Sex Distribution (F/M)	Country
Bojesen 2022[94]	Single-arm, prospective	8 (-/8)	Mean: 80.13 SD: 6.98		4/4	Denmark
Bruns 2019[234]	Single-arm, prospective	14 (-/14)	Median: 79 IQR: 74-86		9/5	Netherlands
Dronkers 2010[232]	Randomised, controlled, prospective	42 (20/22)	<u>Control</u> Mean: 68.8 SD: 6.4	<u>Intervention</u> Mean: 71.1 SD: 6.3	11/31	Netherlands
Koh 2022[95]	Mixed methodology: partially single-arm; partially non-randomised, prospective/retrospective, controlled	81 (23/58)	Median: 77 IQR: 70-90	Median:78.5 IQR: 70-93	36/45	Singapore
Li 2013[91]	Non-randomised, controlled, prospective	87 (45/42)	Mean: 66.4 SD: 12	Mean: 67.4 SD: 11	36/51	Canada
López-Rodríguez-Arias 2021[233]	Randomised, controlled, prospective	20 (10/10)	Median 66 IQR 61.8-71.5		7/13	Spain
Suen 2021[230]	Single-arm, prospective	22 (-/22)	Median: 72.5 IQR: 69-79		10/12	Australia
Van Rooijen 2019[231]	Non-randomised, controlled, prospective	50 (30/20)	Median 71 IQR 46-89		23/27	Netherlands

Table 2.1- Study baseline characteristics. Abbreviations: F= female; IQR= inter-quartile range; M= male; n= number of patients; SD= standard deviation

Study	Control Details	Intervention Details	Outcome Measures[a]		Outcome Measure Timepoints
			Clinical	Functional	
Bojesen 2022[94]	No control group	**Multimodal:** Exercise - supervised HIIT and RET 3 x/week for >4 weeks and home-based exercise encouraged Nutrition - advice and supplementation Other - 'medical optimisation' including expanded blood tests, consultation/ pharmacological intervention/ referral where deemed clinically appropriate	Days at home within 30 days of surgery LOS Operative modality Postoperative complications Postoperative day of: full mobilisation/ removal of urinary catheter/ oral nutrition Readmission Stoma formation	1-RM various modalities 30 second stair climb STS-30 **6MWT** **HGS** Isometric leg extension strength	Baseline 1 day preoperative 4 weeks postoperative
Bruns 2019[234]	No control group	**Multimodal:** 18-32 days Exercise - daily strength-training Nutritional – supplementation Other - digital activity companion (Fit4SurgeryTV) to promote nutritional and exercise interventions	LOS Mortality Operative modality Postoperative complications	ADLs Frailty level Gait speed **HGS** SPPB	Baseline 1 day preoperative Postoperative
Dronkers 2010[232]	Randomised after entry to study. Home-based exercise advice only	**Uni-modal:** 2-4 weeks Exercise - supervised 2x/week including RET, inspiratory muscle training, AET and functional training, in addition to home-based training of walking or cycling for 30 minutes/ day and inspiratory muscle training	**LOS** Post- operative: **Complications**/ O_2 requirements/ fever/ pain medication/ sputum retention/ coughing and mobilization	HGS Step count	Baseline Preoperative Postoperative

Koh 2022[95]	Similar cohort of patients prior to initiation of intervention. Standard care	**Multimodal:** Exercise - 3 weeks RET and weekly physiotherapy review Nutrition - 3 weeks oral nutrition on dietetic advice Other - 'optimisation' via geriatrician consultation and transthoracic echocardiogram and cardiovascular consultation, early evaluation of home situation	Discharge location **LOS** Morbidity Mortality Operative modality **Postoperative complications** Time to first bowel movement Time to first flatus	STS-30 **6MWT** Frailty level Functional reach Gait speed **HGS**	Baseline[b] Preoperative Postoperative
Li 2013[157]	Consecutive patients prior to initiation of intervention. Standard care.	**Multimodal:** Duration determined by wait time until surgery Exercise - unsupervised, individualized exercise (combined AET and RET) Nutrition - nutritional assessment, advice & supplementation Other - psychological assessment & advice	**LOS** **Postoperative complications**	**6MWT** Self-reported physical activity	Baseline 1 week preoperative 4 weeks postoperative 8 weeks postoperative
López-Rodríguez-Arias 2021[93]	Standard care.	**Multimodal:** 30 days prior to and 30 days post-surgery, home-based Exercise - personalised physical exercise (AET & RET) delivered via video Nutrition - advice & supplementation Other - recommendations on relaxation and breathing exercises to be performed twice a week	**LOS** **Postoperative complications**		Baseline 1 Day preoperative 6-Week postoperative 12 weeks postoperative[c]

Suen 2021[162]	No control group.	**Multimodal:** 2-4 weeks Exercise - supervised exercise (aerobic and RET) 2x/week Nutrition - nutritional advice given via written information Other - twice-weekly nurse-led phone/ in-person support		10-RM various modalities STS-30 **6MWT** **HGS**	Baseline Preoperative 4 weeks postoperative
Van Rooijen 2019[231]	Group allocation based on intervention availability at time of enrollment. Standard care.	**Multimodal:** 4 weeks Exercise - supervised HIIT & RET Nutrition - advice & supplementation Other - psychological session/s	Anastomosis Duration of surgery **LOS** Mortality **Postoperative complications** Readmission Reintervention Surgical modality	1-RM various modalities 6MWT STS-30 HGS Timed up-and-go	Baseline Preoperative[b] 4 weeks postoperative 1-year postoperative

Table 2.2- Characteristics of interventions and outcome measures. Abbreviations: 1-RM= One-Repetition Maximum; 6MWT= Six-Minute Walk Test; ADLs= Activities of Daily Living; AET= Aerobic Exercise Training; HGS= Handgrip Strength; HIIT= High-Intensity Exercise Training; LOS= Length-of-Stay; RET= Resistance Exercise Training; SPPBT: Short Physical Performance Battery; STS-30= 30 second sit-to-stand

*Outcome measures in **bold** indicate those included in meta-analysis.*

[a] Non-exhaustive list of outcomes, only those deemed clinical or functional included.

[b] Partially/ wholly intervention group only[c] Patients with adjuvant chemotherapy excluded.

2.5.3 Risk of Bias in Studies

Two studies[232,233] were assessed for risk of bias using the ROB-2 with the remaining six studies[91,94,95,230,231,234] assessed with ROBINS-I. All studies carried a 'high' or 'critical' risk of bias in at least one domain and therefore overall (Figure 2.2, Figure 2.3, Figure 2.4, & Figure 2.5)[224]. Both studies assessed using ROB-2, were judged to have critical risk of bias due to 'selection of the reported results', primarily resulting from the large number of outcomes reported over different time points and the lack of reporting of some of the pre-registered outcomes/inability to find trial registration. Other domains for these randomised, controlled trials were either 'low risk' or of 'some concerns' only. Studies assessed by ROBINS-I were heterogeneous in design ranging from single-arm, prospective trials to non-randomised, controlled trials. A 2022 study by Koh et al.,[95] used mixed methodology with some outcomes compared with a control group, and others not. All six studies were deemed to display a 'serious' or 'critical' risk of bias due to confounding, in part due to the non-randomised/single-arm nature of these studies. These six studies also performed poorly in the domain of 'bias in selection of the reported result', due to multiple outcome measures being reported across multiple time points. Most studies were clear in classification of their interventions, but selection of participants was non-uniform, with results ranging from a 'low' to a 'critical' risk of bias in this domain.

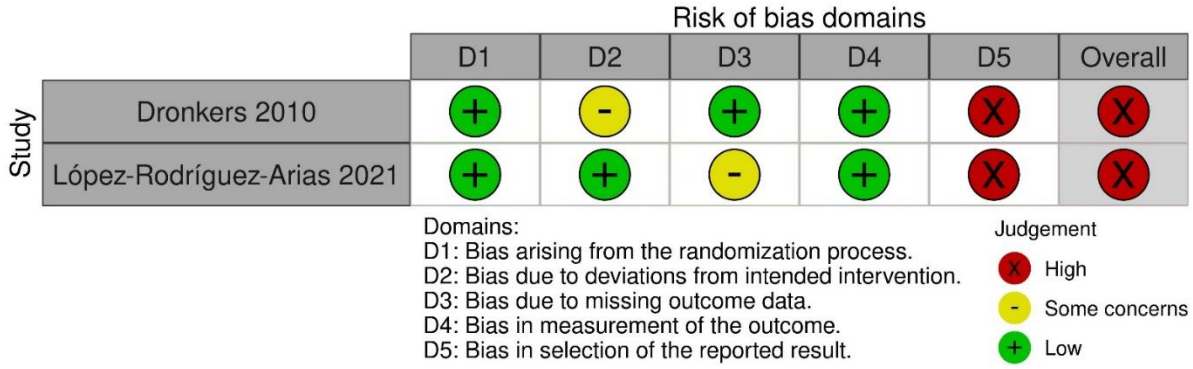


Figure 2.2- Traffic light plot from Cochrane Risk of Bias 2 (ROB-2) assessment tool[235]

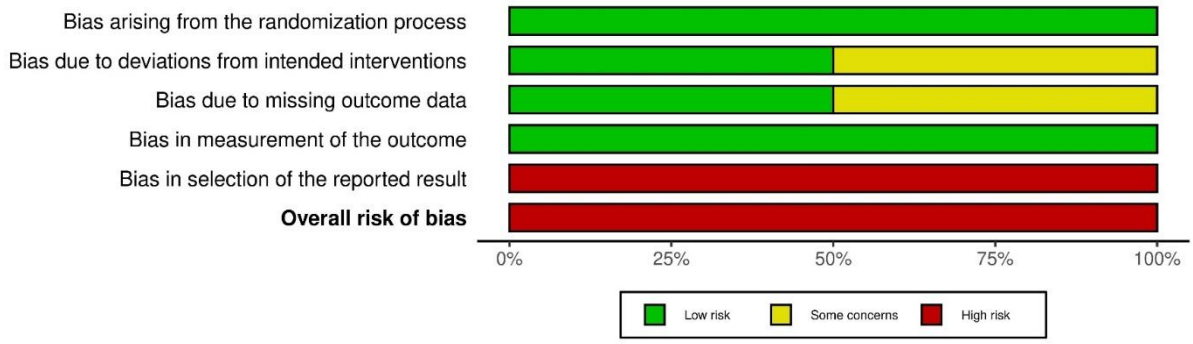


Figure 2.3-Summary plot from Cochrane Risk of Bias 2 (ROB-2) assessment tool[235]

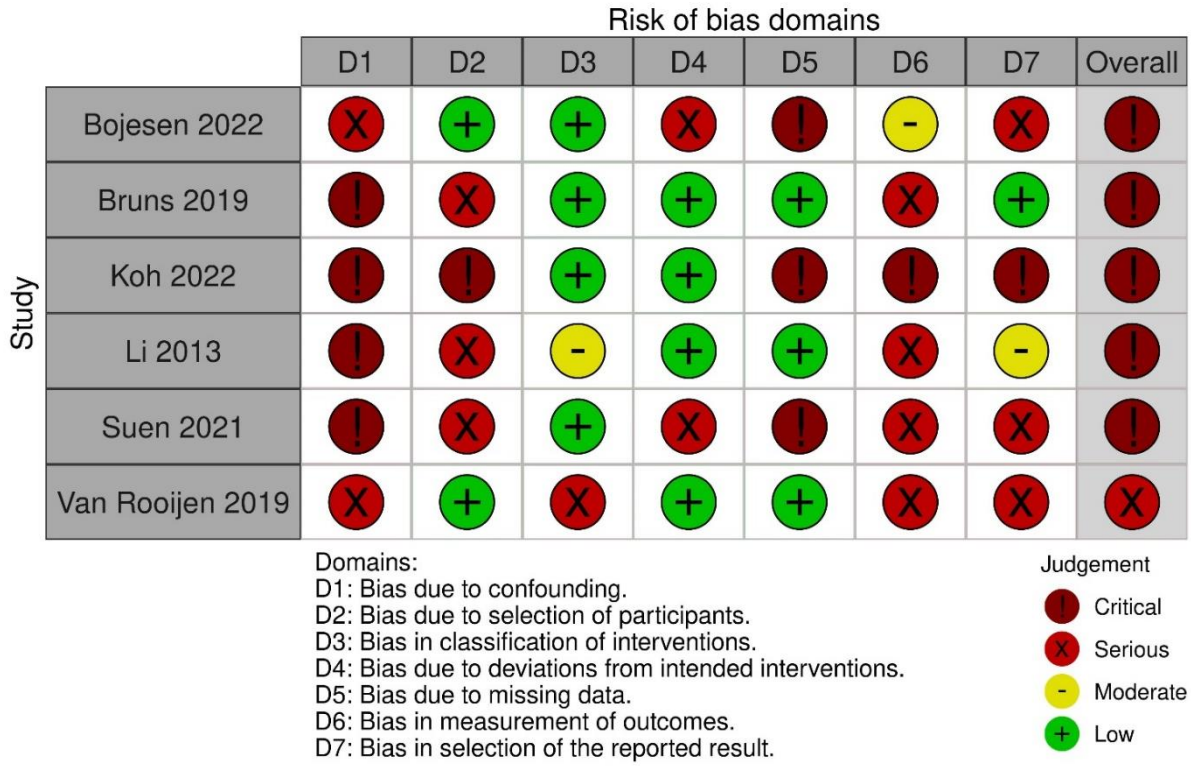


Figure 2.4-Traffic light plot from Cochrane Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) assessment tool[224]

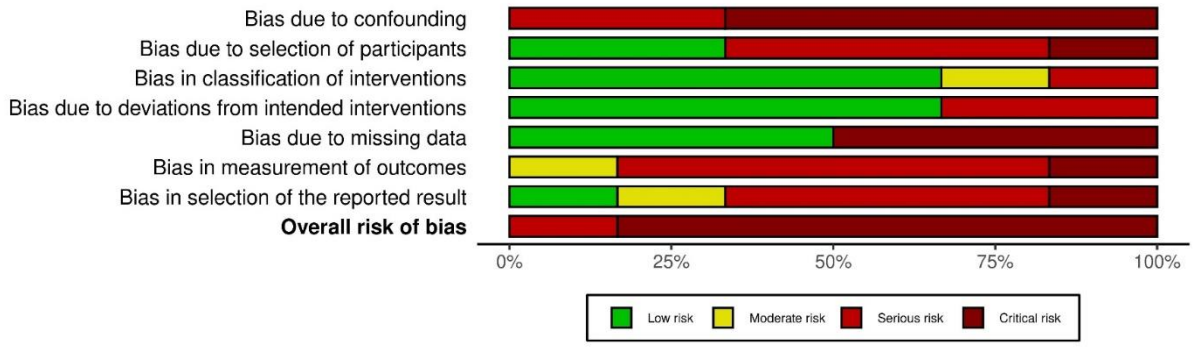


Figure 2.5-Summary plot from Cochrane Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) assessment tool[224]

2.5.4 Meta-Analysis

Robust data was available for meta-analysis on two clinical (postoperative complications and LOS) and two functional (6MWT and HGS) outcomes. For clinical outcomes, only reports on two-armed studies were included in analysis as baseline characteristics did not exist (e.g., LOS). For functional outcomes all reports were included in analysis if baseline and post-intervention results were described. Four out of five reports that measured 6MWT, five out of seven that measured postoperative complications; four out of six that measured HGS and five out of seven that measured LOS were included in meta-analysis.

2.5.4.1 Mortality

Thirty-day mortality was detailed in three reports (Bruns 2019[234], Koh 2022[95], Van Rooijen 2019[231]) with a combined incidence of zero so this outcome measure was not included in meta-analysis.

2.5.4.2 Postoperative Complications

Postoperative complications were defined as grade I or more on the Clavien-Dindo classification of surgical complications scale[236]. There was no difference in the incidence of postoperative complications between the groups although estimates were imprecise (OR: 0.77, 95% CI: 0.47 to 1.29). There was no evidence of statistical heterogeneity (I^2=0%) (Figure 2.6).

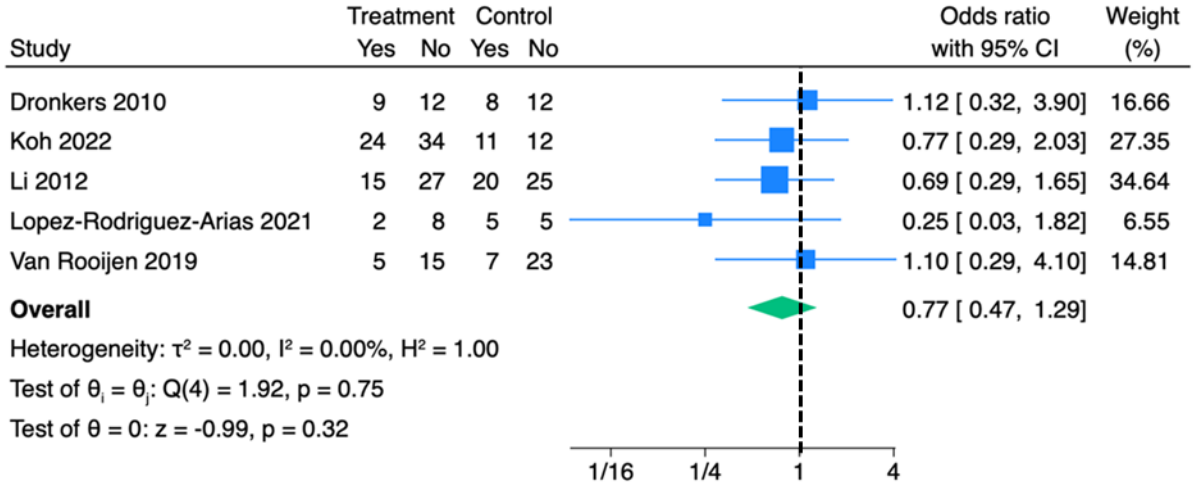


Figure 2.6- Meta-analysis of the effects of resistance exercise training-based prehabilitation in individuals with colorectal cancer scheduled for surgery with curative intent on the outcome of postoperative complications. Data from four studies (Dronkers 2010[232]; Koh 2022[95]; Lopez-Rodriguez-Arias[93] 2024; Van Rooijen 2019[231]) were included and were proportionally weighted 16.66%, 27.35%, 34.64% and, 14.81% respectively. The overall odds ratio is 0.77 with 95% confidence intervals of 0.47 to 1.29.

2.5.4.3 Length-of-Stay

LOS was defined as the number of nights between surgery and discharge during index admission. LOS was not reduced with intervention although estimates were imprecise (MD -3.02, 95% CI -6.26 to 0.21). There was moderate statistical heterogeneity (I^2=72%) (*Figure 2.7*).

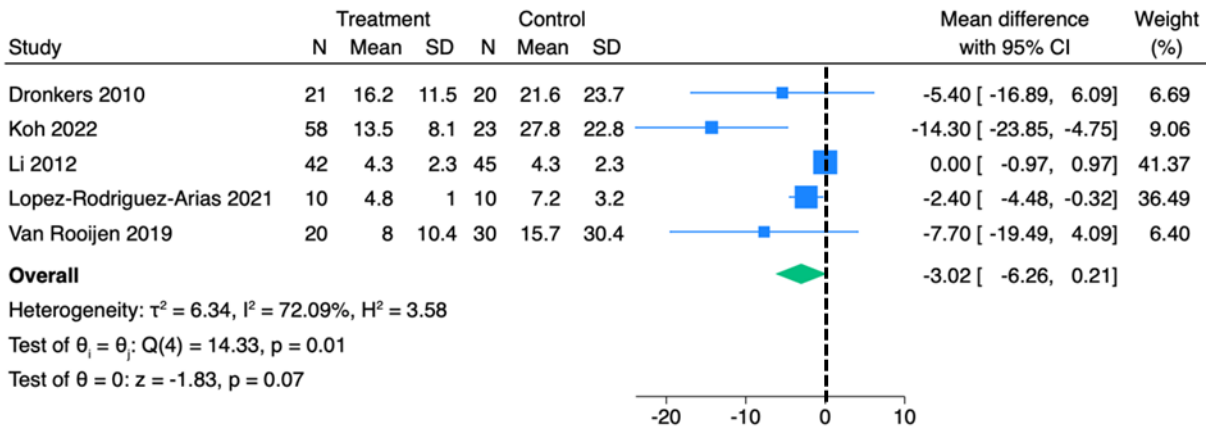


Figure 2.7- Meta-analysis of the effects of resistance exercise training-based prehabilitation in individuals with CRC scheduled for surgery with curative intent on the outcome of length of stay. Data from five studies (Dronkers 2010[232]; Koh 2022[95]; Li 2012[91]; Lopez-Rodriguez-Arias[93] 2024; Van Rooijen 2019[231]) were included and were proportionally weighted 6.69%, 9.06%, 41.37%, 36.49% and, 6.4% respectively. The overall odds ratio is -3.02 with 95% confidence intervals of -6.26 to 0.21.

2.5.4.4 Six-Minute Walk Test

6MWT is defined as the length, in meters, that an individual can walk on a flat surface in six minutes[237]. There was an increase in 6MWT between baseline and preoperative values in those undergoing intervention (MD: 34.1m, 95% CI: 16m to 52.3m) with evidence of moderate statistical heterogeneity (I^2=44%) (*Figure 2.8*).

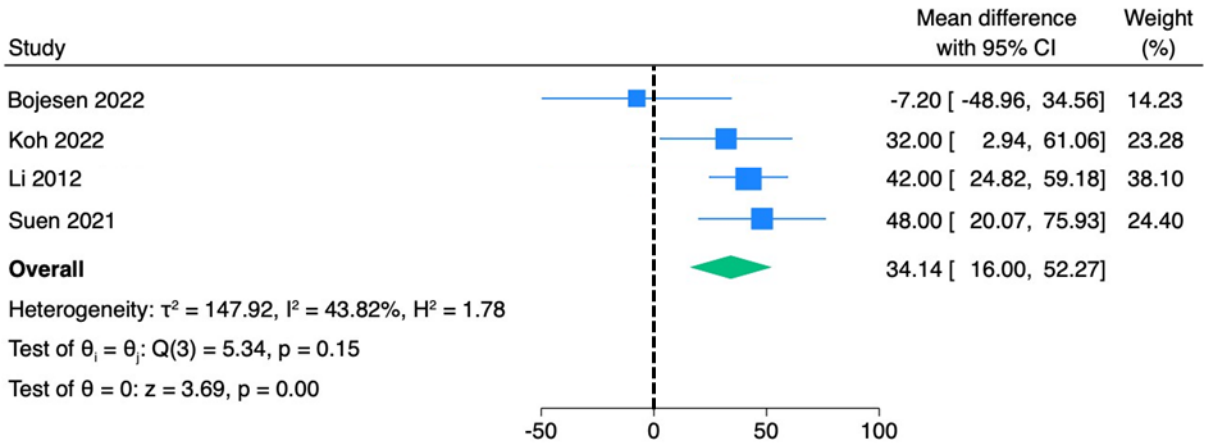


Figure 2.8- Meta-analysis of the effects of resistance exercise training-based prehabilitation in individuals with CRC scheduled for surgery with curative intent on the outcome of six-minute walk test (meters). Data from four studies (Dronkers 2010[232]; Koh 2022[95]; Li 2012[91]; Suen[230]) were included and were proportionally weighted 14.23%, 23.28%, 38.10%, and, 24.40% respectively. The overall odds ratio is 34.14 with 95% confidence intervals of 16.0 to 52.27.

2.5.4.5 Handgrip Strength

HGS was defined as the maximum static force in kilograms that can be applied to a dynamometer[238]. Where results for both hands were reported, the maximum value achieved was selected for analysis. There was no increase in HGS from baseline to preoperative values in those undergoing intervention (MD 0.22kg, 95% CI -0.83kg to 1.27kg) with no evidence of statistical heterogeneity (I^2=4%) (Figure 2.9).

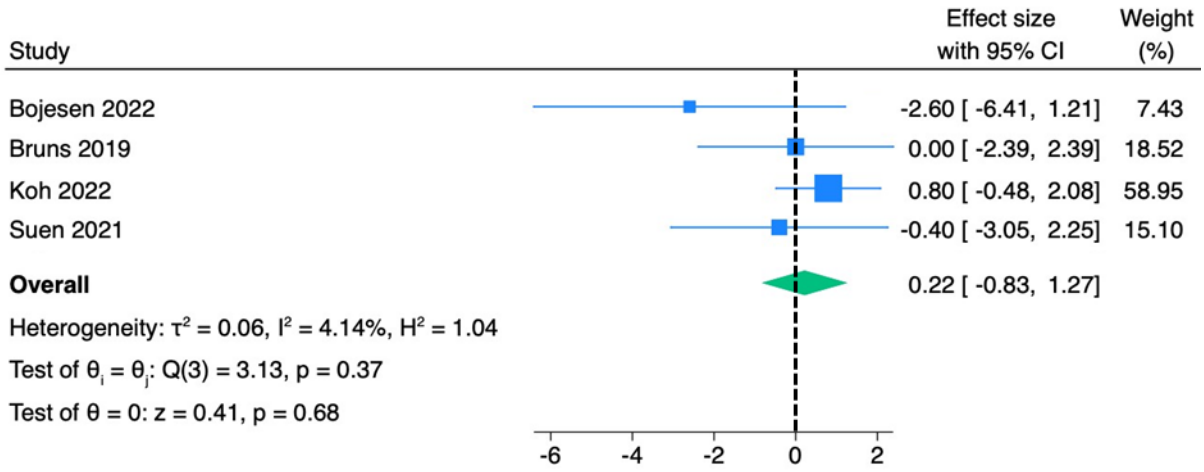


Figure 2.9- Meta-analysis of the effects of resistance exercise training-based prehabilitation in individuals with colorectal cancer scheduled for surgery with curative intent on the outcome of handgrip strength. Data from four studies (Bojesen 2022[94]; Bruns 2019[234]; Koh 2022[230]; Suen) were included and were proportionally weighted 7.43%, 18.52%, 58.95%, and, 15.10% respectively. The overall odds ratio is 0.22 with 95% confidence intervals of -0.83 to 1.27.

2.5.5 Other Clinical & Functional Outcomes

Details of all clinical and functional outcomes in each report can be found in Table 2.2. Many outcomes were reported in a single report only and even amongst similar outcomes, discrepancies between exact assessment regimens made meta-analysis impossible. For example, when measuring capability to ambulate from a chair, four reports listed 30 second sit-to-stand (STS-30) repetitions or similar [94,95,230,231] but one failed to report this metric[231], one reported differences in absolute values[94], one reported medians and ranges, but for an undisclosed number of individuals[95], and one reported mean and SDs[230]. Despite this, RET-based prehabilitation appears to have a neutral or positive effect on the outcome of STS-30 repetitions. Bojesen et al. reported two out of seven individuals displayed an increase of one STS-30 repetition, two a displayed a decrease of one and the remaining three experienced no change[94]. Koh et al. reported an increase in the median STS-30 repetitions from 11 (range 4-26) to 12 (3-28)[95]; Suen et al reported an increase in the mean STS-30 repetitions from 11.2 (SD 3.6) to 12.8 (SD 3.9)[230].

2.5.5.1 Operative Modality

Four reports[94,95,231,234] reported operative modality. Bojesen et al., reported six out of seven (85.7%) patients who had operative intervention had laparoscopically/robotic-assisted surgery; four (57%) had primary anastomosis[94]. Bruns et al., reported all 14 patients were operated on laparoscopically initially, with one (7.1%) requiring open conversion[234]. Koh et al., reported a significant difference in operative modalities between the intervention and control groups with 21 (36.2%) open, 36 (62.1%) laparoscopic and one (1.7%) laparoscopic-converted-to-open in the intervention group compared with 16 (69.6%) open and seven (30.4%) laparoscopic operations in the control group (p=0.02)[95]. Van Rooijen et al., reported similar operative modalities across intervention and control groups, with nineteen (95%) of

the intervention and 22 (88%) of the control group undergoing initially laparoscopic surgery. Three (16%) patients in the control group and four (16%) patients in the intervention groups required open conversion[231].

2.5.5.2 Readmission

Two reports[94,231] detailed readmission rates. Two patients (28.6%) were readmitted after initial discharge in the report by Bojesen et al[94]. Van Rooijen et al., reported only a single readmission, in the control group[231].

2.5.6 Certainty of Evidence

The certainty of evidence for each outcome of meta-analysis is low given the inherent risk of bias in the study designs, inconsistency in outcomes and the inability to assess for publication bias. This is further compounded by the relatively small sample sizes and time over which the individual studies were undertaken[229,239].

2.6 Discussion

To our knowledge, this is the first meta-analysis of the effects of RET-based prehabilitation on clinical and functional outcomes in individuals with CRC scheduled for surgery with curative intent as primary therapy. Analysis has demonstrated a small but statistically significant increase in 6MWT distance, a measure which is validated in this cohort to represent both CRF (VO_{2peak}) and subjective functional outcomes (i.e., perceived physical function)[240]. Further, the mean increase of just over 34 metres is within the threshold of the minimally clinically important difference (MCID) of 22-42 metres reported for individuals with lung cancer; that is, the smallest change in an outcome considered to be clinically relevant[241]. To our knowledge a MCID for 6MWT has not been established in relation to surgical outcomes in CRC, although a value of 14-30 meters has been defined in other disease cohorts[242]. Despite a lack of 6MWT

MCID for those with CRC, threshold values for CRF indicating need for a higher level of postoperative care do exist in this population[243]. Given that 6MWT distance has been shown to associate with CRF[244], especially in those with sub-optimal values, it is plausible that these improvements in 6MWT distance may represent improvements in CRF. Furthermore, the observed increase is in keeping with similar effect sizes from a review focussing on exercise prehabilitation in operable cancer where the authors demonstrated an increase in 6MWT distance of 24.1m (95% CI: 2.6m to 45.7m), though this was pre- versus postoperatively. This effect was not demonstrated in the control group[116]. A 2022 systematic review and meta-analysis concentrating on the effects of multimodal prehabilitation in older adults prior to a major abdominal operation also demonstrated a similar increase in 6MWT distance (MD: 35.1m 95% CI: 11.6m to 58.4m)[245]. A more contemporary trial in a similar population (operable CRC) utilising multimodal prehabilitation has demonstrated a larger increase in 6MWT distance (MD: 96m) with no effect seen in the control group, though these results should be considered with caution owing to the relatively small sample size (interventional arm n=35)[246].

Meta-analysis showed no significant difference in postoperative complications, LOS or HGS between individuals who had RET-based prehabilitation and those who did not. Other outcomes did not reach the criteria for meta-analysis, partly due to the design of some studies and partly due to heterogeneity in outcome measures. Given the inherent bias defined in all included studies, primarily due to the inability to blind intervention coupled with the reporting of multiple outcomes as detailed in the risk of bias analysis, confidence in the certainty of results should is low.

2.6.1 Limitations

Firstly, the results of the meta-analysis are limited by the small numbers of participants in each individual study. Despite a total of 324 patients in the included study reports, meta-analysis was only possible on a small proportion of datapoints, reducing the reliability of the results. Secondly, the risk of bias in all studies was considerable due to a variety of factors, but none more so than the inability to blind participants to their group status. Thirdly, the included studies varied in their geographical and temporal settings, in addition to the marked heterogeneity in intervention design. Although good evidence exists for the use of multimodal prehabilitation, all but one study in this review added other components of prehabilitation to exercise, making the results of exercise alone difficult to ascertain. No studies considered RET alone. Fourthly, no deaths were reported within 30 days of intervention meaning mortality is unlikely to be significantly affected by prehabilitation. This is unsurprising given the rarity of this outcome in this setting. Mortality, though rare, is more likely to be driven by individual characteristics of a patient in addition to local factors such as surgeon, clinical team, facilities, experience, and resource[247,248]. Diet and other factors such as habitual physical activity and patient comorbidities may also influence clinical and functional outcomes in this population, but the small number of studies eligible for inclusion in this review meant sub-analysis based on these factors was not possible. Finally, multiple outcome measures without appropriate statistical correction were reported and differing evaluations of similar outcomes hampered meta-analysis in some domains.

2.6.2 Future Work

The role of RET-based prehabilitation in CRC remains an area of active interest and at least three trials are ongoing to further delineate its effects[249–251]. Although this meta-analysis shows some improvement in functional capacity, more work is required with RET-only

prehabilitation protocols as the majority of literature focuses on multimodal prehabilitation which makes the effects of RET in isolation difficult to ascertain. Although historically aerobic exercise training[252], or more recently HIIT[253], has been shown to be associated with physiological adaptation associated with improvements in CRF, emerging evidence suggests that RET may also be able to elicit these effects[254], whilst also eliciting hypertrophy and improvements in muscle function[255], outcomes known to positively impact postoperative status [256].

Considering the time and financial implications of RET-based programmes for a provider, and indeed individuals with cancer, negative or neutral findings are equally as important as positive ones. Future studies may consider focussing on LOS as a primary outcome, considering the cost impact of inpatient care and the reduction in UK inpatient bed capacity in recent years[257]. LOS is often improved by prehabilitation and timely conversion of inpatient care to outpatient-based therapies are likely beneficial for most healthcare stakeholders, although rigorous statistical powering will need to be considered when evaluating this[165]. Other outcome measures may be patient-specific such as time to 'return to full activity' or patient-identified, which may be more nuanced, and thus are harder to capture via traditional methods. Further consideration would also be required for specific patient groups (i.e., those with comorbidities) and specific cancer treatment modalities such as surgery with a requirement for close postoperative monitoring.

Specific to the aims of this thesis, this systematic review and meta-analysis concludes: i) there are no published studies focussing on the effects of exercise-only prehabilitation with combined HIIT and RET in patients with CRC scheduled for surgery with curative intent and;

ii) RET-based prehabilitation has the potential, in this cohort, to improve functional metrics, though the effects on physiological and clinical outcomes are unclear.

3. Nutritional Interventions in Cancer Prehabilitation

3.1 Introduction

Although the majority of this thesis is focussed on exercise prehabilitation, the interactions between exercise and nutrition, especially for skeletal muscle outcomes, cannot be ignored. Indeed, when exploring the literature for the systematic review and meta-analysis presented in Chapter 2, the majority of multimodal prehabilitation interventions include a nutritional component[158].

In relation to skeletal muscle, MPS and thus function is largely dependent on adequate nutrition both in terms of calorific content and substrate availability (i.e., amino acids). Skeletal muscle is highly plastic and in addition to adaption to the stresses imposed upon it, in healthy individuals, the balance between MPS and MPB exists in a dynamic equilibrium with MPB dominating in the fasting state and MPS in the fed state[129]. The presence of cancer and associated cancer cachexia brings specific challenges to maintaining and utilising adequate nutrition and this chapter focusses on the specific nutritional challenges in cancer and the most recent evidence surrounding prehabilitation strategies with a nutritional focus in cancer care.

Given the important role of nutrition in cancer prehabilitation and care, a narrative review, detailed below, was undertaken to delineate the most important and recent considerations in this field. A narrative review over alternative methods of literature synthesis such as a scoping review as this best allows the introduction of core concepts and key papers as well as a critique of the contemporary literature whilst maintaining a broad scope.

A large proportion of this chapter has been published in *'Current Opinion in Clinical Nutrition and Metabolic Care'*[165].

3.2 Introduction to Nutritional Prehabilitation in Cancer Care

Cancer prehabilitation is a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of elective intervention (i.e., surgical resection). This is often based around the identification of impairments, which may be physical and/or psychological, and the subsequent delivery of targeted interventions to improve a patient's 'resilience' to treatment. There is a growing body of evidence to support the notion that cancer prehabilitation can reduce both the incidence and severity of current and future clinical insults[160]. Specific to nutritional prehabilitation, individuals with cancer often face nutritional challenges, with up to 80% of individuals with cancer found to have varying degrees of malnutrition[56], largely attributed to inflammatory mediators released in response to tumour cells[258]. As such, optimisation of nutritional status and associated physiological parameters is often a key target of prehabilitation regimes.

3.3 Nutritional Support as an Independent Prehabilitation for Cancer Surgery

Cancers such as oesophago-gastric and head and neck tumours usually have a more marked and dramatic nutritional impact on individuals at the time of presentation due to symptoms such as dysphagia, which, coupled with a tendency towards a later staging at diagnosis, can seriously hinder attempts to achieve a curative outcome[259]. In these cancer types and others such as pancreatic cancer; or patients who receive neoadjuvant treatment[260,261], both nutritional screening, subsequent assessment of risk and then intervention, is key to improving morbidity, mortality and psychological outcomes in those undergoing oncological resection[262]. In support of this, evidence from Gillis and colleagues used pooled data from five prehabilitation studies to demonstrate that in patients with CRC, those with malnutrition suffer poor physical and mental health before elective resection[263].

Regarding nutritional screening, many studies have looked at methods of identifying individuals at risk of malnutrition prior to cancer surgery, with a commonly stated aim of facilitating appropriate nutritional intervention. Despite this, a universal recommendation, either within or across cancer types, on how best to screen individuals with cancer has not been reached. A recent systematic review by Deftereos *et al.,* focussing on gastrointestinal (GI) cancers, suggested that recommendations regarding the use of one screening tool over another could not be made, but that screening tools well-validated in general clinical populations, and if possible other oncology populations, should be used[264].

Despite a wealth of literature on nutritional screening and assessment tools, fewer studies have looked at the impact of nutritional interventions alone to attenuate the known risks associated with poor nutritional status such as poor wound healing and infectious complications. Further, the varying effects of different cancers on often heterogeneous cohorts make the formulation of guidelines difficult. As such, those studies that do exist often focus on the groups of individuals in whom malnutrition is most prevalent and/or impactful, however, even in these high-risk groups limited evidence exists. Cantwell *et al.,* performed a systematic review of nutritional prehabilitation (excluding parenteral nutrition) in head and neck cancer, and found not only a low yield of eligible studies (n=2) but also no significant improvements in surgical outcomes or physical function[265].

Oral nutritional supplementation (ONS) is a widely used method to add nutrients in individuals at-risk of malnutrition or who are under nourished and not achieving their target dietary intake, but the impact of its use in the preoperative period and whether it should be used selectively or in all individuals with cancer having surgery is still debated. A systematic review by Reece and colleagues exploring the impact of ONS for patients undergoing surgery for GI cancer reported limited evidence for the use of ONS to increase dietary intake or

positively influence body weight. They did however conclude that this was likely due to populations, interventions, outcomes and follow-up timeframes each being variable across studies, and that further research into optimal interventions and their timing is needed [266]. Further, with regards to the possibility of preoperative ONS improving postoperative feeding tolerance, He *et al.,* randomised 67 patients undergoing sub-total or total gastrectomy to preoperative ONS or dietary advice alone. They found that preoperative ONS did not improve the incidence of GI intolerance, and there was no significant difference in postoperative complication rates between the two groups[267].

Clearly for any nutritional intervention to have a positive impact, feasibility in terms of delivery and uptake/compliance is key. With regards to the delivery and uptake (i.e., whether individuals engage and consume them) of ONS there is evidence to support its ease in delivery to individuals. In a single-site randomized trial, Serrano *et al.,* conducted a feasibility trial comparing ONS with placebo [268]. Providing 30-days of preoperative ONS which continued for 5-days after surgery, no significant differences in the rate of postoperative complications were reported, although a slightly higher rate of infectious complications in the placebo group was observed. Importantly for a feasibility study, the overall compliance rate was high at 80%. Deftereos *et al.,* undertook a mixed-methods multi-centre study to analyse the implementation of a standardised nutrition care pathway in individuals with upper GI cancer having surgery[269]. They used a validated theoretical framework for implementation and performed surveys and interviews the staff involved. Individuals were highly appreciative of the service, which included a dietetic-led structured and standardized preoperative outpatient service, and dieticians found there to be more proactive engagement with nutritional support. However, the main barriers were the need for significant funding to enable a dietician-led care pathway as well as integrating the service to the existing pathways,

suggestive that a 'one-size fits all' approach may not be optimal in creating a successful nutritional prehabilitation service.

One ongoing trial which may be able to determine whether ONS does impact postoperative complications is the PeriNutri trial. A prospective, multi-centre randomised controlled trial, PeriNutri will explore if perioperative ONS in patients with colon cancer undergoing resectional surgery decreases the rate of postoperative 30-day morbidity and also includes a 5-year follow-up for disease-free and overall survival[270]. This trial offers the possibility of a high-quality study to explore the impact of ONS on both short- and long-term postoperative morbidity in individuals with CRC , although the conclusion may need to be slightly more nuanced when adjusting for other factors such as immediate postoperative complications (i.e., ileus) that may impact the ability of patients to adequately absorb ONS in the inpatient period. Further, given the gold-standard for CRC management in the elective setting is ERAS-based (which is multimodal), it may still be difficult to tease out the specific effects elicited by nutritional interventions.

The use of preoperative parenteral nutritional support (PNS) is less well studied, with most studies tending to look at PNS in the immediate postoperative in-hospital period [271,272]. This may be due to the enhanced logistical burden associated with its PNS, as well the higher risk profile such as line infections and displacement. Huang *et al.,* found that although the post-surgical complication rate did not improve after giving PNS to 204 sarcopenic patients undergoing radical gastrectomy, it did reduce the rate of intra-abdominal infections (PNS *vs.* control, 5.4% *vs.* 1.2%, P=0.032). Hospital costs did however increase[273]. Given the increased financial costs associated with PNS in addition to the risk profile and lack of evidence for its superiority compared to ONS, it is often used only in selected cases.

3.4 Nutrition as Part of Multimodal Prehabilitation

Time from cancer diagnosis to treatment is understandably expeditious to minimise disease progression and given this, any preoperative intervention must be effective within this time window. Considering this time constraint, much research has focussed on multimodal prehabilitation, commonly including a nutritional component, with a view to implementing as much positive change in a short as time as possible. However, this approach has led to a wide variety of interventions, outcome measures and, on a global level, uncertainty as to the most promising forms of prehabilitation. Further, little insight into the underpinning mechanisms of adaptation in response to these interventions has been garnered to date.

To illustrate the magnitude of heterogeneity in multimodal prehabilitation it is worth considering the differing modalities employed. Most regimes include some aspect of exercise or physical activity (of varying frequency, intensity, time and type) and nutritional supplementation/advice[160,161], delivered both with and without further interventions. These additional components include, for example, nurse-led phone support[230], psychological support[87–92,163,274], motivational support[71], alcohol (reduction) and smoking (cessation) interventions[71,88], 'medical optimisation'[88,92,94,95], and relaxation techniques[93].

Even when considering just the nutritional components of these interventions, there remains a vast gulf in the degree to which patients are prehabilitated, with many studies offering only advice [87,88,163,230,275,276] whilst others provide routine supplementation [71,90,93–95,160]. Beyond this, Bojesen *et al.,* although arguably not undertaking prehabilitation in its purest sense, offered nutritional screening alone, leaving management of the screening results up to the clinical care team. This study reported an absolute risk reduction in a complicated postoperative course by over 10% [62]. Conversely, on the other end of the spectrum, Lopes *et al.,* took complete control of patient's dietary intake and supplied all nutritional intake to

participants. This led to improvements in functional outcomes such as HGS and exercise capacity[92]. To further illustrate this point of intervention variance, a comprehensive systematic review of prehabilitation in patients with oesophageal cancer included five studies that included nutritional intervention (versus exercise alone). Again, this ranged from nutritional advice only to varying amounts of differing supplementation (prescribed protein supplementation and direct supplementation with leucine metabolite b-hydroxy-b-methylbutyrate)[56]. Although the conclusion of this review was that most prehabilitation programmes confer at least some benefit in terms of improved physical performance, nutritional state and QoL, clearly this widely varying research base acts as a barrier to implementation of a universal prehabilitation nutritional intervention. This concern, even in homogeneous groups of cancers, is an opinion eloquently summarized by Heil *et al.,* who concluded that conflicting evidence and complex logistical issues were perceived as significant barriers to implementing prehabilitation in CRC surgery[103].

Another consideration regarding intervention heterogeneity is group selection. By definition, prehabilitation is undertaken in cohorts awaiting an intervention, but as outlined above, many studies focus specifically on high(er)-risk individuals[62,88,94,95] or individuals with more advanced cancers[89,90]. Results in these groups are promising, and concentrating health resources in specific groups of individuals may lead to improved outcomes on both an individual and systematic level. However, it may be questioned if this research focus limits the knowledge base around individuals who are at lower risk of poor outcomes. Healthier individuals and those with less advanced cancers are arguably more likely to return to their pre-cancer status after the insult of cancer and its treatment, so perhaps optimising these individuals prior to surgical intervention would not reduce mortality and significant morbidity but may well lead to a faster return to 'normality' and relatively increased QoL.

Despite this proposition, the concept of high-risk individuals being most responsive to nutritional screening, assessment and/or prehabilitation is well-illustrated by Bojesen *et al.,* who assessed patients for anaemia, low functional capacity and nutritional status. Post-assessment and based only on the assumption of action taken on these results (i.e. referral for nutritional counselling and supplementation), patients could expect an absolute risk reduction of a complicated postoperative course of almost 11%[62], suggesting that risk-screening alone could improve postoperative outcomes. It may however also be that the nutritional status of individuals with oesophageal cancer (as studied by Bojesen and colleagues) is considerably worse than individuals with other cancers, due to difficulties in, for example, swallowing solid foods, and that nutritional prehabilitation that addresses this (i.e., ONS) is more effective in those most affected before intervention[230,277].

Beyond a lack of consistency in interventions and individuals with a wide variety of cancer being studied, the pursuit of optimising prehabilitation strategies in patients with cancer is further hampered by the plethora of outcome measures. Ignoring feasibility and pilot outcomes, most dependant variables studied can be divided into i) clinical, ii) functional, iii) nutritional and iv) 'other' outcomes (Figure 3.1). Clinical outcomes commonly include LOS[71,87,90,94,95,160,276,278], complications/morbidity[62,87,88,90,94,95,160,278], mortality[94,95,278], readmission[71,87,160] and unplanned ITU admissions [62]. Functional outcomes include walking parameters[90,95,215,276], strength[94,95,230,276], and CPET-derived parameters[94]. Nutritional outcomes include body composition[87,95,230] and nutritional-intake information[56,90,276], whilst 'other' measures include QoL[56,87,90,95], psychological-associated outcomes[87,276], habit cessation[87,90], sleep quality[87,276] and financial cost of care[95,276]. As with the employed interventions, these broad categories veil a large spread of measurements. Focussing on the specifics of nutritional outcomes, these are most commonly assessed by a multitude of body

composition parameters[56,87,90,95,230], dietary habits[87], faecal microbiota[87], and pre-/albumin levels[276]- again providing an evidence-base which is challenging to synthesise and translate to recommendations.

Inclusion of some outcomes, particularly clinical, may be explained by availability bias; for example, mortality is rarely, if at all, significantly impacted yet is easy to measure[56,160,161,163,233,277,278]. However, such a range of outcome metrics, taken at different time points, makes comparison and further analysis impossible[88,94,161,279].

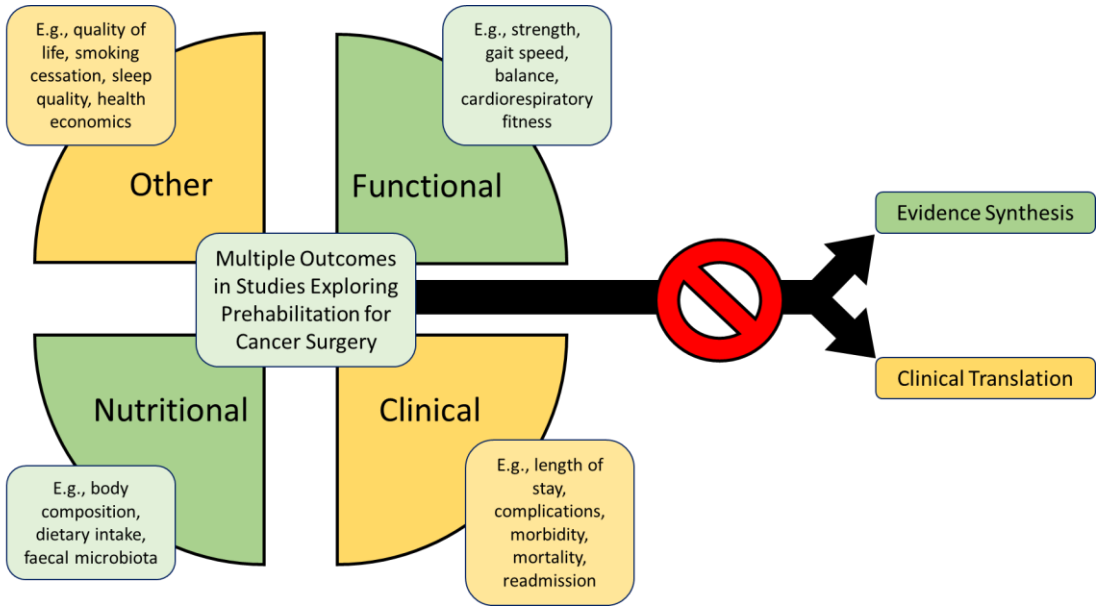


Figure 3.1- Schematic representation of how the heterogeneity of outcomes in studies exploring nutritional prehabilitation for cancer surgery limit data synthesis and clinical translation. Reproduced from Wall et al.[165]

3.5 Conclusion

In summary, recent studies investigating both nutritional only and multimodal prehabilitation for cancer surgery appear as a mosaic of interventions and outcomes which serves as a clear limitation to clinical translation. This is reflected in the American Society of Clinical Oncology (ACSO) guidelines which recommends exercise during cancer treatment, but suggests more

research is required for nutritional interventions[56]. However, stepping back from the minutia of individual studies reveals a somewhat clearer picture. Multimodal prehabilitation consistently improves LOS[90,95,160,276,278] and QoL[56,95], and reduces both complication burden and healthcare associated costs[62,88,90,160]. Importantly given the patient groups in focus, this may lead to an earlier time to adjuvant chemotherapy and/or return to everyday living, and more time spent with loved ones.

Based on existent literature, future work could further investigate the financial cost of prehabilitation versus the cost of LOS, the use of wearable devices to aid prehabilitation such as suggested by Waller *et al.,*[163], and/or the involvement of partners in a prehabilitation as suggested by Paterson *et al.,*[280]. A final and interesting consideration for future research for nutritional prehabilitation is the interaction between nutrition and exercise during multimodal prehabilitation; specifically, as suggested by Gillis *et al.,* does optimised nutrition allow an individual to gain the most from a given exercise regime[169]?

3.6 Discussion

There is a fundamental and complex interaction between nutrition and exercise but the evidence surrounding the use of nutritional prehabilitation in cancer care is disjointed and unclear. The issue stems from, the large number of interventions and outcome measures as well as the consideration of 'cancer' as a single entity; which it is not. A standardised dataset would be helpful in this area but is unlikely to happen without international consensus.

Though this thesis focusses on a single intervention type (exercise-only prehabilitation) in a specific disease (CRC/ dysplasia), it is important to consider where this research lies in the wider context. The results detailed here cannot necessarily be extrapolated to other cancer types or other intervention types, and perhaps focussing on such specifics, despite reducing

the ability to draw wider conclusions, will give an insight into what is different about exercise prehabilitation and CRC.

Adequate nutrition is required to maintain muscle due to the dynamic nature of MPS and MPB, and this is more so in those with cancer, those who are older and those who are sarcopenic, all of which are seen commonly in CRC. This chapter has discussed interesting considerations in screening for nutritional issues and in treating 'allcomers' and this principle can be just as easily applied to exercise prehabilitation: does prehabilitation benefit no one, everyone, or a select group? And can these people be screened for in a timely fashion?

Regardless, exercise-based prehabilitation in CRC should be viewed through the lens of nutritional adequacy. For exercise to have any benefit it must take place in the presence of adequate nutrition. Nutritional prehabilitation should be considered with a focus on enteral options in appropriate cases; probably the majority of individuals. High-risk individuals perhaps have the most to gain from nutritional prehabilitation, yet lower-risk cases may benefit from marginal and hence difficult to measure improvements. Nutritional care pathways are an effective intervention to identify and intervene with expert dietetic input, but these require significant resource and stake holder involvement, and it is a possibility that the combination of nutritional and exercised-based prehabilitation may work synergistically in cancer, but well-designed studies are required to initially investigate any effects, and later, the mechanistic underpinnings. This would improve both screening, targeting and monitoring of such responses.

In relation to the experimental aims of this thesis, though no nutritional intervention is studied, nutritional requirements, as detailed, are essential for improving physiological

resilience via exercise therapy and thus are included in many multimodal prehabilitation programmes.

4. High-Intensity Interval Training (HIIT) Alone Versus HIIT Plus Resistance Exercise Training (ReHIIT) as Prehabilitation for Operable Colorectal Cancer: A Focus on Physiological Resilience

4.1 Introduction

Physiology is the '*branch of biology that deals with the functions and activities of life or of living matter and the physical and chemical phenomena involved*'[281]. Physiology, by definitions is a '*normal*' response to a stimulus, and is essential to the survival of lifeforms that inhabit a dynamic environment.

Humans physiologically adapt to exercise in several ways. Human skeletal muscle, in response to exercise can change nutrient stores, metabolic enzymes, and amount of contractile protein with the specific adaptations differing depending on the type and frequency of exercise, coupled with the age, genetics, sex, and nutritional and training history of an individual[282]. Though there are a wealth of measures used to delineate an individual's response to exercise, this thesis focusses on physiological, clinical and functional adaptations.

Resilience can be thought of as the ability to '*bounce back*'[283], and in a physiological sense, '*the ability to resist functional decline following acute and/or chronic stressors'*[284]. Though much of the consideration of physiological resilience has been in athletes[284], the traditional focus with respect to resilience in cancer individuals has been predominantly psychological[285]. The combination of physiological and psychological abilities, as well as the complex interplay between the two is termed '*intrinsic capacity*' and is increasingly recognised as an important factor in healthy ageing, which includes overcoming some of the challenges associated with age such as a propensity for comorbidities such as cancer[286,287].

As discussed, both the presence of CRC, and the demographic in which it predominates leaves individuals vulnerable to physiological decline in the period before an operation. The stress of the operation and the postoperative recovery can overwhelm individuals both psychologically and physiologically and leave patients worse off than prior, affecting their ability to perform ADLs and worsening their QoL[288]. Preoperative physiological capacity is linked to postoperative outcomes in CRC surgery[289], and thus strengthening the physiological capacity and resilience of an individual prior to an operation may allow them to *better bounce back*, or even *bounce back better*.

4.2 Aims

The aims of this chapter are to investigate the effects of adding RET to HIIT prehabilitation in patients with CRC scheduled for curative intent on parameters associated with physiological resilience.

4.3 Methods

The experimental portion of this thesis reports results from the EPiC study. Although not all outcomes of the EPiC study are reported herein due to some being out of scope for this thesis, this methods section will define the processes surrounding the EPiC study, and will comment, where appropriate about the inclusion of each outcome in this thesis. A template for intervention description and replication (TIDieR) checklist[290] can be found in the appendices (Appendix B- TIDieR Checklist).

4.3.1 The Exercise Prehabilitation in Colorectal Cancer (EPiC) Study

The EPiC study (Figure 4.1 & Figure 4.2) is a single-centre, unblinded, interventional, randomised, non-controlled trial to assess the effects of exercise prehabilitation in patients

with CRC scheduled for resection with curative intent funded by the Medical Research Council (MRC; Medical Research Council, Polaris House, North Star Avenue, Swindon, SN2 1FL). The trial began recruitment on 28/07/2023.

The primary objective of the EPiC study is: *'to compare composite change in AT and whole-body muscle mass',* both of which are endpoints reported in this chapter.

The secondary objectives of EPiC are: *i) to compare changes in each of cardiorespiratory and skeletal muscle function with HIIT vs. ReHIIT; ii) to determine the effects of HIIT vs. ReHIIT on biological markers of postoperative recovery; iii) to determine the relationship between biological features of CRC and exercise adaptation, and probable prognostic markers of responses to prehabilitation and; iv) to determine the effects of HIIT vs. ReHIIT on clinical outcomes postoperatively.*

The primary endpoint of the study is: *A composite of change in AT determined via CPET (Hedges g effect size: 1.32) and whole-body muscle mass measured by dual x-ray absorptiometry (DXA) (Hedges g effect size: 1.1) with HIIT vs. ReHIIT.*

The secondary endpoints of the study are: *Changes in MPS, MPB, whole-body contractile mass, $VO2_{PEAK}$, VL muscle architecture, neuromuscular function, mitochondrial respiration, and anabolic cell signalling with HIIT vs ReHIIT and; differences in clinical outcomes, dietary intake, measures of functionality (including physical activity) and self-reported QoL with HIIT vs ReHIIT.*

Figure 4.1- The Exercise Prehabilitation in Colorectal Cancer (EPiC) Study Logos

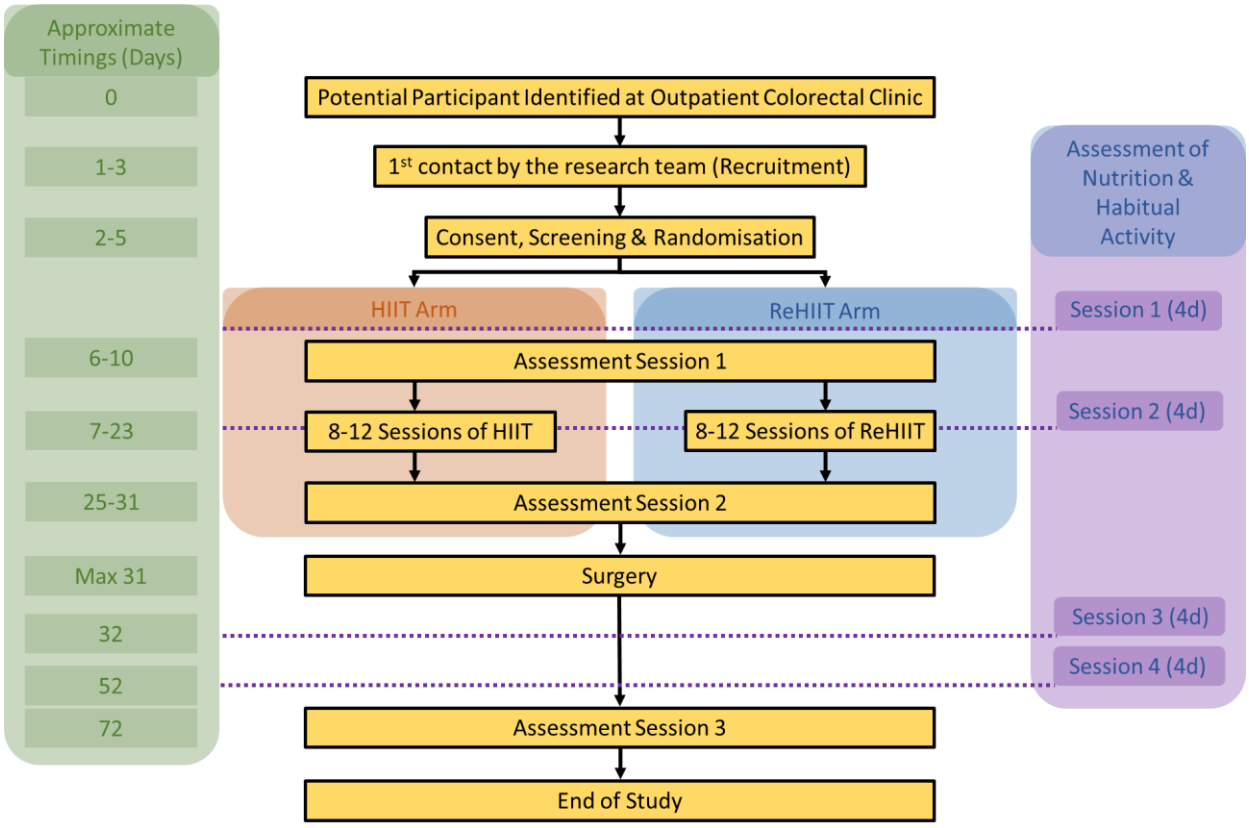


Figure 4.2- A schematic overview of the Exercise Prehabilitation in Colorectal Cancer (EPiC) timeline.

Though the entire purpose, objectives and aims of the EPiC study are beyond the scope of this thesis, the experimental chapters (Chapters 4 & 5) are wholly determined from data derived from the EPiC study.

4.3.1.1 Registration

The EPiC study is registered with ISRCTN (Number: ISRCTN18133394; DOI: https://doi.org/10.1186/ISRCTN18133394).

4.3.1.2 Ethics & Approvals

Ethical application for the EPiC study began on 04/10/2022 to the Health Research Authority (HRA) via the *Integrated Research Application System* (IRAS; project ID: 321484) after favourable opinion from the trial sponsor (University of Nottingham; sponsor reference: 23005). The *South Central- Oxford C* REC ethical review took place on 31/03/2023 and initial recommendations were issued on 03/04/2023 (REC reference: 23/SC/0115). Full approval was issued on 19/04/2023 (Appendix C- Initial REC Letter of Approval). Later amendments were approved on 10/08/2023 and 22/11/2023. The protocol for the EPiC study is available in Appendix D- EPiC Study Protocol.

As part of the HRA ethics applications, specific approval was required for use of ionising radiation (DXA). This was sought from, and approved by, a Medical Physics Expert (MPE) and Clinical Radiation Expert to support the IRAS application.

After HRA REC approval, *Confirmation of Capacity and Capability* was sought and received for the EPiC trial from *University Hospitals of Derby and Burton NHS Trust (UHDB) Research and Development Department* at the *Royal Derby Hospital (RDH)* and *Queens Hospital Burton*.

4.3.1.3 Inclusion & Exclusion

Inclusion and exclusion criteria were based on i) participant safety; ii) scientific utility and; iii) informed, voluntary participant consent. Inclusion criteria were:

- Age ≥18 year at the time of discussion at the MDT
- No maximum age range so long as the participant was deemed fit for surgery by the clinical team
- MDT outcome of a tissue-proven, or radiologically and clinically suspected colorectal neoplasia or dysplasia with the intention to treat with curative surgery
- Due to undergo elective operative resection (by any route) with curative intent
- Ability to and willingness to participate in exercise regimes and assessments
- Able to travel to the RDH for the duration of the study to facilitate exercise sessions
- Availability for the study period to attend a minimum of eight exercise sessions and three assessment sessions

Participants who did not take anticoagulant medication (with the exception of low-dose ((≤75mg/day) aspirin), were eligible for inclusion in all trial assessments. Those on alternative, combined or higher-dose anticoagulation than specified were eligible for participation in the trial with the exception of muscle biopsy and related deuterium oxide (D_2O) consumption/ saliva sampling.

Exclusion criteria were:

- Inability to offer informed consent
- Undergoing emergency surgery
- Past medical history including:
    - Myocardial infarction within the last 6 months or unstable angina

- Heart failure (New York Heart Association Class III/IV[291])
- Uncontrolled hypertension (Blood pressure systolic >160 and/or diastolic >100mmHg)
- Previous stroke/Transient ischaemic attack
- Aneurysm of a named blood vessel
- Exercise-induced, or brittle asthma

- Abnormal blood and/or ECG results (at the discrepancy of the study doctor)
- Individuals who were unable to undergo CPET based on ATS/ACCP guidelines[292]
- Pre-existing clotting disorders known to the patient
- Family history of severe bleeding requiring medical intervention
- Not enough time between enrolment into the study and scheduled operation date in order to facilitate assessments and exercise sessions
- Concomitant enrolment in another study which will affect the results of either study
- Pregnant or breastfeeding

4.3.1.4 Recruitment

Power calculations determined the n of each arm to be 18 for a power of 90%. Computed simulations determined n to be 20 so a target of 22 per group was chosen to ensure a power of >90%. Based on an assumed drop-out rate of 20% and a post-surgery complication rate of 7%, the study aims to recruit 56 participants, with 28 randomised into each arm.

All participants were recruited from the RDH CRC MDT. Potential participants were recruited by a member of the clinical team after they had been informed of their diagnosis and agreed a management plan. Willing patients were given a digital copy of the *Participant Information Sheet* (PIS; Appendix E- Participant Information Sheet) and were followed by a member of the

research team a minimum of 24 hours later to discuss any concerns or ask any questions. Those wanting to proceed, were invited to a screening session.

4.3.1.5 Screening

Screening sessions were undertaken face-to-face in *The Medical School*, RDH (Uttoxeter Road, Derby, UK) by a suitably trained member of the research team (Appendix E- Screening Sheet). Basic demographic and clinical information were recorded; blood tests and an ECG were performed which were checked by the study doctor. In addition, consent was formalised via a consent form (Appendix F- Consent Form), and paper copies of the PIS and DXA information sheet (Appendix G- DXA Information Sheet) were issued. Eligible participants were then randomised into one of two interventions arms and the participant's general practitioner (GP) informed via letter (Appendix H- GP Letter).

4.3.1.6 Randomisation

Participants who were deemed eligible after screening were randomised by a member of the research team. Participants were stratified by sex and age-group and allocations were drawn from sealed, opaque envelopes.

4.3.1.7 Interventions

Participants were randomised to either HIIT alone, or RET in addition to HIIT (ReHIIT). Participants were required to undertake between eight and 12 sessions of exercise between the baseline and preoperative assessment days. Each exercise session was supervised one-to-one at The Medical School, RDH. Participants were offered water throughout and allowed to take phone calls, use the toilet etc. Though participants were encouraged to complete all sets in all exercise modalities, this was not enforced, and each participant was free to complete

only the exercises they wanted to. Participants completed, on average, between two and five sessions per week.

4.3.1.7.1 High-Intensity Interval Training Group

Participants randomised to the HIIT group were scheduled to undertaken between eight and 12 sessions between the first and second assessment day which corresponded to the preoperative period. HIIT sessions were supervised by a research team member with a current certification in *Advanced* (ALS) *or Intermediate Life Support* (ILS) with a second team member with a certification of *Basic Life Support* (BLS) or higher immediately accessible. Exercise was stopped if there were safety concerns. HIIT sessions (regardless of study arm) were documented contemporaneously using the *HIIT Log* (Appendix I- HIIT Log).

During the first session, participants were exercised based on their maximum wattage attained during CPET on the first assessment day. All HIIT sessions were completed on a bicycle ergometer (Lode, Groningen, The Netherlands) which was programmed using *Lode Ergometry Manager* (Version 9.4.7.0). After an unloaded warm-up period of two minutes, participants were exercised at 90% of their maximum wattage of initial CPET for one minute followed by 90 seconds rest at a proportionally low wattage. If they were able to complete this and achieved a modified Borg score[293] (a rating of perceived exertion from zero to 10) of <9, the next one minute 'set' was performed at 95% (i.e. an increase of 5%) of the maximum wattage achieved on CPET. This process was repeated until either the reported Borg score was ≥9 or until five one-minute periods of exercise were completed (maximum 110% of wattage achieved at CPET). Participants then completed a further 3.5 minutes of minimally loaded or unloaded cycling before dismounting. For the remaining HIIT sessions, participants were exercised on the same protocol, but based on the highest level achieved at the first HIIT

session (Figure 4.3). For example, if a participant achieved a 110w during the fifth period of intense exercise at the initial session, the next session would utilise five 'sets' of 110w high-intensity intervals. Participants were asked to rate each high intensity period using the modified Borg scale (0-10) and the wattage was increased by 5% should they be able to complete all five periods with a Borg score of <9 or if the research team members felt they were not exercising to maximal effort. Blood pressure readings (CORTEX METRONIK BL-6; CORTEX Biophysik GmbH, Leipzig, Germany) were taken prior to HIIT, at peak exertion and after recovery and SpO_2 (peripheral haemoglobin oxygen saturation levels) and HR monitoring (Datascope Trio; Datascope, New Jersey, USA) was undertaken *beat-to-beat* throughout. These parameters were recorded during exercise in line with local standard operating procedures (SOPs).

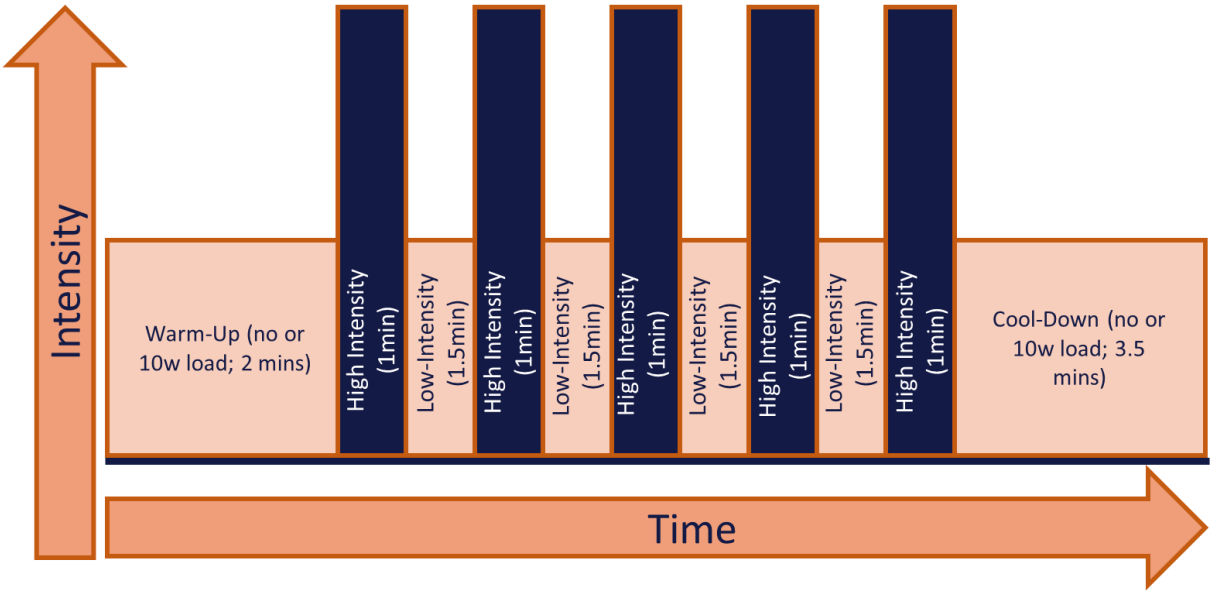


Figure 4.3- A schematic of the EPiC HIIT Session protocol from the 2nd exercise session onwards.

4.3.1.7.2 Resistance Exercise Training in addition to High-Intensity Interval Training Group

Participants randomised to the ReHIIT group undertook the HIIT protocol as described above. In addition, they also performed RET sessions immediately after completing HIIT. Sessions were documented contemporaneously using the *RET Log* (Appendix J- RET Log). All training took place using standard gymnasium equipment with standardised weights. Use of the equipment was demonstrated and was observed by a member of the research team who also verbally encouraged participants. Participants were encouraged to complete a warm-up set followed by three sets of six to 10 repetitions in each of the following:

- Latissimus Dorsi (Lat) pulldown
- Seated row
- Chest press
- Leg press
- Leg extension

- Leg curl

The initial weight of the 'loaded' sets was calculated as 70% of the one-repetition maximum (1-RM; the maximal weight that can be lifted once, whilst maintaining appropriate technique[294]) calculation from the baseline assessment session. Over the course of the sessions, if a participant achieved six of more repetitions for three full sets, the weight was increased for the next session. If the participants were unable to complete at least one repetition for all three sets, the weight was decreased for the next session. Weight was also altered at the research team's discretion e.g. if a participant displayed poor 'form', to minimise potential for injury. The absolute increase or decrease in weight was based on the divisions of the weight stack on the equipment (Figure 4.4).

Figure 4.4- An example weight stack from the resistance machines. Weight could only be added in increments limiting exact measures.

4.3.1.8 Assessment Days

Three assessment days took place per completed participant over the course of approximately 10 weeks (Figure 4.5). After screening, *Assessment Day 1* (V1; baseline) took place prior to any intervention; *Assessment Day 2* (V2; preoperative) took place after completion of the intervention period, but before a participants operation; and *Assessment Day 3* (V3; 6-week postoperative) took place approximately six weeks postoperatively. Each assessment day was performed in the same order (Appendix K- EPiC Collection Log). Participants were offered transport to and from The Medical School, RDH where all assessments took place, performed by appropriately trained members of the research team as per local SOPs and ethical approval. Each assessment day took approximately six hours to complete. Participants were asked to attend the assessment days after fasting (except water *ad libitum*) for a minimum of six hours and were asked to consume tracer samples and collect urine and saliva in the days preceding the assessment day. Testing modalities, their rationale and their undertaking are described below and in Chapter 5. Methods used on each assessment day are completely described here but not all measured outcomes are reported in this thesis. Non-reported measures are detailed in the sections below.

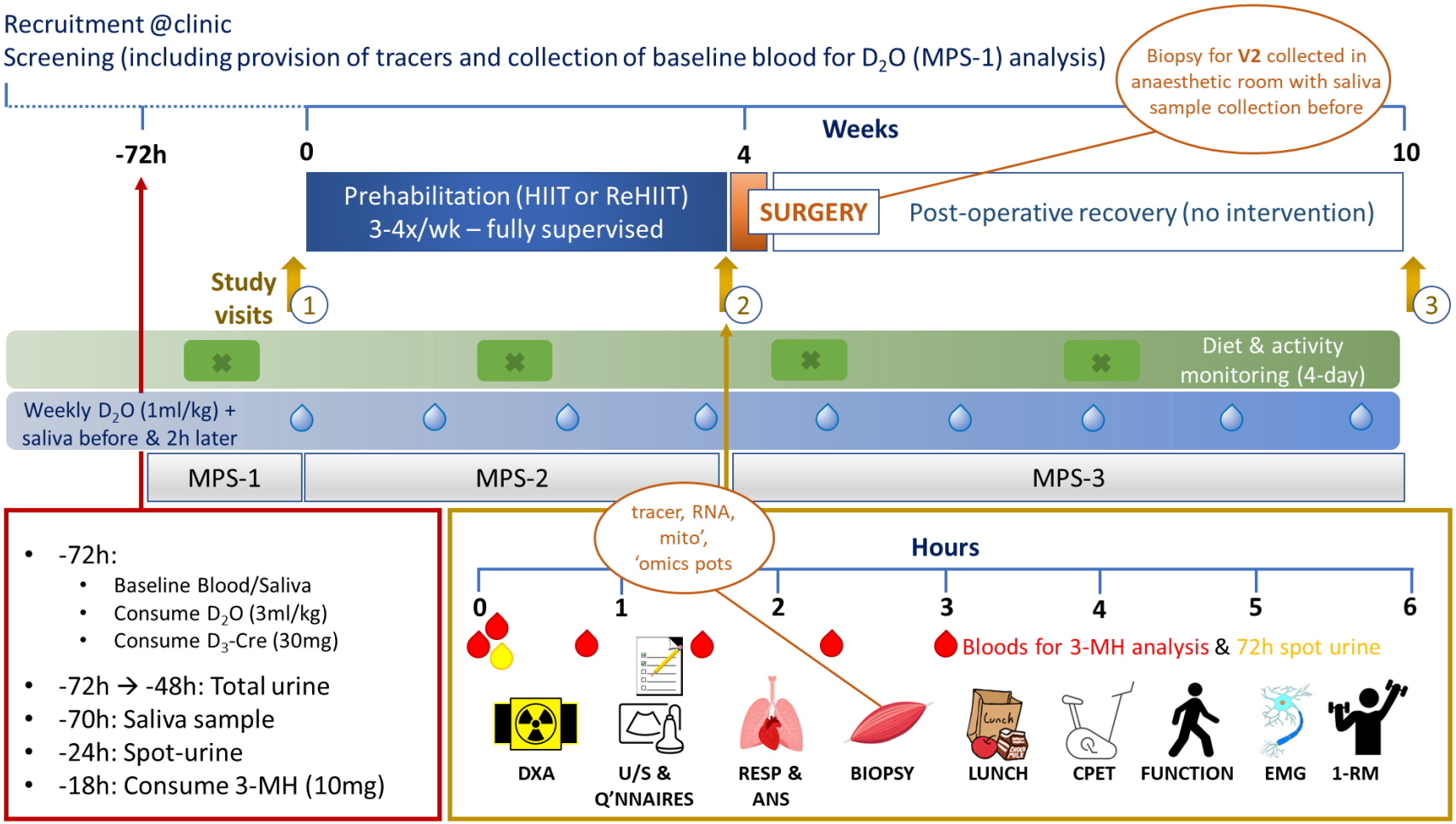


Figure 4.5- A schematic overview of the EPiC assessment timeline, including tracer drinks; urine, saliva and blood sampling and diet and habitual activity monitoring.

4.3.2 Measurements of Physiological Resilience

4.3.2.1 Cardiorespiratory Fitness

CRF is a broad term relating to the capacity of the circulatory and respiratory systems to supply oxygen to skeletal muscle mitochondria to optimise aerobic respiration during physical exertion[295]. Aswell as being a measure of general 'fitness' i.e. functional capacity and aerobic power, CRF is a strong determinant of cardiovascular disease and cardiovascular disease mortality, the leading cause of death worldwide[295,296]. Exercise can affect cardiac structure and function, promoting beneficial remodelling to the degree where exercise is a core component of cardiac rehabilitation. These effects might be responsible for some of the reduction in cardiovascular mortality seen in cohorts who exercise[297].

Well-powered studies have shown a general decline in CRF from the late 20th to the early 21st century[298], and considering increasing age is associated with a decline in CRF, the considerations of CRF in cancer cohorts is important, especially when considering the physiological challenge of surgery in addition to the neoplastic burden[299].

CRF predicts mortality and LOS after major elective surgery in older cohorts[300], and increased CRF is associated with decreased risk of CRC[301] and indeed of total cancer mortality[302].

It follows then, that to fully inform a patient of their operative risk prior to surgery, a robust measure of CRF should be considered along with their individualistic risk factor profile.

4.3.2.1.1 Cardiopulmonary Exercise Testing

CPET is widely used to assess CRF. It can reliably offer an objective and comprehensive measure of CRF allowing for the development of local guidelines which may influence patient care, such as admission to critical care[292]. CPET is a graded exercise challenge which employs non-invasive measurements of gas exchange, ECG tracing, analysis of HR, blood pressure and

SpO_2 to determine the capacity of the cardiorespiratory system under physical load. Given the physical stress of surgery, it follows then that CPET-measured markers are associated with surgical outcome following non-cardiopulmonary surgery and that CPET can correctly stratify patients based on surgical risk[303]. CPET can help predict adverse postoperative outcomes in patients undergoing major CRC surgery and can also suggest ways of optimising patients prior to intervention, such as targeted therapies aimed to improve CRF[304].

Though CPET is by definition a physiological stressor, with appropriate monitoring, there is no absolute reason why individuals with cancer cannot undergo this testing modality[292] and indeed, those who do not have the CRF reserve to undergo CPET are unlikely to have the reserve for major surgery.

CPET is usually performed in a single session but can measure multiple CRF parameters. Though treadmill and arm crank ergometry[305] are commonly used during CPET, in a clinical setting cycle ergometry is the mainstay of testing, partially due to cost and space savings, but mainly due to the evidence base in individuals with comorbidities as well as the relative ease to which blood pressure, continuous ECG monitoring and blood gas collection (where used) can be undertaken. Cycle ergometry also requires less weight bearing and is widely considered safer[305].

4.3.2.1.1.1 VO_{2Peak} & VO_{2Max}

VO_{2Peak} is the peak oxygen uptake attained during an incremental test to exhaustion. It can be expressed in absolute (mL/min) or relative to body mass (mL/Kg/min) terms. It is the highest value attained for oxygen uptake during exercise, often occurring in the final, and thus most power-hungry period of the test[306]. VO_{2Max} is an individual's highest possible oxygen update. VO_{2Peak} may not represent the maximal amount of O_2 an individual can consume (VO_{2Max}),

only how much they have consumed at peak exercise and therefore, VO_{2Peak} must be ≤ VO_{2Max}[307](Figure 4.6). Absolute and relative values are useful for comparing changes in an individual (absolute) and between individuals of different weights (relative). Further, measurements relative to lean mass allow a comparison between parenchymal (muscle) tissue e.g. in an individual who has lost weight between measurements[308].

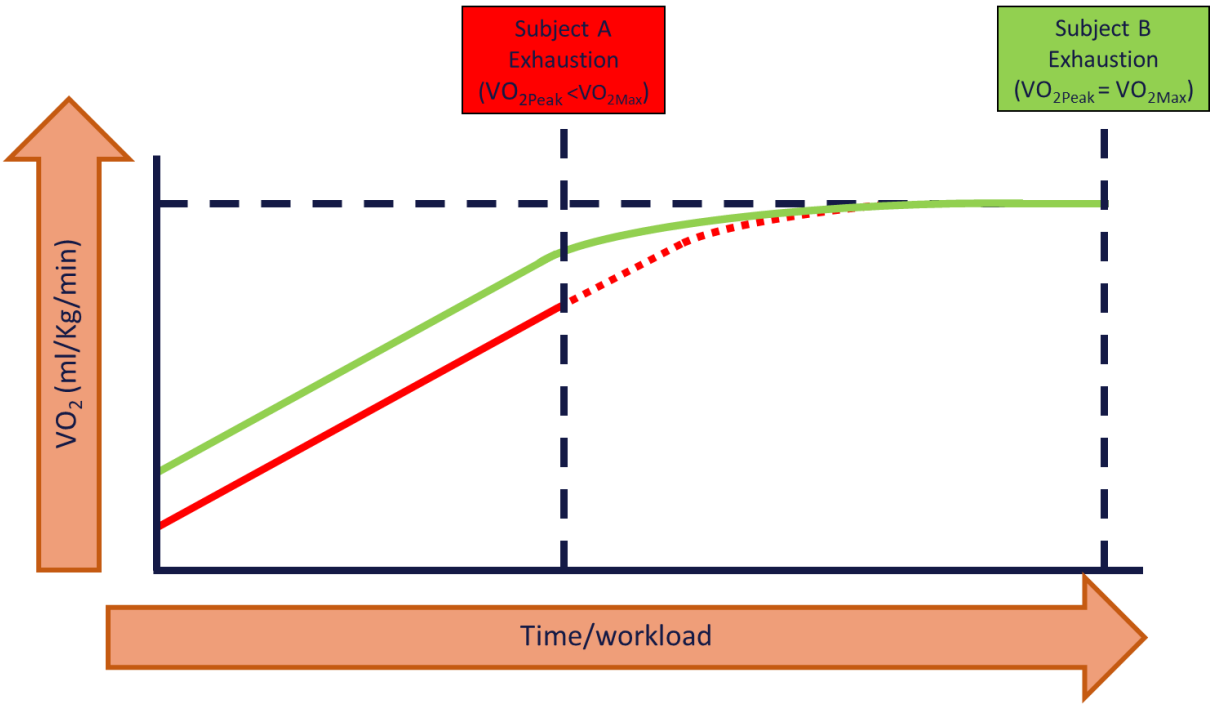


Figure 4.6- VO_{2Peak} & $VO2_{Max}$. In this example, subject A has reached exhaustion earlier than Subject B. Subject A has the physiological reserve to increase their measured VO_{2Peak} (denoted by the dashed red line), but has not achieved that during this test, and therefore has not achieved their physiological VO_{2Max}. This can be interpreted from the test by the linearity of the red line. Subject B in contrast, has achieved their physiological VO_{2Peak} as, by exhaustion, the green line is horizontal, denoting the same value of VO_2 (mL/mg/min) despite increasing time/workload. That is, their ability to utilise O_2 is maximised and no more is being consumed despite an increasing workload. Adapted from Rose et al[306].

VO_{2Peak} measured via CPET is accepted to be a robust measure of CRF and is accepted as the '*gold standard*' in preoperative testing[309]. Furthermore, supervised exercise training is associated with significant improvements in VO_{2Peak} following a diagnosis of early-stage cancer, with minimal adverse events[310].

VO_{2Peak} varies with age and sex. Males have a higher age-matched value than females for VO_{2Peak} but both males and females display a steady decline with age, regardless of activity levels. Most studies show young males (age 20-30) to have a VO_{2Peak} value between 40 and 55mL/kg/min, with similarly aged females achieving 35-40mL/kg/min. This value declines to 25-35mL/kg/min for males and 15-25mL/kg/min for females aged >70 (Figure 4.7) [311].

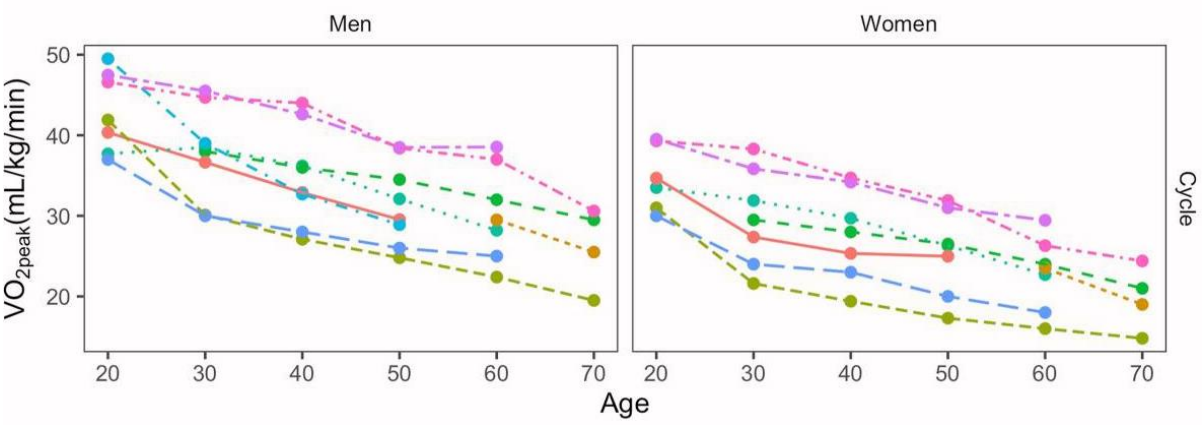


Figure 4.7- VO_{2Peak} by age from nine studies. Taken from a review by Letnes et al[311]. Note the predominantly lower values in age matched women vs. men & the general decline with age.

4.3.2.1.1.2 Anaerobic Threshold

The AT is defined as the level of oxygen uptake (VO_2) above which anaerobic metabolism supplements oxidative phosphorylation with additional CO_2 production. This can be visualised by plotting pulmonary CO_2 output (VCO_2) versus VO_2, whereby an inflection point signifies AT, i.e. CO_2 production increases and O_2 uptake by blood is static. AT may be described in absolute terms, as a value of VO_2; as a percentage of VO_{2Peak} or VO_{2Max} or the gas exchange threshold (GET) VO_2 mL/Kg/min^{-1} [306].

AT is widely used to define and help optimise issues ascertaining to preoperative CRF and in individuals undergoing surgery for CRC, AT has been shown to be predictive of postoperative complications and LOS[312].

A normal range for AT is 40-60% of an individuals' predicted VO_{2Max} with a value lower than this suggesting poor oxygen delivery to muscles[313]. As with VO_{2Peak} this value is lower in females and declines significantly with age. An AT of <11mL/kg/min predicts postoperative survival with high sensitivity and specificity[314] and evidence suggests that those with an AT of <11mL/kg/min should be managed in higher-level care such as the intensive care unit in the postoperative period[82], though other factors need to be taken into account such as those with a slightly higher value for AT, but more complex medical needs. There are various methods for determining AT from CPET with the v-slope method being the most utilised whereby a plot of (consumed) VO_2 is plotted against (expired) CO_2 (Figure 4.8)[315].

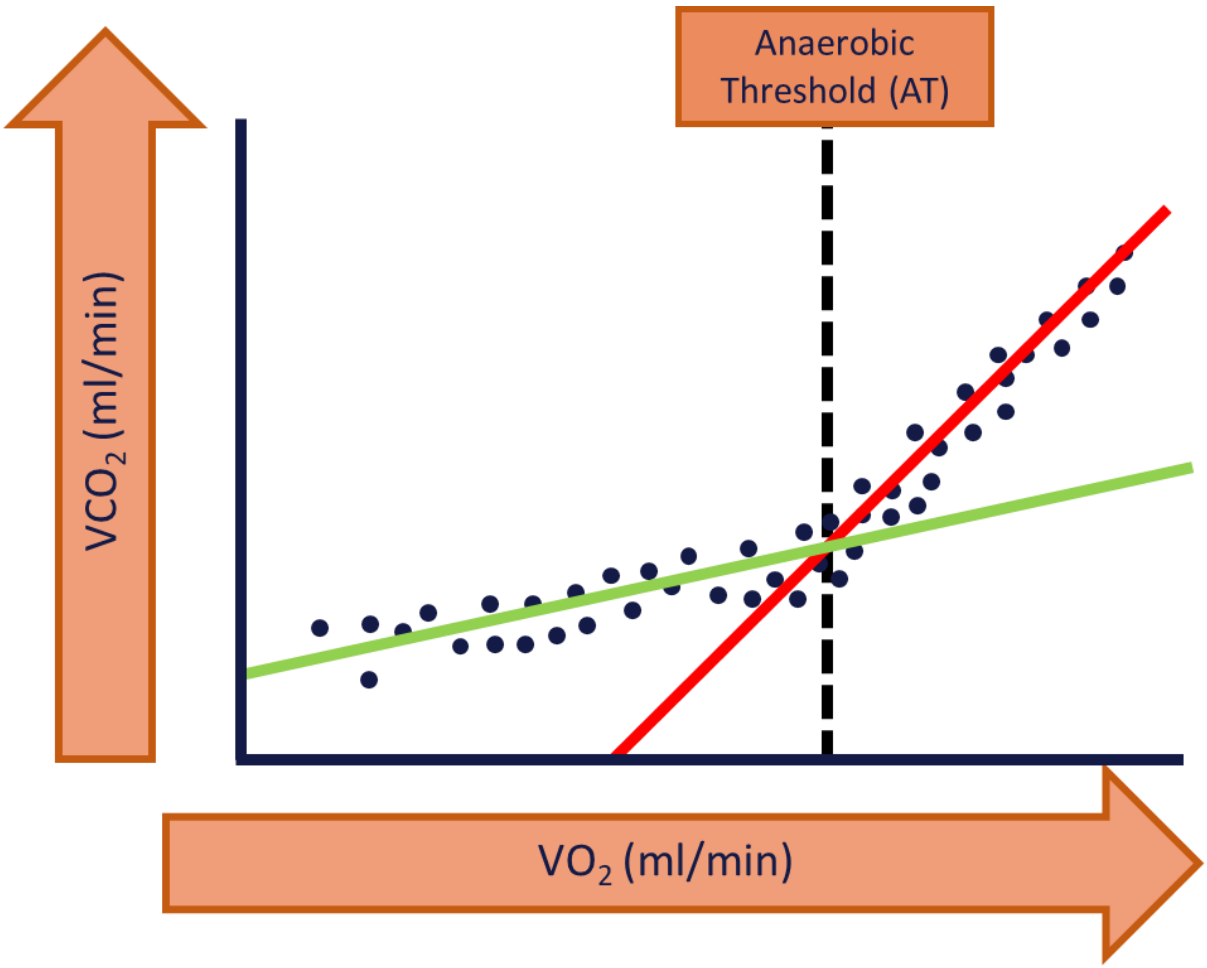


Figure 4.8- A schematic representation of the v-slope method for determining anaerobic threshold (AT). Each dot represents a paired measurement of inspired O_2 and expired CO_2. Independent assessors, aided by software, estimate two lines of best fit (green and red lines). The gas exchange threshold is identified by the intersection of the two lines of best fit for the relationship between VCO_2 and VO_2. Prior to the AT, for a given oxygen uptake (VO_2), expired carbon dioxide (VCO_2) will be the same or less. After the AT, VO_2 will less be than the associated

VCO_2 as carbon dioxide production is supplemented by anaerobic respiration. Adapted from Rose et al[306].

4.3.2.1.1.3 Heart Rate Recovery

The fall in HR immediately after exercise is termed heart-rate recovery (HRR). HRR is a function of reactivation of the parasympathetic nervous system and varies amongst individuals, with a cutoff value of ≤12 beats per minute (BPM) suggesting an abnormal parasympathetic response[316]. A low speed in the reduction from maximum HR from a graded workout is a predictor of overall mortality even in those with cardiac disease and can act as a non-invasive method of assessing parasympathetic activity[317].

4.3.2.1.2 Cardiorespiratory Fitness Testing Methodology

Cardiopulmonary exercise testing (CPET) was undertaken on a *Cortex Meta 3000* system with gas analysis via *Cortex Metalyzer 3B* (CORTEX Biophysik GmbH, Leipzig, Germany) calibrated to ambient pressure and temperature immediately prior to each test. Interpretation and module integration was undertaken by *MetaSoft Studio* version 5.14.0 (CORTEX Biophysik GmbH). After an introductory talk on the safety and scientific aspects of CPET, participants were fitted with an appropriately sized mask (*7450 V2*, Hans Rudolph, Kansas, USA), mounted with Hans Rudolph 5-strap headgear, and an airtight seal was ensured. ECG electrodes were placed and a satisfactory, continuous trace ensured. A Bluetooth-enabled device (*Custo cardio 300*; custo med GmbH, Ottobrunn, Germany) transferred ECG data to integrated software (custo diagnostic version 4.6.18; custo med GmbH). Non-invasive monitoring of blood pressure was performed with an appropriately sized blood pressure cuff and monitor (*CORTEX METRONIK BL-6*; CORTEX Biophysik GmbH) every two minutes or more frequently, and oxygen saturations were monitored continuously with an SpO_2 monitor (*Datascope Trio*;

Datascope, New Jersey, USA) with alarms set as per participant demographics. Participants were asked to mount the CPET bike (Lode Corival, Lode, Groningen, The Netherlands) after appropriate alterations were made to the handlebar and seat height. Participants were reminded that all parts of the study were voluntary, and although they should expect discomfort, they should not experience distress and could stop the test at any time for any, or no, reason. Participants were also asked to inform the research team if they experienced chest pain, unexpected shortness of breath, nausea, dizziness or any other concerning symptoms and the test would be halted immediately.

A CPET 'ramp', a workload programme that demands increasing power-output over time (Figure 4.9), was selected for each participant by the research team based on an informal survey of their fitness levels, age, size and sex. An 'ideal' test required a participant to reach exhaustion between eight and 12 minutes of the ramp[318]. CPET ramps were kept constant for all assessment days. Each ramp started with two minutes of no cycling for gas calibration, followed by two minutes of unloaded cycling followed by initiation of a ramp protocol. Participant were encouraged to remain seated, and maintain a constant cadence between 60 and 80 revolutions per minute (but consistent throughout) based on a screen readout on the CPET bike. Efforts were made to ensure no other information pertaining to the test was available to the participant (e.g. wattage, duration etc.). Participants were encouraged to continue the ramp protocol to exhaustion whilst a doctor, with current NHS practice and current ALS certification, monitored safety endpoints as defined by the ATS/ACCP guidelines[292]. Once exhaustion or a safety endpoint was reached, the ramp was reduced and participants were monitored with unloaded or minimally loaded cycling for a four-minute recovery period (Figure 4.9). Each CPET was recorded on *Metasoft Studio* (details above) and

later interpreted by two independent assessors blinded to intervention group and assessment timeline.

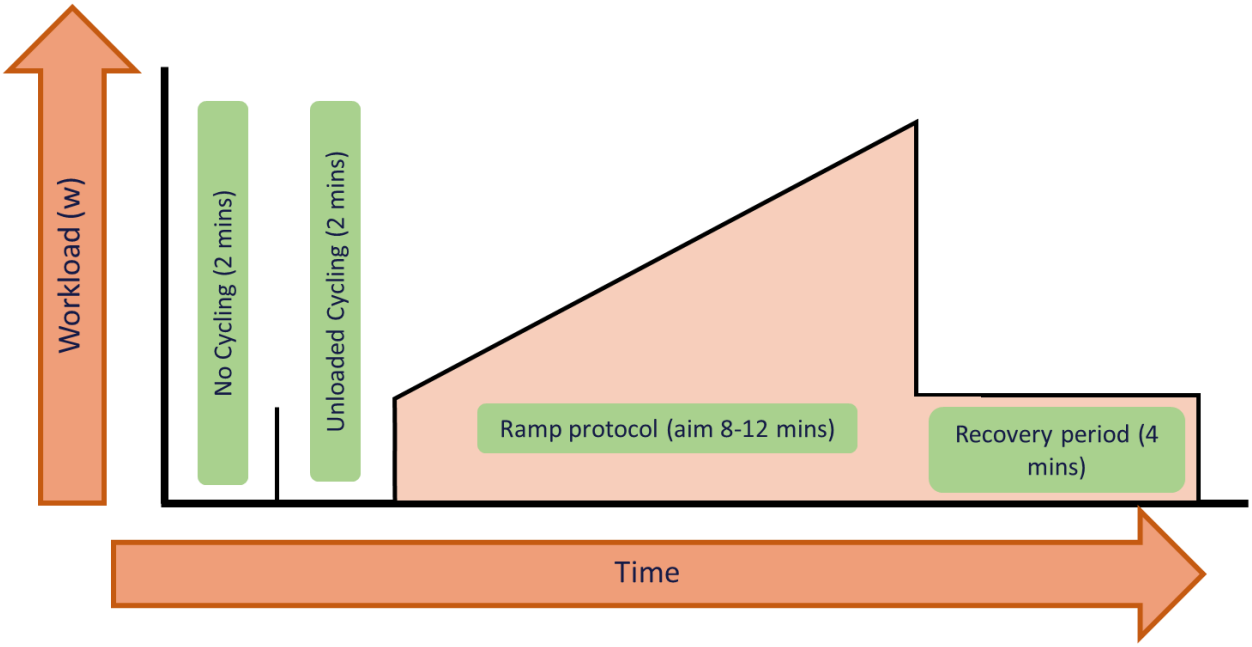


Figure 4.9- A schematic of an example CPET ramp protocol used in the EPiC study

Maximum wattage, maximum HR, HR after one minute of recovery (HRR), VO_{2Peak}, and AT were recorded for each participant at each assessment. Maximum wattage, HR readings and VO_{2Peak} were read directly from the software. AT was interpreted by two independent observers, with disagreements settled by consensus and the option of a third observer using a combination of the V-slope method, modified V-slope method and ventilatory equivalents for O_2 and end tidal CO_2.[319]

4.3.2.2 Body Composition

Body mass is composed of fat mass and fat-free mass (FFM; lean mass). FFM is in turn composed of muscle mass, body cells mass, total body water and bone mineral mass[320]. Much of the reduction in FFM with age comes with the progressive diminishing of muscle mass

associated with the aging process, which makes up part of the complex condition of *sarcopenia*[36].

The link between exercise and FFM is long established. A 1991 meta-analysis concluded that weight training can facilitate body fat loss but also preserve or increase FFM[321]. Importantly, a low FFM index has been shown to be strongly associated with all-cause mortality in individuals with cancer, with the effect strongest in the older adults[322]. FFM is an important metric both in determining those individuals who are highest risk of mortality and other measures after surgery for cancer.

Total-body estimates of FFM can be derived using DXA. DXA is relatively low-cost and widely available, though it does expose subjects to ionizing radiation and gives no information about muscle quality or architecture. DXA measures body composition through the attenuation of two X-ray energy peaks allowing for the assessment of tissues with differential X-ray impedance. Though not the '*gold standard*', DXA-derived FFM measurements correlate well with both CT and MRI measurements. It is also relatively quick, cheap and is widely available in research settings in comparison to CT and MRI [323].

4.3.2.2.1 Body Composition Methodology

Weight was assessed via calibrated scales (*Marsden MPMS-250*; Marsden Weighing Machine Group Ltd. Rotherham, UK) at each assessment day. Lean mass and %BF were calculated via DXA (*Lunar Prodigy DXA* & software version 18, GE Healthcare, Illinois, USA). Prior to DXA, participants consent for receiving ionising radiation was ensured, they were asked to empty their bladder and remove any metal from their body or clothing where appropriate. A suitably trained technician performed the DXA scan in accordance with local SOPs after the ionizing

dose had been prescribed by the study doctor. Ethical approval for the use of DXA is described above.

4.3.2.3 Muscle

Muscle is the tissue responsible for movement within the body but is also an important reservoir for amino acids and providing precursors for hepatic gluconeogenesis[324]. Healthy muscle architecture and function are essential for performing ADLs, especially with advancing age[323]. Patients who have major abdominal surgery are at risk of surgery-related muscle loss[39], and, coupled with the profound muscle wasting seen in cancer cachexia, patients with a neoplastic burden undergoing major abdominal surgery are prone to significant and often debilitating muscle loss[325]. Furthermore, non-operative cancer therapy, such as chemotherapy, can negatively affect muscle function and growth[326]. Skeletal muscle mass is a strong predictor of CRF in obese individuals, more so than age, sex, BMI and other measures of body composition[327], which is not surprising given muscle's fundamental role in locomotion.

'*Sarcopenia*' is the progressive and generalised loss of muscle mass and function that occurs with ageing. It is associated with adverse outcomes such as functional decline, frailty and mortality and is commonly seen in the older adults. Exercise can slow the progression of sarcopenia and improvements in measures of muscle mass, strength and ultimately physical performance can slow or reverse some of the adverse features associated with the condition. Given sarcopenia is a complex syndrome involving muscle mass and function, measures of both need to be considered when combating the pathophysiological entity[328].

There are three types of muscle in humans: skeletal (voluntary), smooth, and cardiac. Skeletal muscle is responsible for all body movement and is essential to normal function. The basic

unit of muscle is the *myofilament*, with multiple myofilaments forming a *myofibril*. Multiple myofibrils act together as a *muscle fibre*, bound together by *endomysium* and multiple muscle fibres form a single *fascicle.* Fasciculi are held together by a connective tissue known as *perimysium* and multiple fasciculi are bound to one another in a connective sheath known as *epimysium* which also incorporates non-contractile elements such as blood vessels. The combination of the individual fasciculi, the supportive tissues such as blood vessels and the encompassing endomysium is known as a *muscle*[329](Figure 4.10).

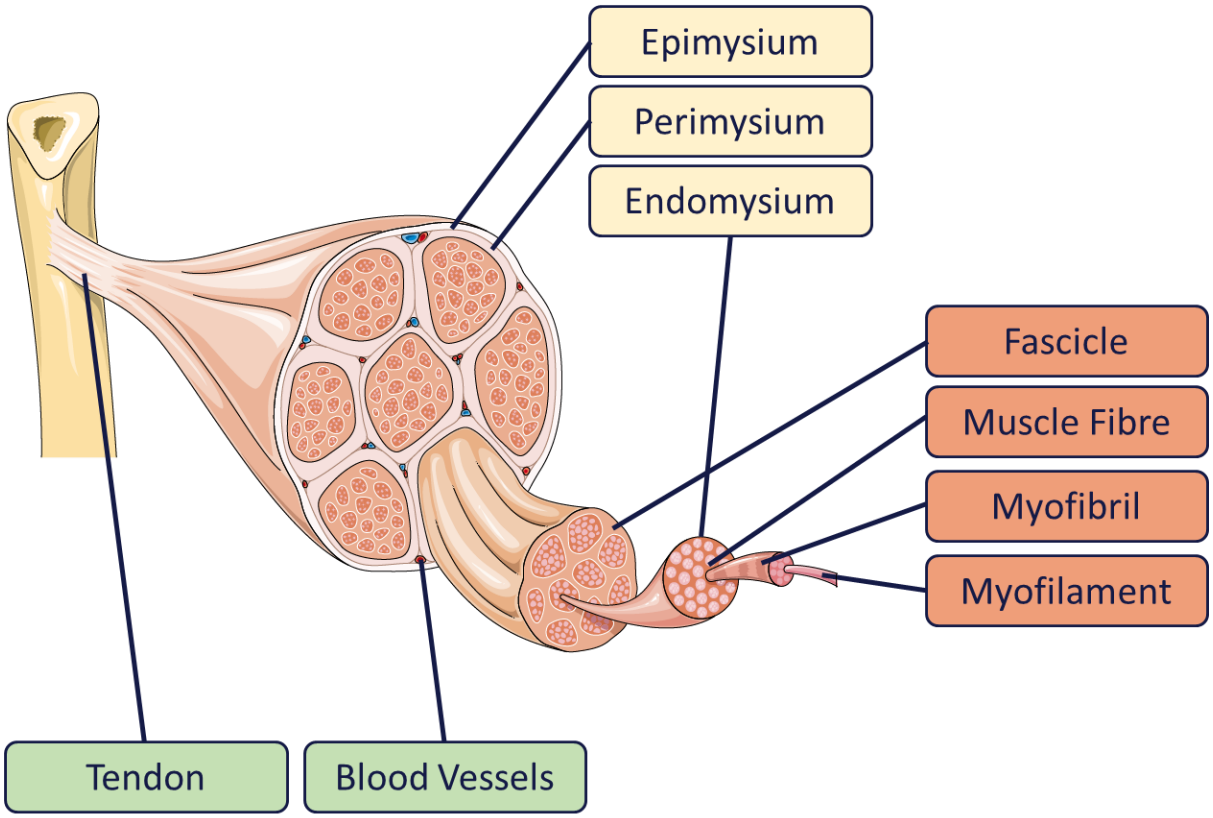


Figure 4.10- Muscle architecture. Adapted from Constantin-Teodosiu[330]*, image from smart.servier.com*[331]*.*

The functional unit of a muscle is the *motor unit* (Figure 4.11). The motor unit is the muscle fibre or group of fibres innervated by a single nerve cell (neuron), with each fibre being innervated by one neuron, though one neuron is usually responsible for innervating multiple

muscle fibres. Muscle contraction is proportionate to the number of motor units recruited and the rate of neuronal firing. Large muscles tend to have large motor units, and though this is associated with a large kinetic force, this is at the expense of fine motor control. Small muscles, conversely, tend to have small motor units, with each neuron being responsible for a small number of muscle fibres. Increasing strength in a muscle contraction, is reliant on *recruitment*, with initially small motor units being activated, followed by larger ones until all motor units forming a muscle are recruited[332] achieving the maximal contraction force.

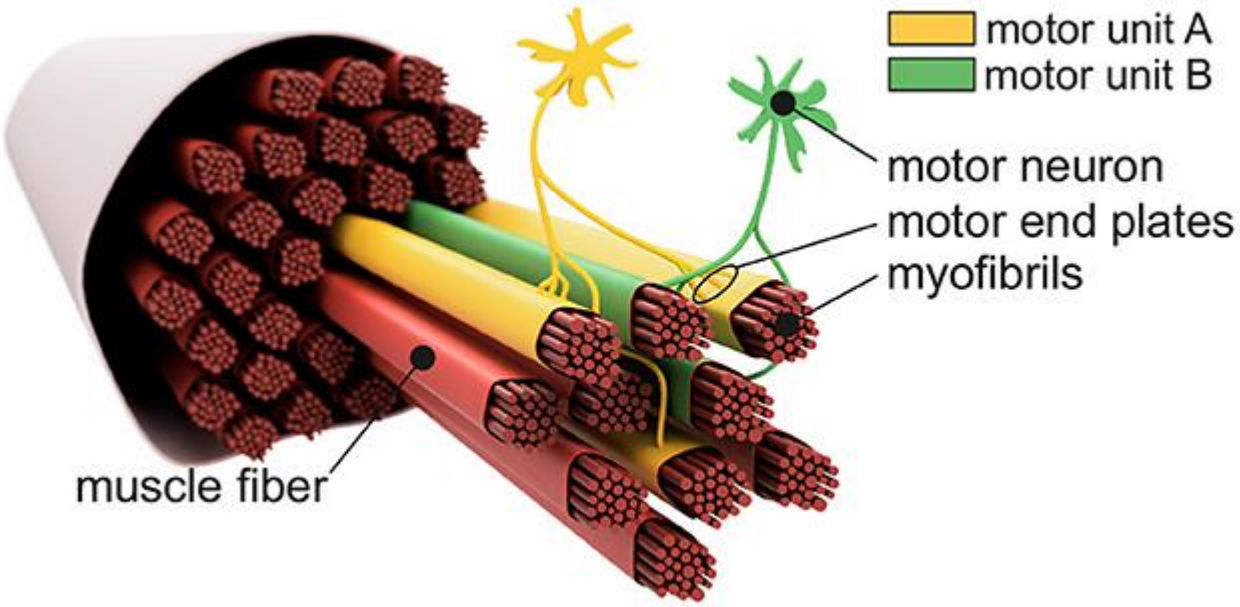


Figure 4.11- An example of two motor units (A & B). The fibres highlighted in yellow are activated by the yellow motor neuron (motor unit A); the fibres highlighted in green, the green motor neuron (motor unit B). Taken from Mechtenberg & Schneider[333].

4.3.2.3.1 Muscle Architecture

The architectural characteristics of muscle can be measured using various parameters (Figure 4.12):

- Cross-sectional area (CSA)

- Muscle thickness: the distance between the superficial and deep aponeuroses
- Pennation angle: the angle of the fascicles relative to the tendon
- Fascicle length: the length of the fascicles running between the aponeuroses/tendon[334].

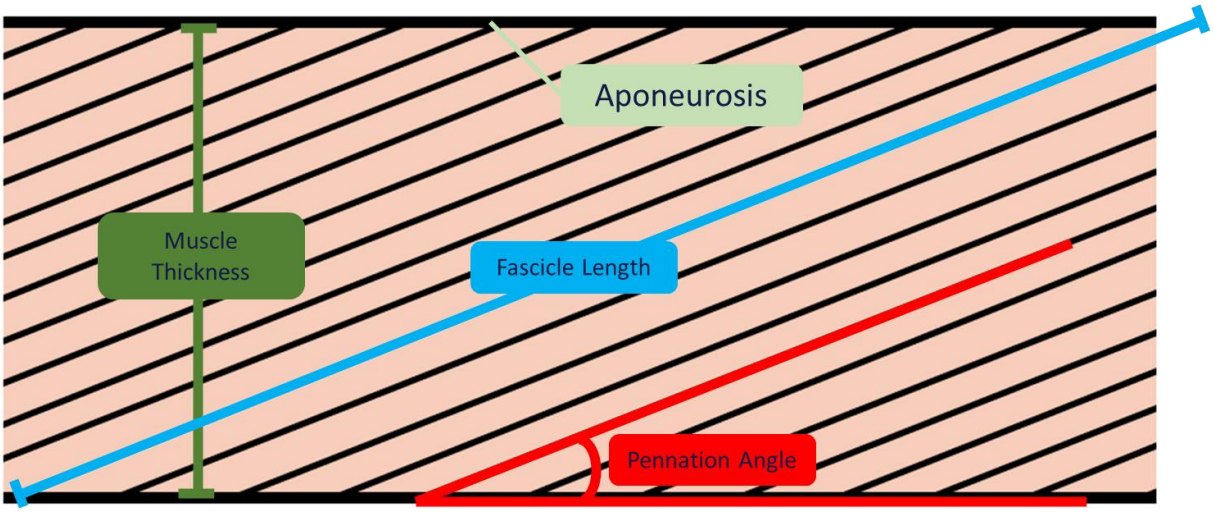


Figure 4.12- A schematic of the architectural characteristics of muscle. Diagonal black lines represent fascicles and the thick, horizontal lines at the top and bottom of the schematic represent the aponeuroses. Note, the length of the measured fascicle (blue) is longer than the imaged muscle, but the aponeurosis can be extrapolated to allow measurement. Adapted from Timmins et al[334].

CSA is representative of muscle size and positively correlated with muscle strength[335]. Both CSA and muscle thickness are increased in following RET interventions in as little as three weeks, even in older adults[336]. Standard RET employees both concentric and eccentric contractions. In a concentric contraction, tension in the muscle rises to meet resistance and remains constant as the muscle shortens; in eccentric contraction, the muscle lengthening as the resistance increases beyond that of the force produced by the muscle[337] (Figure 4.13). Concentric training increases the pennation angle (of VL) and eccentric training, the fascicle

length[334]. Increasing pennation (to a maximum of 90°) allows for a greater CSA of muscle within a given volume and thus a higher force per unit in comparison with a parallel arrangement of fibres[338].

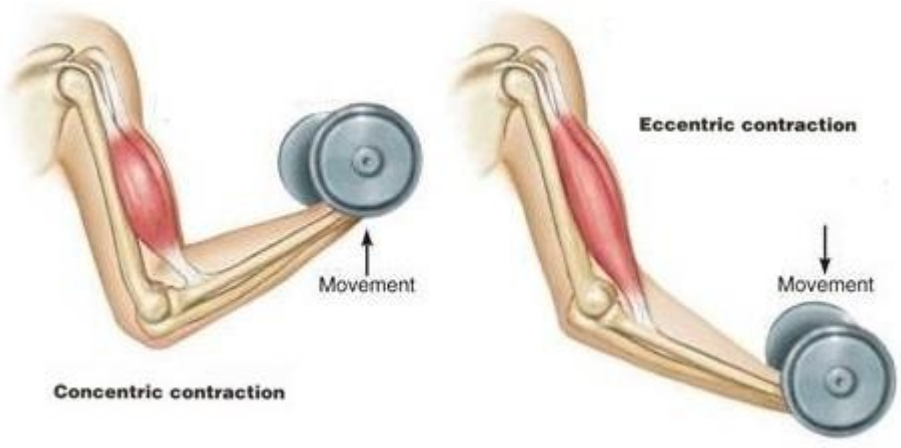


Figure 4.13- Examples of concentric and eccentric muscle contractions. Taken from runningscience.co.za[339].

4.3.2.3.2 Muscle Function

Higher levels of muscular strength may result in better performance and decrease the risk of sports-related injuries in healthy adults. 'Adequate' muscular strength is required to complete ADLs and, in older adults, greater strength improves physical function, QoL and reduces the risk of falls. RET focusses on improving muscle function, and the efficacy of such interventions can be determined using 1-RM; the maximal weight that can be lifted once, whilst maintaining appropriate technique. A 2020 systematic review concluded that 1-RM was a reliable measure of muscular strength regardless of RET, experience, number of familiarisation sessions, exercise selection, anatomical region tested and participant demographics (sex and age)[294].

4.3.2.3.3 Neuromuscular Function

Coordinated movement requires both the intrinsic ability of a muscle and the appropriate recruitment and activation of the motor units that supply it[340]. Considering the motor unit as the smallest unit of muscle function, the ability of the nervous system to simulate a muscle contraction is related to i) the number of motor units activated and; ii) the rate at which the motor neurons discharge action potentials[341]. With advancing age (>50 years) there is a reduction in the strength inherent to each muscle fibre; the total muscle mass available (sarcopenia); and neuromuscular control. This hampers muscle adaptability, and motor performance, and in turn reduces balance, mobility and ADLs[342].

Recruitment of motor units, and thus force generation in a muscle is not a smooth one-off event, but is characterised by dynamic changes in response to sensory feedback leading to the generation of forces around a target (Figure 4.14)[342]. Fluctuations in force can be categorised by the magnitude, and the temporal association (frequency) to one another. Smaller and more frequent 'corrections' in motor unit discharge lead a more accurate force produced over time. The more motor units available for recruitment, the smaller (on average) the motor unit[343] and thus the finer the motor control. With ageing, there is both an increase in the magnitude of the fluctuations and a reduction in their complexity (temporal association)[342]. Further, there is increased instability of the neuromuscular junction[343], a reduction in motor unit remodelling and changes in discharge rates compromising the ability to generate precise force[342]. Specifically, skeletal muscle atrophy that is associated with age (from ~50 years) is matched in terms of motor unit loss[344].

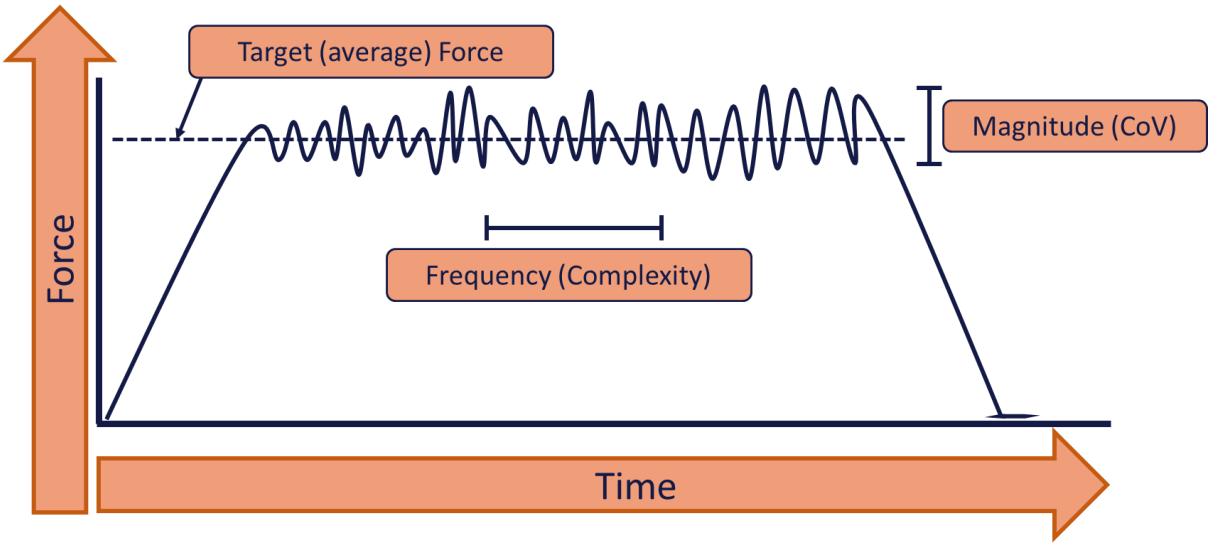


Figure 4.14- Schematic of an isometric contraction. An initial phase of increasing force is followed by a prolonged period of minor fluctuations around a target force. The frequency of the changes in force is considered the complexity and the magnitude of differences between the force produced and the target force is proportional to the CoV. Reproduced from Pethick et al[342].

In isometric contractions, the SD of fluctuations in force scale linearly with the force generated, that is, the larger the force generated, the larger the fluctuations around the target. To combat this, the coefficient of variation (CoV; $\frac{SD}{Mean}$) is commonly used to normalise the fluctuation of forces around the mean over a range of forces produced[342]. A lower value for CoV can be thought of as an increase in force steadiness. Weaker muscles, and muscles with larger motor units have a larger CoV[342] and this can explain a significant amount of variance in performance in functional activities; with higher CoV values relating to poorer scores in walking performance tests and increasing risk of falls in in older adults[345]. The CoV can explain more of the variance in motor performance than the intrinsic strength of an activated muscle[345] and force control is likely more important in terms of functional outcomes than the absolute force a muscle is capable of generating[342].

Considering sarcopenic 'muscle failure'[346] as a reduction in both the amount and 'quality' of muscle as previously described, the combination of this with a reducing ability to precisely control muscle, leads to a lack of functional ability with subsequent impact on ability to perform ADLs and as such, QoL. There is a synergistic relationship between the intrinsic components of a muscle and the neurological stimulation of that muscle (Figure 4.15). Immobility leads to 'disuse muscle atrophy', an effect seen more marked in early immobilisation and in critically unwell individuals[347], yet the loss of motor neurons is seen before a subsequent loss in corresponding muscle mass and associated functional decline[343]. Once motor neurons are lost, they cannot be regained and thus the importance of maintaining muscle function throughout life[340]. Exercise training can slow but not stop this concurrent decline in muscle function/mass and motor unit loss[344], but even light RET can slow some of the increase of CoV seen with ageing[345].

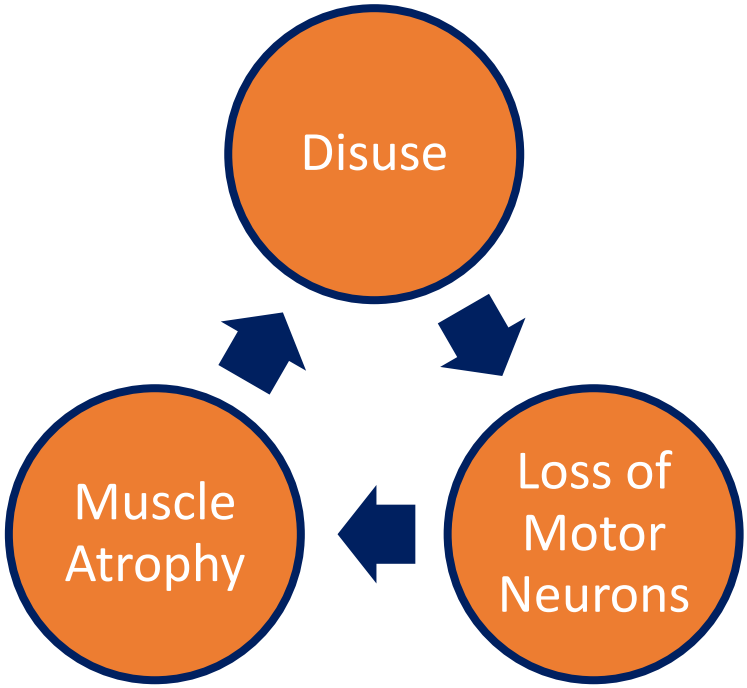


Figure 4.15- A perpetual cycle. Muscle disuse leads to a loss (and function) of motor neurons, which leads to atrophy, which leads to muscle disuse.

Considering cancer, already cachectic muscle is likely to suffer from poor motor unit function. In a murine model with CRC, a loss of motor unit connectivity may contribute to skeletal muscle wasting, perpetuating the cycle described above (Figure 4.15). Novel therapies in the perioperative period such as neuromuscular electrical stimulation can reduce muscle atrophy immediately postoperatively after major abdominal surgery[348]. Given this, an ability to 'bounce back' earlier after an operation may reduce the decline seen in this critical period and this may be stimulated with RET.

4.3.2.3.4 Assessment of Muscle Methodology

4.3.2.3.4.1 Vastus Lateralis Muscle Architecture

The mid-point of the right VL was identified between the greater trochanter and the inferior border of the patella. An ultrasound machine (MyLab™50 scanner, Esaote, Genoa, Italy) with a wide probe (LA923, Esaote), was used to image the VL and still images were captured

parallel to the muscle fibres to evaluate pennation angle. A narrow probe (LA523, Esaote) was then used to capture still images of the midpoint of the right VL for assessment of muscle thickness. Finally, using a panoramic image capture setting (VPAN), the narrow probe was used to gather images which were interrogated for CSA. Each of the aforementioned measurements were taken three times, ensuring the probe was removed and mid-point of the right VL re-evaluated each time.

The captured images (nine per participant per assessment day) were then assessed by a single observer using ImageJ (version 1.54; Wayne Rasband and contributors, National Institutes of Health, USA[349]). Pennation angle was defined as the angle of the intersection of an individual fascicle and the aponeurosis[350]. Angles relating to three fibres were recorded from each image using the angle tool and the process was repeated for all three images, totalling nine measurements of pennation angle per participant per assessment day. Results are reported as a mean of these measurements. After calibrating, measurements of CSA and thickness were performed using the same software using the 'polygon' and 'straight' tools respectively and repeated three times on each of three different images, with the results reported as a mean (Figure 4.16). These methods have previously been validated against the '*Gold standard*' of MRI in measuring changes in muscle seen architecture with hypertrophy and atrophy[351].

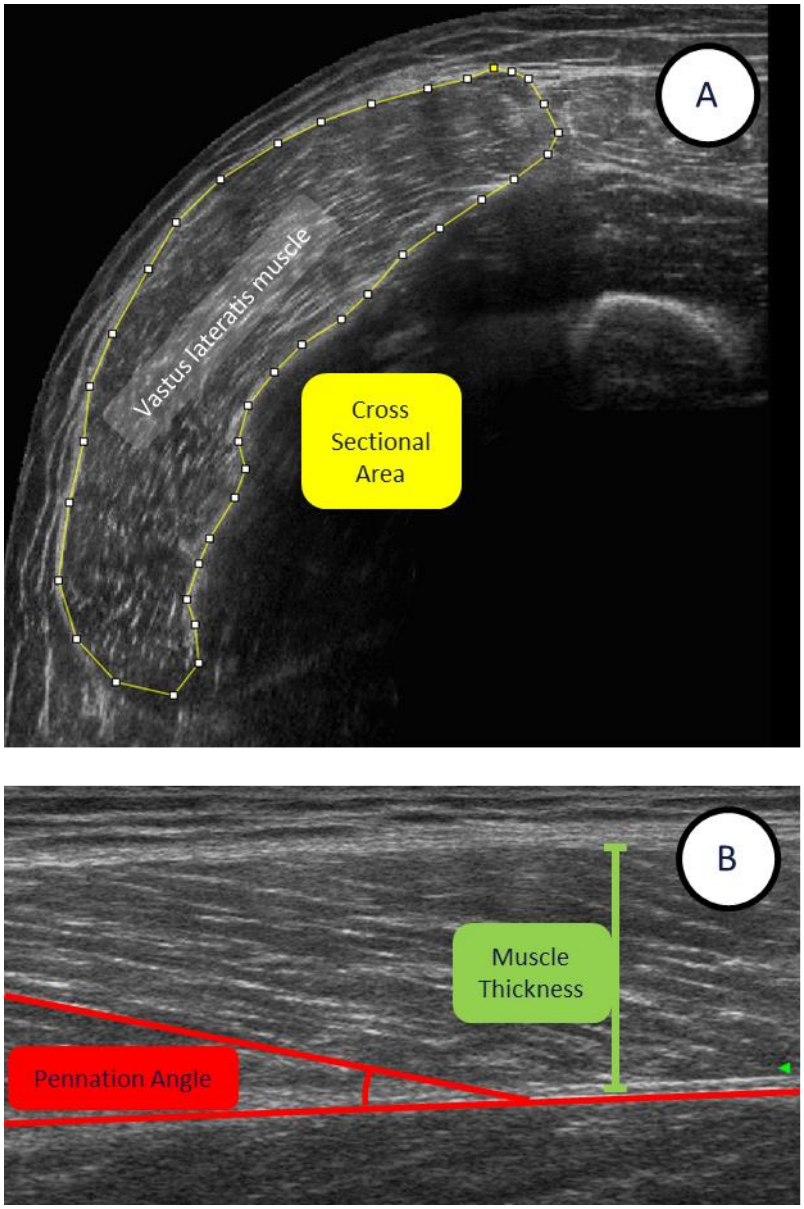


Figure 4.16- Examples of measurements of vastus lateralis cross sectional area (A) and pennation angle & muscle thickness (B). Images of EPiC participants using the methods described in section 4.3.2.3.4.1, cross sectional area highlighted with ImageJ polygon tool[349].

4.3.2.3.4.2 Muscle Function

1-RMs in six modalities were recorded for each participant. Participants were given a demonstration of how to safely use the gymnasium equipment and their understanding ensured. Then, under supervision of a member of the research team, participants would

perform a set of four to eight repetitions with a weight anticipated to be well below the participants 1-RM. This was to ensure adequate form and discuss technique. After a two-minute rest period, a weight was selected by a member of the research team, expected to be at, or above, the 1-RM of the participant. If the participant could lift the weight, maintaining adequate form they were allowed a two-minute rest, and the weight would be increased. If they could not, the weight would be decreased. Once the highest weight increment at which a participant could lift was identified, participants were verbally encouraged to repeat as many repetitions of this as possible in a single set. A calculation ($\frac{Weight}{1.0278-(0.0278\ x\ Number\ of\ Repetitions)}$), described by *Bryzycki* was then used to determine the 1-RM value[352].

4.3.2.3.4.3 Neuromuscular Function

Maximum voluntary isometric contractions (MVC) for the right knee extensors were recorded for each participant using purpose-built equipment ('*The Derby Chair*') in a manor described in detail by Guo *et al.* 2022[353]. Participants were seated upright with knees and hips flexed to 90° and freely swinging above the floor. A waistbelt counteracted truncal movement and the right leg was immobilised above the ankle with a non-compliant strap connected to an isometric force dynamometer (Load cell amplifier; LCA1,12V1A medical PSU, GDM25B12-P1J, Sunpower Electronics, Reading, UK) which measured the force from knee extension. After a standardised warm-up of submaximal contractions, a verbal prompt was given, and participants were encouraged to extend their knee with as much force as possible. This was repeated three times with the best value from three attempts recorded as MVC. Concurrently, participants looked at a computer screen where software (Spike software

version 9.06; Cambridge Electronic Design, Cambridge, United Kingdom) gave a visual aid to help to compare forces between attempts.

Based on the value for MVC, participants were then asked to hold a voluntary contraction at 10%, 25% and 40% of the value of MVC for 15 seconds after a brief (~2s) increase to the target force. Again, this was aided by a visual aid the denoting measured versus target force (Figure 4.17). The figures of 10%, 25% and 40% were chosen as this range is representative of ADLs including walking and climbing stairs[354].

Data were analysed using OT BioLab+ version 1.6.0.0 (OT Bioelettronica S.rl.; Torino, Italy) with the outputted .mat file further analysed using MATLAB R2023a version 9.14.0.2286388 (The MathWorks Inc.; Massachusetts, USA) to calculate CoV.

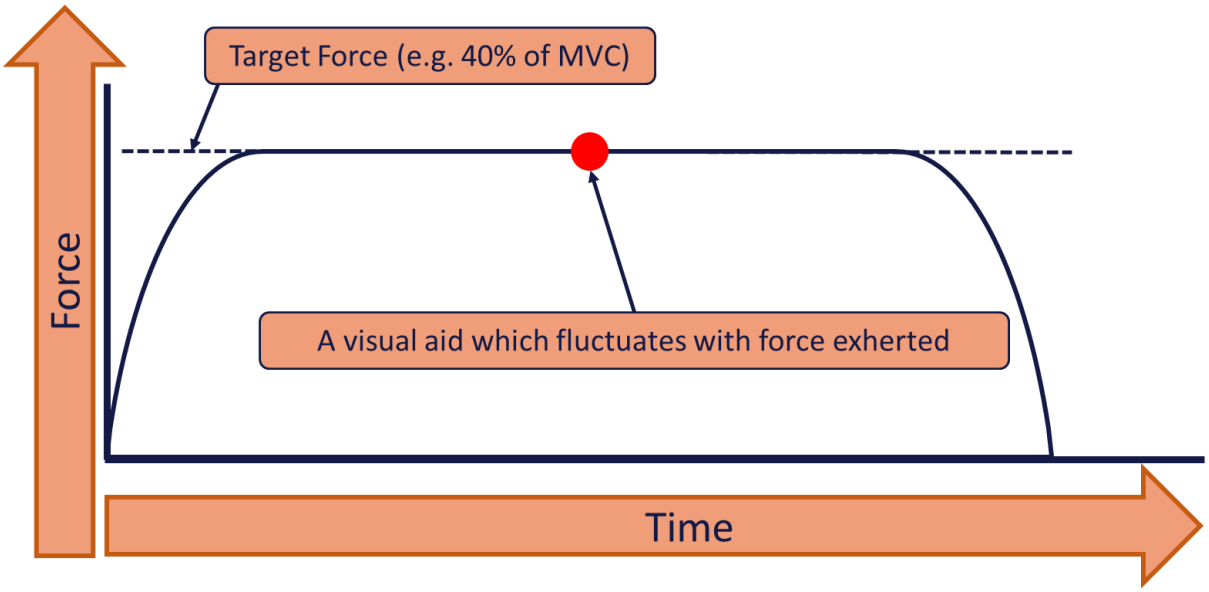


Figure 4.17- A schematic of the visual aid given to participants during measurement of CoV for 10%, 25% and 40% of MVC. The red circle represents the force produced by a participant.

If the particiapnt produced a larger force, the circle would move upwards, deviating from the target force line.

4.3.2.4 Other Aspects of EPiC Assessment

Though not described in this thesis, further assessments on autonomic nervous function (ANF), MPS, MPB, muscle protein turnover, and dietary monitoring were also undertaken.

4.3.2.4.1 Autonomic Nervous Function

ANF was recorded using an iPad (Apple inc.; California, USA) app, ANS Analysis (Commit GmbH; Salzgitter, Germany), paired via Bluetooth with a HR monitor (R1 Duo Comfortex ANT+; SIGMA-ELEKTRO, Neustadt, Germany). Participants were initially asked to lie supine, in a relaxed fashion whilst their HR was monitored. A second assessment monitored the autonomic response to standing up whereby the change in HR was monitored after switching from a period of lying to a period of standing. No further analysis of ANF measured by these means are described or reported on in this thesis.

4.3.2.4.2 Muscle Protein Synthesis, Breakdown & Turnover

To track MPS, MPB and whole-body contractile mass participants were asked to take tracers (Deuterium Oxide, D3-Methylhistidine and D3-Creatine; see Appendix D- EPiC Study Protocol) and the concentration of chemicals in the tracers were tracked. Beyond a description of the process undertaken regarding tracers and specimen collection, no further analysis of MPS, MPB or whole-body contractile mass is described or reported on in this thesis.

4.3.2.4.2.1 Muscle Protein Synthesis

To track MPS, participants consumed 3mL/Kg of D_2O 72 hours prior to their first assessment day, 72 hours after their first assessment day, and every seven days thereafter until surgery. They then continued to consume D_2O every seven days starting on the day immediately after

surgery. 1-5ml saliva samples were taken immediately prior to, and two hours after, each dose of D_2O in addition to further saliva sampling on the assessment days. Participants were instructed to fast for 30 minutes prior to each saliva sample. On each assessment day, willing and able participants had a biopsy of the left VL muscle which was performed by a doctor with current NHS practice using anatomical or ultrasound guidance and local anaesthetic.

4.3.2.4.2.2 Muscle Protein Breakdown

Each participant consumed D3-Methylhistidine (D3-MH) 18 hours prior to the start of each assessment day. At the beginning of the assessment day, after a period of at least 6 hours fasting, participants had a cannula inserted for venous sampling. Blood was taken at 0, 45, 135, 180 and 225 minutes using the cannula which was kept functional using 0.9% normal saline. Participants were allowed to drink water throughout this period.

4.3.2.4.2.3 Whole-Body Contractile Mass

Participants consumed 30mg of D3-Creatine (D3-Cr) 72 hours prior to the start of each assessment day to help quantify whole-body muscle mass. In addition, total urine collection was performed between 72 and 48 hours prior to the assessment day, with further spot collections at 24 hours before and on the morning of the assessment day.

4.3.2.4.3 Dietary Intake Monitoring

Measurement of dietary intake was performed using a paper diet diary in which participants were asked to record, what food and drink they consumed over four, 24-hour, periods at four periods over the study: after screening but prior to starting exercise; during the exercise intervention; immediately postoperatively and approximately three to four weeks postoperatively. No further analysis or of this is described or reported in this thesis.

4.3.2.4.1 Balance

Balance was measured on all assessment days. Participants were asked to remove their shoes and stand on a pressure sensitive plate (footscan 1m EL; RScan International NV, Paal, Belgium), keeping as still as possible for 30 seconds using both feet, right foot only and left foot only (totalling three readings). Data were recorded on footscan (version 9; Materialise NV, Leuven, Belgium). Participants who could not balance on a single limb for 30 seconds were instructed to weight shift onto both limbs and then back onto the measured limb, maximising the proportion of the 30 seconds window that was on the appropriate limb. No further analysis of balance using this method is described or reported on in this thesis.

4.3.2.4.1 Spirometry

Spirometry was undertaken using a calibrated spirometer (Microlab Mk8 Spirometer; Vyaire Medical GmbH, Höchberg, Germany). Demographic information was recorded to aid interpretation. Participants were instructed to sit upright and a nasal clip was fitted ensuring no air was lost via the nose. Participants were then told to inhale as much as possible, and exhale as fast as possible and for as long as possible. Verbal encouragement was given throughout and a minimum of three and a maximum of eight recordings were taken in line with the British Thoracic Society Guidelines[355]. Results were stored for each participant. No further analysis of spirometry using this method is described or reported on in this thesis.

4.3.3 Statistical Analysis

Power calculations for the whole EPiC study were performed by Dr Doyo Enki, Senior Medical Statistician, University of Nottingham. Based on a power of 90%, the n of each arm was determined to be 18. Computed simulations determined n=20 so a target of n=22 per arm was chosen to ensure power >90%. Based on an assumed attrition rate in similar studies

conducted by the group of ~20%, and postoperative clinical complication rate of ~7%, the aimed recruitment was n=56; 28 in each arm. Full details are available in Appendix D- EPiC Study Protocol. All other statistical analysis described in this thesis was performed using GraphPad Prism (GraphPad Version 10.2.0, GraphPad Software, Boston, USA).

Differences in baseline statistics were compared using Student's t-test for normally distributed data. Categorical data, where ≥80% of values were >5, were interrogated via Pearson's Chi-squared; if this assumption was not met, Fisher's exact test was utilised[356]. Normally distributed data were analysed using an unpaired t-test (two groups) or two-way ANOVA (>two groups); mixed-effects modelling using *Tukey's Honestly Significant Difference Test* was used to allow for missing data. Non-normally distributed data were analysed using non-parametric testing: a Mann-Whitney U test (two groups) or a Kruskal-Wallis H test (> two groups). Results are reported as mean values ± SD for normally distributed data, and median and interquartile range (IQR) for non-normally distributed data. Graphically, for normally distributed data, error bars represent SD and for non-normally distributed data, error bars represent IQR. Statistical significance is commented on with regard to p-value and effect size. A p-value of ≤0.05 is considered significant and is referred to graphically with an asterisk (*); a p≤0.01 is referred to as '**'; p≤0.001 '***' etc. Non-commented on comparisons can be considered statistically non-significant, but where important, non-significance has been commented on (NS).

4.3.3.1 Missing Data

Mixed-effects modelling as described in chapter 4.3.3 was used to allow for missing data. Missing data is reported both from the number of participants included and for absolute values. Only participants who generated any datapoint for each test is included in the missing

data statistics. For example, if data were available for 26 participants (out of 28 total), this means that two participants did not undergo testing in the reported modality at any time. If a participant underwent testing at a single timepoint only, this would be described as two missing values.

4.4 Results

4.4.1 Participant Demographics

Between July 2023 and December 2024, a total of 152 patients were identified as 'potentially eligible' for the EPiC study; 28 participants were enrolled (Figure 4.18).

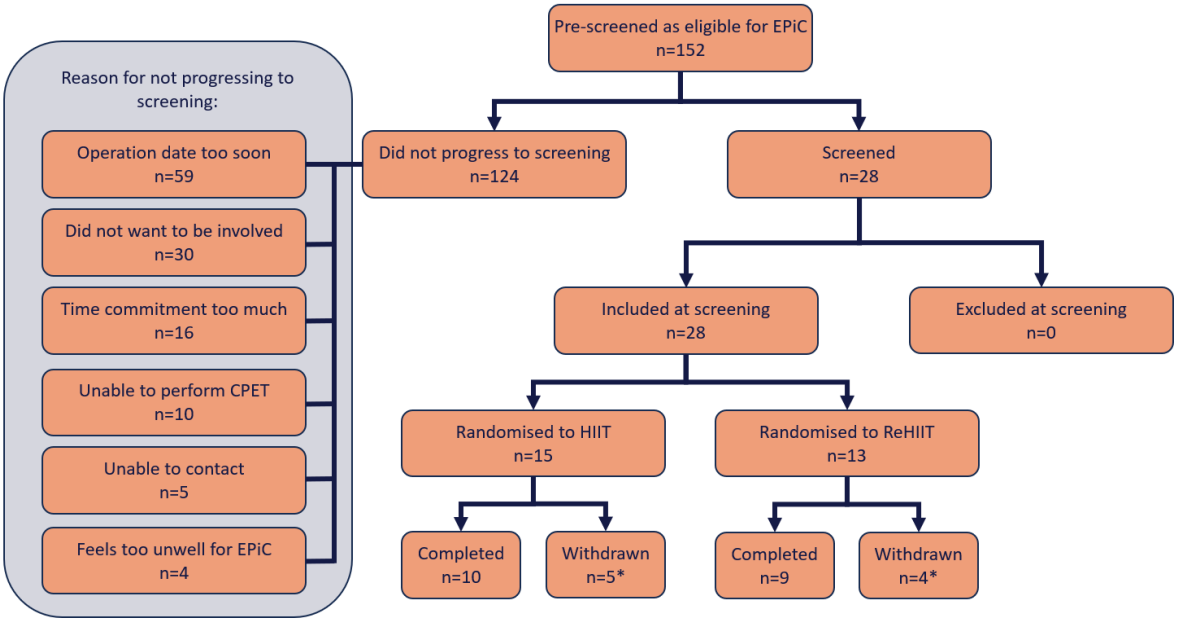


*Figure 4.18- A flow diagram detailing pre-screening, screening, enrolment, randomisation and completion of the EPiC study between July 2023 and December 2024. *- Reasons for withdrawal detailed in Table 4.2.*

15 participants were randomised to the HIIT group and 13 to the ReHIIT group; 19 participants completed all three assessment days (HIIT=10; ReHIIT=9); four completed the baseline and preoperative assessment day only (HIIT=2; ReHIIT=2); four only completed the baseline assessment day (HIIT=3; ReHIIT=1) and one participant enrolled but did not attend any assessment days (ReHIIT). Participant demographics are summarised in Table 4.1; reasons for withdrawal are detailed in Table 4.2.

		HIIT	ReHIIT	p-Value
n (%)		15 (53.6)	13 (46.4)	-
Age [mean, (SD)]		63.8 (7.30)	63.6 (10.19)	0.96[a]
Sex [M:F]		8:7	6:7	0.70[b]
Tumour Location (n)	Caecum	4	2	-
	Ascending Colon	4	3	
	Transverse Colon	0	1	
	Descending Colon	2	2	
	Sigmoid Colon	3	5	
	Rectum	2	0	
Operation Type	Right Hemicolectomy	7	5	-
	Extended Right Hemicolectomy	1	0	
	Left Hemicolectomy	0	2	
	Anterior Resection	5	4	
	Subtotal Colectomy	0	1	
	Panproctocolectomy	1	0	
	Completion Colectomy	0	1	
	N/A	1	0	
Operative Approach	Open	6	4	0.64[b] (excluding N/A)
	Laparoscopic	5	7	
	Robotic	3	2	
	N/A	1	0	
Postoperative Histology	Adenocarcinoma	13	13	1.00[c] (excluding N/A)
	Low-grade Dysplasia	1	0	
	N/A	1	0	
Adjuvant Chemotherapy	Yes	5	7	0.34[b] (excluding N/A)
	No	9	6	
	N/A	1	0	
Length of Exercise Period* (Baseline Assessment +1 to Preoperative Assessment -1; days) [mean, (SD)]		22.9 (8.52)	25.7 (11.00)	0.57[a]
Completed Exercise Intervention (y:n)		12:3	11:2	1.00[c]
Number of Exercise sessions* [mean, (SD)]		n=12 8.8 (0.99)	n=11 9.5 (0.99)	0.16[a]
Time (days) between Operation and 6-week Postoperative Assessment Day* [mean, (SD)]		n=10 43.3 (4.05)	n=9 42.2 (2.66)	0.53[a]

*Table 4.1- Participant Demographics from the EPiC Study. [a]- Student's t-test; [b]- Pearson's Chi-squared test; [c]- Fisher's Exact test. *****- Data included for participants who completed the exercise period only.*

Group	ID	Point of Withdrawal	Reason for Withdrawal
ReHIIT	EPiC_004_LH	Prior to V1	Felt unwell, then not enough time for exercise sessions
ReHIIT	EPiC_006_TD	Prior to V2	Operation date brought forward
HIIT	EPiC_007_MK	Between V2 and V3	Operation postponed
HIIT	EPiC_008_DW	Prior to V2	Operation date brought forward
HIIT	EPiC_012_JC	On V1	Medical Decision due to issues found on CPET
ReHIIT	EPiC_013_RH	Between V2 and V3	Did not feel well enough for A3
HIIT	EPiC_018_RH	Between V2 and V3	Unwell on date of A3 then started chemotherapy
HIIT	EPiC_021_MS	Between V2 and V3	Withdrawn at the research teams discrepancy
ReHIIT	EPiC_027_SL	Between V2 and V3	Did not feel well enough for A3

Table 4.2- Reasons for, and timing of, withdrawal from the EPiC study. V1= Assessment 1; V2= Assessment 2; V3= Assessment 3.

4.4.1 Cardiorespiratory Fitness

4.4.1.1 Maximum Wattage

Data were available for 26 participants with 10 missing values. There was no statistically significant difference in maximum wattage between HIIT and ReHIIT groups at baseline (MD: -11.24 w; CIs: -52.66 – 30.19; p=0.58). The HIIT group had a significant increase in maximum wattage between baseline and preoperative assessments (MD: 11.25 w; CIs: 5.43 – 17.07; p=0.0008) and a significant decrease in maximum wattage between preoperative and 6-week postoperative assessments (MD: -10.20w; CIs: -17.02 – -3.38; p=0.006). There was no difference in the HIIT group between baseline and 6-week postoperative assessment (p=0.99). The ReHIIT group had a significant increase in maximum wattage between baseline and preoperative assessments (MD: 11.73 w; CIs: 5.29 – 18.16; p=0.0014) and a significant decrease in maximum wattage between preoperative and 6-week postoperative assessments (MD: -18.8 w; CIs: -32.6 – -4.94; p=0.01). There was no difference between baseline and 6-week postoperative assessment in the HIIT (p=0.99) or ReHIIT group (p=0.23). Overall, there was a significant time (p<0.0001) but not exercise group (p=0.48) effect (Figure 4.19).

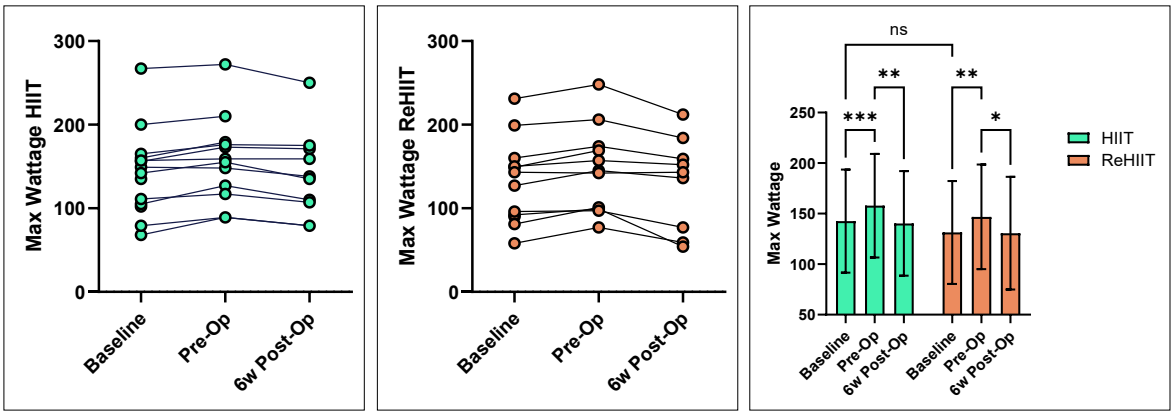


Figure 4.19- Individual changes in maximum wattage for participants in the HIIT group; ReHIIT group and; mean difference in maximum wattage for HIIT & ReHIIT groups between

baseline, preoperative and 6-week postoperative assessments. A total of 68 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.1.2 Maximum Heart Rate

Data were available for 26 participants with 10 missing values. There was no statistically significant difference in maximum HR between HIIT and ReHIIT groups at baseline (MD: -2.9 BPM; CIs: -15.4 – 9.55; p=0.63). There was no significant time (p=0.86) or exercise group (p=0.76) effect (Figure 4.20).

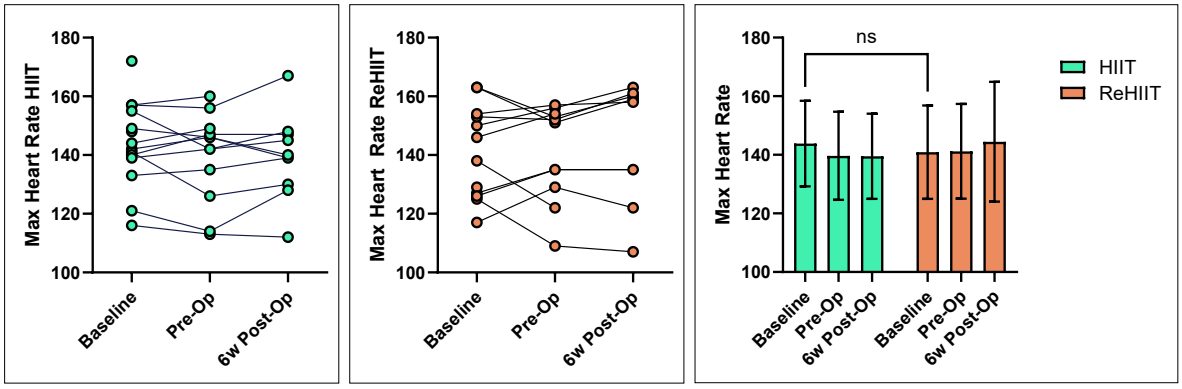


Figure 4.20- Individual changes in maximum heart rate for participants in the HIIT group; ReHIIT group and; mean difference in maximum heart rate for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 68 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.1.3 Heart Rate Recovery

Data were available for 26 participants with 14 missing values. There was no statistically significant difference in HRR between HIIT and ReHIIT groups at baseline (MD: -3.12 BPM 1min; CIs: -11.47 – 5.24; p=0.45). There was a significant time (p=0.01) but no exercise group (p=0.94) effect (Figure 4.21). There were no significant changes in either group between any study timepoint.

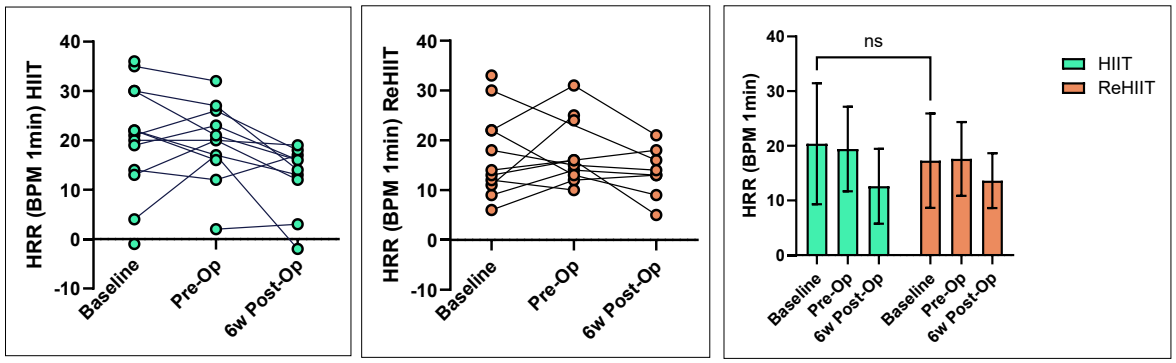


Figure 4.21- Individual changes in heart rate recovery for participants in the HIIT group; ReHIIT group and; mean difference in heart rate recovery for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 64 datapoints; datapoints may appear stacked. Analysis Analysis via mixed-effects analysis.

4.4.1.4 VO_{2Peak}

4.4.1.4.1 Absolute VO_{2Peak}

Data were available for 26 participants with 10 missing values. There was no statistically significant difference in VO_{2Peak} between HIIT and ReHIIT groups at baseline (MD: -0.02 L/min; CIs: -0.51 – 0.46; p=0.92). The HIIT group had a significant increase in VO_{2Peak} between baseline and preoperative assessment (MD: 0.16 L/min; CIs: 0.04 – 0.28; p=0.0097) and a significant decrease in VO_{2Peak} between preoperative and 6-week postoperative assessment (MD: -0.16 L/min; CIs: -0.24 – -0.07; p=0.0012). The ReHIIT group had a significant increase in VO_{2Peak} between baseline and preoperative assessment (MD: 0.10 L /min; CIs: 0.02 – 0.18; p=0.01) and a significant decrease in VO_{2Peak} between preoperative and 6-week postoperative assessment (MD: -0.27 L/min; CIs: -0.47 – -0.07; p=0.01). There was no difference in the HIIT (p=0.72) or ReHIIT (p=0.19) group between baseline and 6-week postoperative assessment. Overall, there was a significant time (p=0.0499) but not exercise group (p=0.68) effect (Figure 4.22).

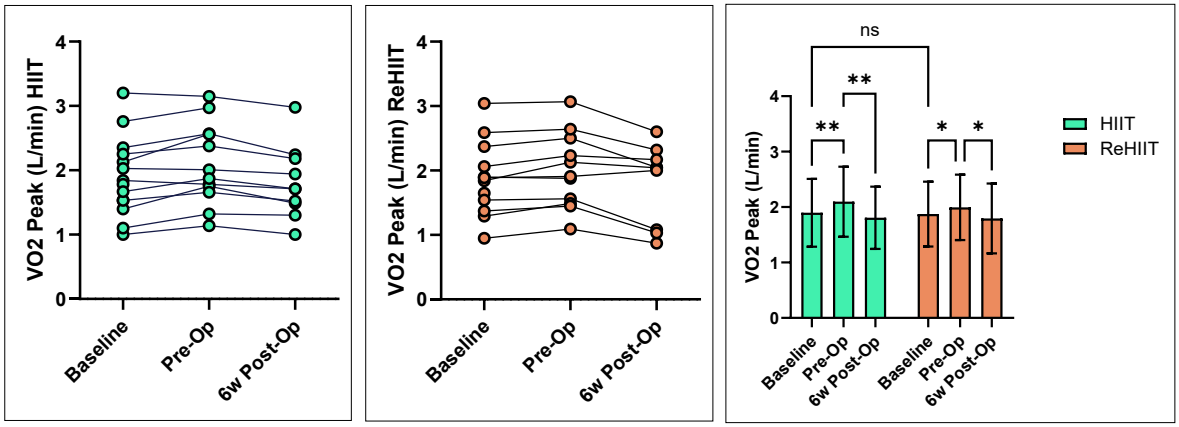


Figure 4.22- Individual changes in Absolute VO_{2Peak} for participants in the HIIT group; ReHIIT group and; mean difference in VO_{2Peak} for HIIT & ReHIIT groups between baseline,

preoperative and 6-week postoperative assessments. A total of 68 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.1.4.2 VO_{2Peak} per Kilogram Bodyweight

Data were available for 26 participants with 10 missing values. There was no statistically significant difference in VO_{2Peak}/Kg body weight (BW) between HIIT and ReHIIT groups at baseline (MD: 1.04 mL/Kg BW/min; CIs: -6.56 – 4.47; p=0.70). The HIIT group had a significant increase in VO_{2Peak}/Kg BW between baseline and preoperative assessments (MD: 1.73 mL/Kg BW/min; CIs: 0.62 – 2.85; p=0.004) and a significant decrease in VO_{2Peak}/Kg BW between preoperative and 6-week postoperative assessments (MD: -1.19 mL/Kg BW/min; CIs: -2.03 – -0.36; p=0.008). There was no difference in the HIIT group between baseline and 6-week postoperative assessment (p=0.71). The ReHIIT group had a significant increase in VO_{2Peak}/Kg BW between baseline and preoperative assessments (MD: 1.40 mL/Kg BW/min; CIs: 0.54 – 2.24; p=0.003) and a significant decrease in VO_{2Peak}/Kg BW between preoperative and 6-week postoperative assessments (MD: -2.21 mL/Kg BW/min; CIs: -4.18 – -0.25; p=0.23). There was no difference in the HIIT (p=0.71) or ReHIIT (p=0.60) group between baseline and 6-week postoperative assessment. Overall, there was no significant time (p=0.05) or exercise group (p=0.56) effect (Figure 4.23).

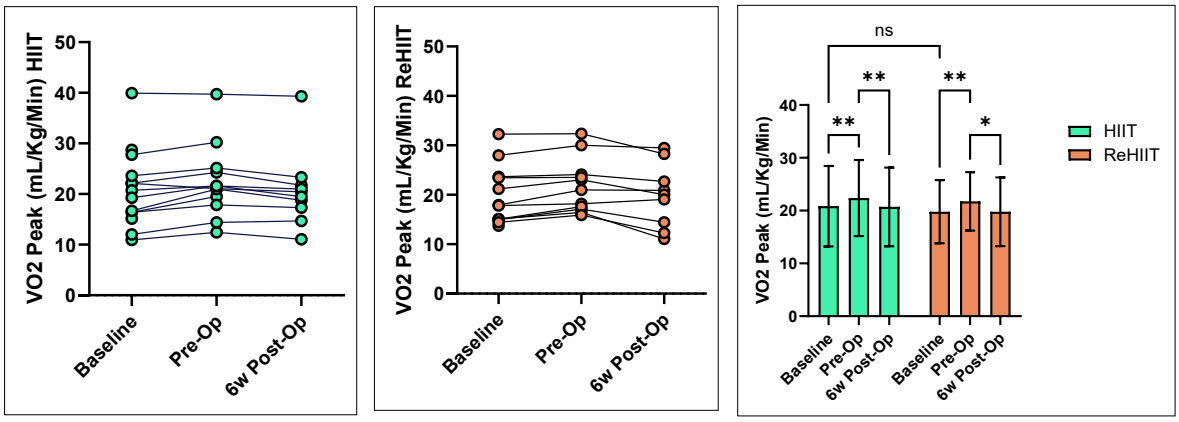


Figure 4.23- Individual changes in VO_{2Peak}/Kg body weight (BW) for participants in the HIIT group; ReHIIT group and; mean difference in VO_{2Peak}/Kg BW for HIIT & ReHIIT groups between

baseline, preoperative and 6-week postoperative assessments. A total of 68 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.1.4.3 VO_{2Peak} per Kilogram Lean Mass

Data were available for 21 participants with 9 missing values. There was no statistically significant difference in VO_{2Peak}/Kg lean mass (LM) between HIIT and ReHIIT groups at baseline (MD: 0.53 mL/Kg LM/min; CIs: -9.58 – 10.6; p=0.91). The HIIT group had a significant decrease in VO_{2Peak}/Kg LM between preoperative and 6-week postoperative assessments (MD: -3.2 mL/Kg LM/min; CIs: -5.57 – -0.83; p=0.01). There was no difference in the HIIT (p=0.39) or ReHIIT (p=0.15) group between baseline and 6-week postoperative assessment. Overall, there was no significant time (p=0.06) or exercise group (p=0.68) effect (Figure 4.24).

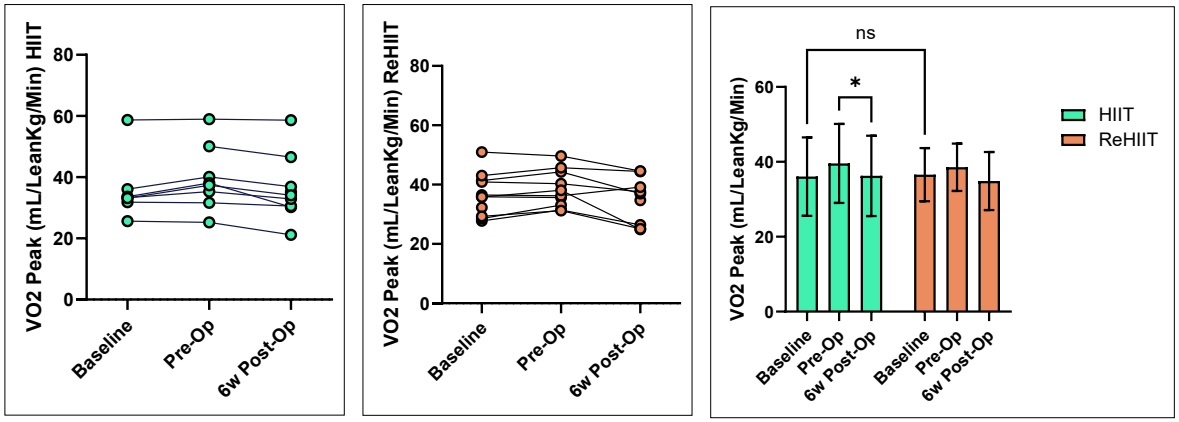


Figure 4.24- Individual changes in VO_{2Peak}/Kg lean mass (LM) for participants in the HIIT group; ReHIIT group and; mean difference in VO_{2Peak}/Kg LM for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 54 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.1.5 Anaerobic Threshold

4.4.1.5.1 Absolute Anaerobic Threshold

Data were available for 26 participants with 10 missing values. There was no statistically significant difference in AT between HIIT and ReHIIT groups at baseline (MD: 0.09 L/min; CIs: -0.23 – 0.41; p=0.56). There was a significant decrease in AT between preoperative and 6-week postoperative assessment in the ReHIIT group (MD: -0.21 L/min; CIs: -0.34 – -0.10; p=0.002). There was a significant time (p=0.01) but not exercise group (p=0.97) effect (Figure 4.25).

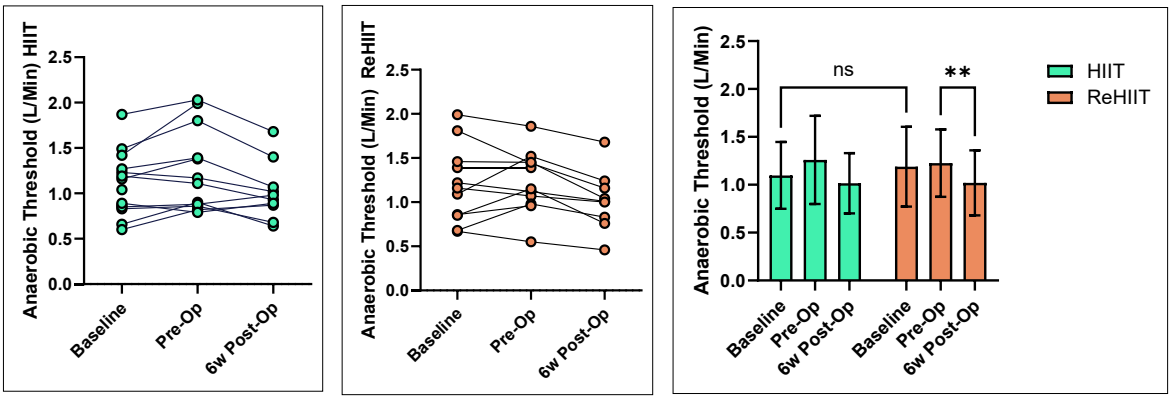


Figure 4.25- Individual changes in absolute anaerobic threshold for participants in the HIIT group; ReHIIT group and; mean difference in absolute anaerobic threshold for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 68 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.1.5.2 Anaerobic Threshold per Kilogram Bodyweight

Data were available for 26 participants with 10 missing values. There was no statistically significant difference in AT/Kg BW between HIIT and ReHIIT groups at baseline (MD: 0.59 mL/Kg BW/min; CIs: -3.16 – 4.34; p=0.75). There was a significant decrease in AT per Kg BW between preoperative and 6-week postoperative assessment days in the ReHIIT group (MD: -2.03 mL/Kg/min; CIs: -3.53 – -0.54; p=0.01). There was a significant time (p=0.01) but not exercise group (p=0.97) effect (Figure 4.26).

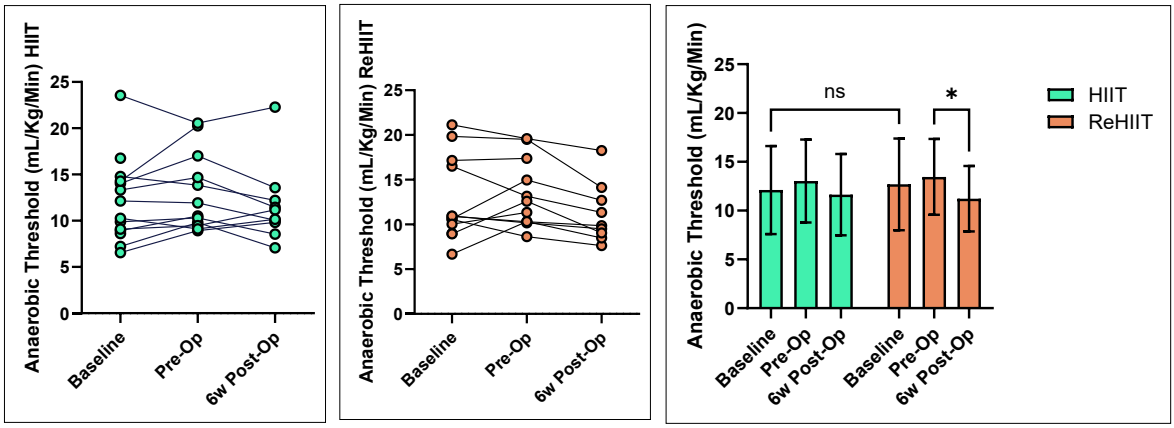


Figure 4.26- Individual changes in anaerobic threshold/ Kg bodyweight (BW) for participants in the HIIT group; ReHIIT group and; mean difference in anaerobic threshold/ Kg BW for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 68 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.1.5.3 Anaerobic Threshold per Kilogram Lean Mass

Data were available for 21 participants with 9 missing values. There was no statistically significant difference in AT/ Kg LM between HIIT and ReHIIT groups at baseline (MD: 2.97 mL/Kg LM/min; CIs: -2.67 – 8.60; p=0.28). There was a significant decrease in AT/ Kg LM between preoperative and 6-week postoperative assessment in the ReHIIT group (MD: -3.52 mL/Kg LM/min; CIs: -6.36 – -0.68; p=0.02). There was a significant time (p=0.03) but not exercise group (p=0.67) effect (Figure 4.27).

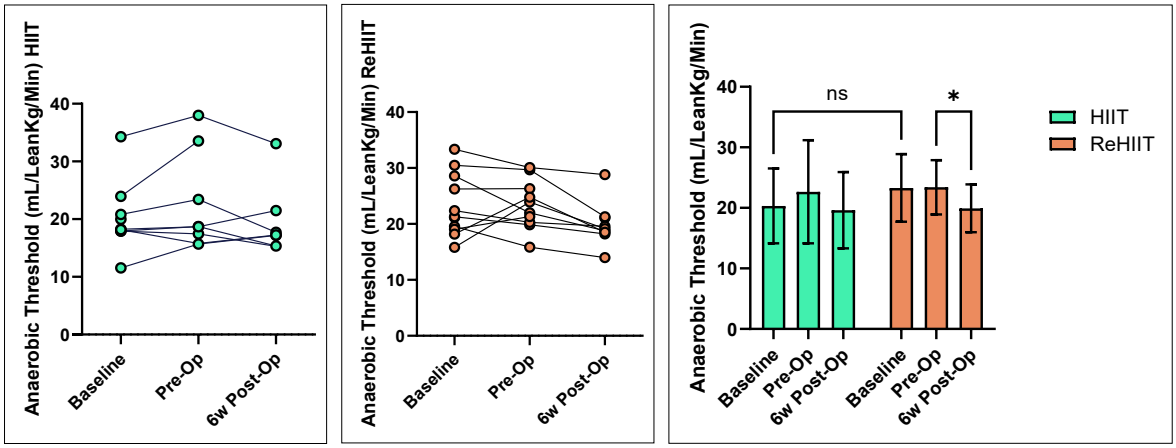


Figure 4.27- Individual changes in anaerobic threshold/ Kg lean mass (LM) for participants in the HIIT group; ReHIIT group and; mean difference in anaerobic threshold/ Kg LM for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 54 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.2 Body Composition

4.4.2.1 Weight

Data were available for 27 participants with 12 missing values. There was no statistically significant difference in weight between HIIT and ReHIIT groups at baseline (MD: 3.12 Kg; CIs: -9.70 – 15.94; p=0.62). There was a significant decrease in weight between baseline and 6-week postoperative (MD: -2.7 Kg; CIs: -4.84 – -0.62; p=0.01) and preoperative and 6-week postoperative (MD: -2.16 Kg; CIs: -3.85 – -0.47; p=0.02) assessments in the HIIT group. There was a significant decrease in weight between baseline and 6-week postoperative assessments (MD: -4.8 Kg; CIs: -8.42 – -1.21; p=0.01) in the ReHIIT group. There was a significant time (p<0.0001) but no exercise group (p=0.74) effect (Figure 4.28).

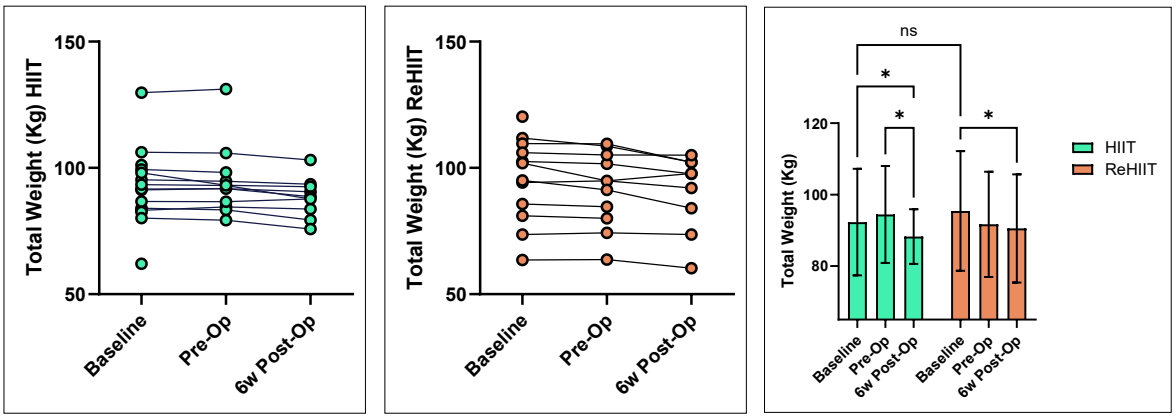


Figure 4.28- Individual changes in total weight for participants in the HIIT group; ReHIIT group and; mean difference in anaerobic total weight for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 69 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.2.2 Lean Mass

Data were available for 22 participants with 11 missing values. There was no statistically significant difference in lean mass between HIIT and ReHIIT groups at baseline (MD: -1.99 Kg; CIs -9.32 – 5.33; p=0.58). There was no significant time (p=0.08) or exercise group (p=0.80) effect (Figure 4.29).

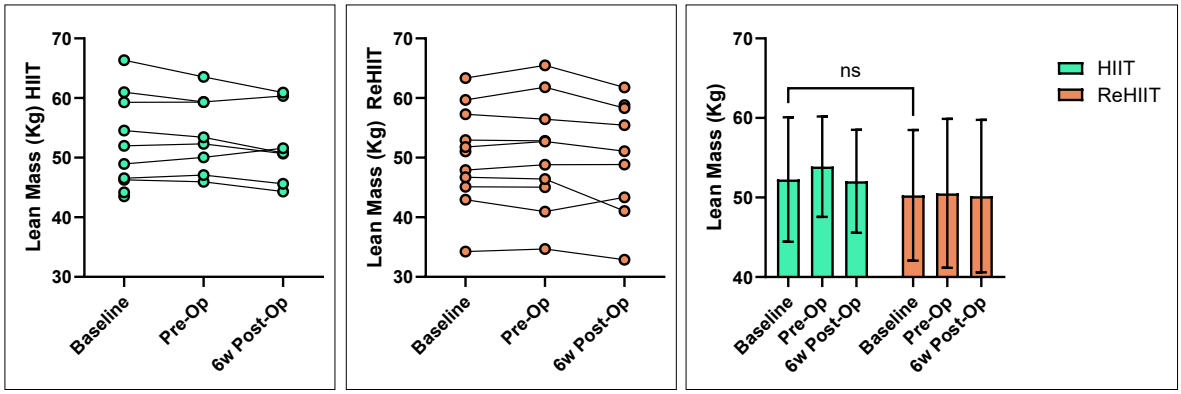


Figure 4.29- Individual changes in lean mass for participants in the HIIT group; ReHIIT group and; mean difference in lean mass for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 55 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.2.3 Percentage Body Fat

Data were available for 22 participants with 11 missing values. There was no statistically significant difference in %BF between HIIT and ReHIIT groups at baseline (MD: 3.84 %; CIs: -4.03 – 11.71; p=0.32). There was a significant decrease in %BF between baseline and preoperative assessment days in the ReHIIT group (MD: -1.14 %; CIs: -1.61 – -0.68; p=0.0002). There was a significant time (p=0.04) but not exercise group (p=0.43) effect (Figure 4.30).

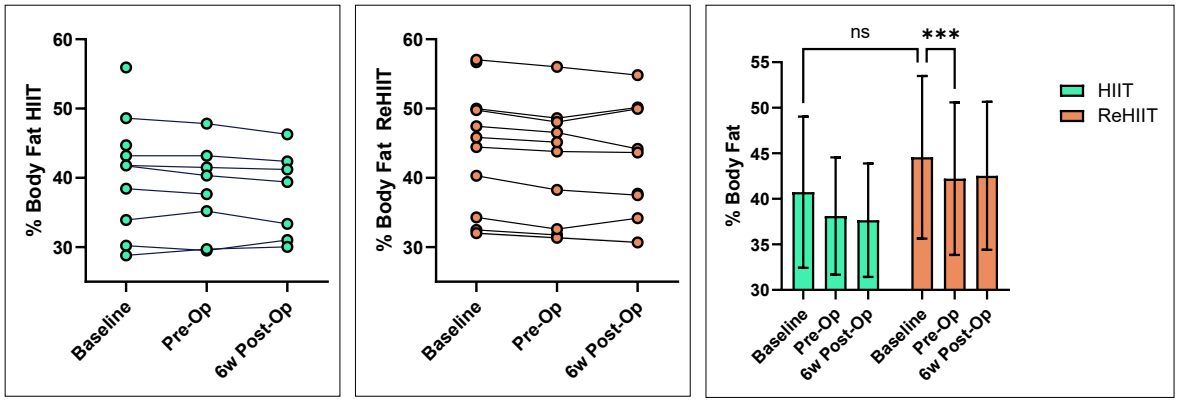


Figure 4.30- Individual changes in % body fat for participants in the HIIT group; ReHIIT group and; mean difference in % body fat for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 55 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.3 Muscle Architecture

4.4.3.1 Vastus Lateralis Muscle Thickness

Data were available for 26 participants with 13 missing values. There was no statistically significant difference in VL thickness between HIIT and ReHIIT groups at baseline (MD: 0.006 cm; CIs: -0.37 – 0.36; p=0.97). There was no significant time (p=0.08) or exercise group (p=0.61) effect (Figure 4.31).

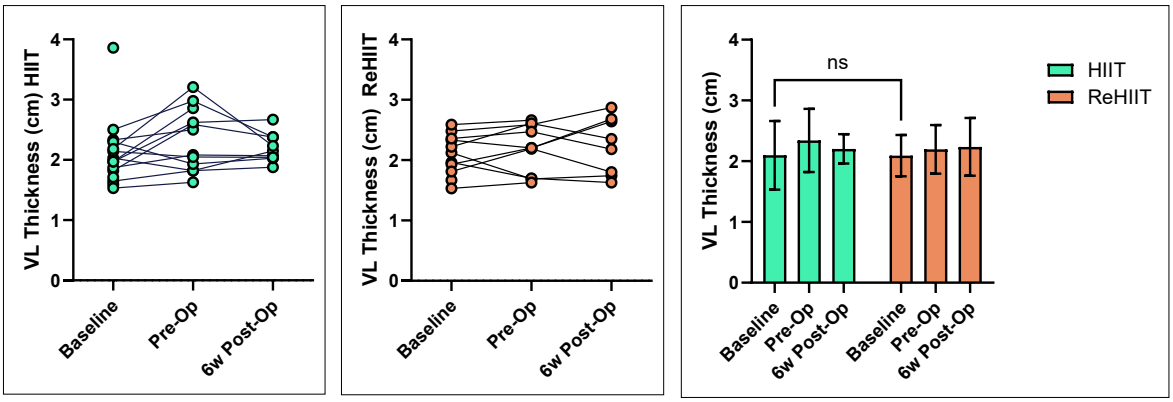


Figure 4.31- Individual changes in vastus lateralis thickness for participants in the HIIT group; ReHIIT group and; mean difference in vastus lateralis thickness for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 65 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.3.2 Vastus Lateralis Muscle Cross-Sectional Area

Data were available for 26 participants with 13 missing values. There was no statistically significant difference in VL CSA between HIIT and ReHIIT groups at baseline (MD: 1.46 cm^2; CIs: -2.25 – 5.17; p=0.42). There was a significant increase in VL CSA between baseline and preoperative assessment days in the HIIT group only (MD:1.72 cm^2; CIs: 0.21 – 3.31; p=0.04). There was a significant time (p=0.04) but not exercise group (p=0.81) effect (Figure 4.32).

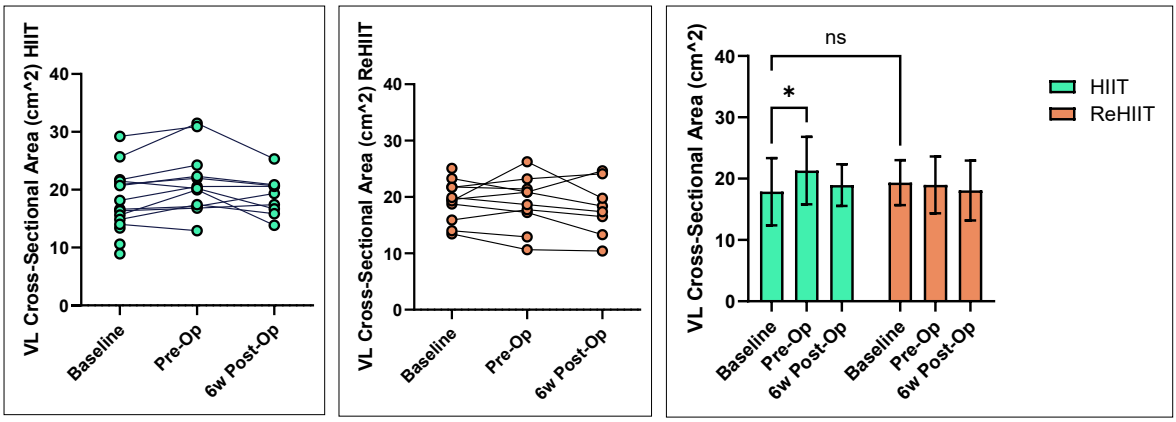


Figure 4.32- Individual changes in vastus lateralis cross-sectional area for participants in the HIIT group; ReHIIT group and; mean difference in vastus lateralis cross-sectional area for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 65 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.3.3 Vastus Lateralis Pennation Angle

Data were available for 26 participants with 13 missing values. There was no statistically significant difference in VL pennation angle between HIIT and ReHIIT groups at baseline (MD: -0.61 °; CIs: -2.64 – 1.41; p=0.53). There was a significant decrease in VL pennation angle between baseline and 6-week postoperative assessment days in the HIIT group (MD: -0.89 °; CIs: -1.67 – -0.10; p=0.03). There was no significant time (p=0.21) or exercise group (p=0.87) effect (Figure 4.33).

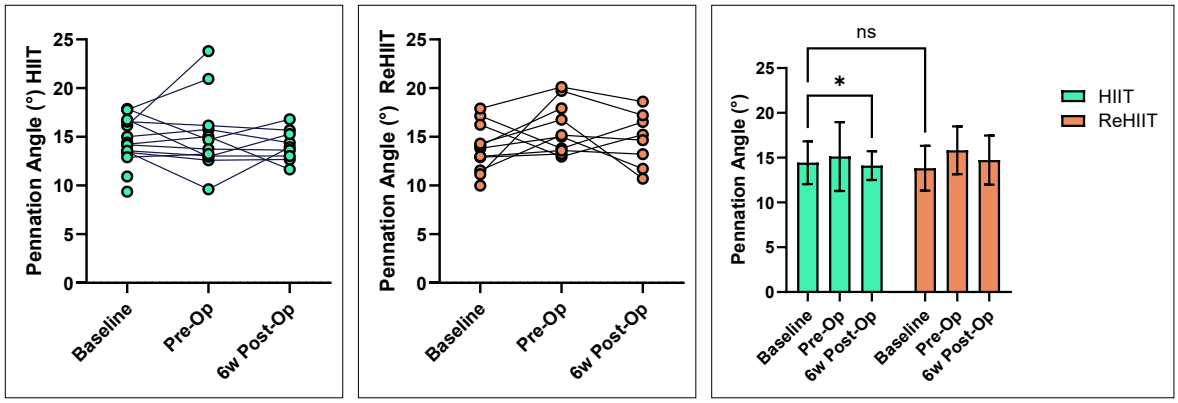


Figure 4.33- Individual changes in vastus lateralis pennation angle for participants in the HIIT group; ReHIIT group and; mean difference in vastus lateralis pennation angle for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 65 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.4 Muscle Function

4.4.4.1 One-Repetition Maximum

4.4.4.1.1 Chest Press

Data were available for 25 participants with 12 missing values. There was no statistically significant difference in chest press 1-RM between HIIT and ReHIIT groups at baseline (MD: -15.87 Kg; CIs: -33.69 – 1.95; p=0.07). There was a significant increase in chest press 1-RM between baseline and preoperative assessment in the ReHIIT group only (MD: 7.61 Kg; CIs: 0.003 – 15.22; p=0.05). There was a significant time (p=0.04) but no exercise group (p=0.18) effect (Figure 4.34).

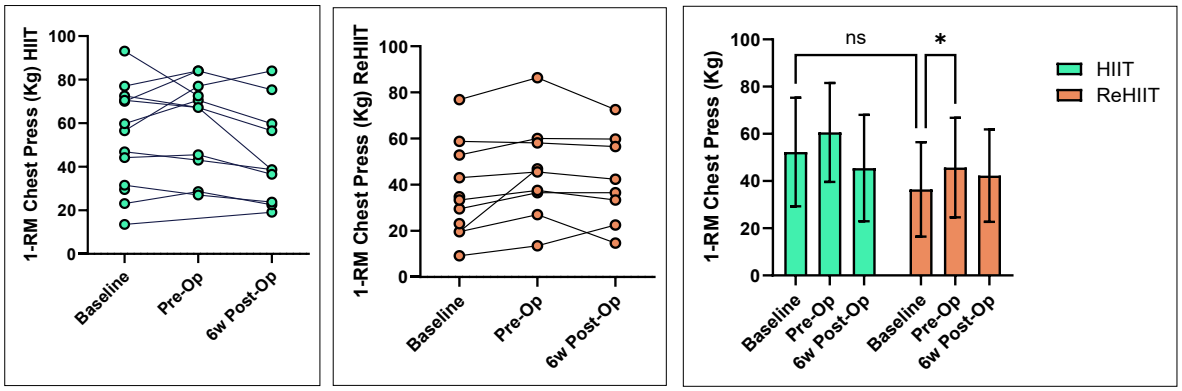


Figure 4.34- Individual changes in 1-RM (chest press) for participants in the HIIT group; ReHIIT group and; mean difference in 1-RM (chest press) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 63 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.4.1.2 Latissimus Dorsi Pulldown

Data were available for 26 participants with 12 missing values. There was a statistically significant difference in lat pulldown 1-RM between HIIT and ReHIIT groups at baseline (MD: -11.94 Kg; CIs: -23.42 – -0.46; p=0.04). There was a significant increase in lat pulldown 1-RM between baseline and preoperative assessment in the ReHIIT group (MD: 11.13 Kg; CIs: 5.77 – 16.48; p=0.0005) and a significant decrease between preoperative and 6-week postoperative assessment (MD: -6.39 Kg; CIs: -9.98 – -2.79; p=0.002). There was a significant time (p=0.02) but no exercise group effect (p=0.44) (Figure 4.35).

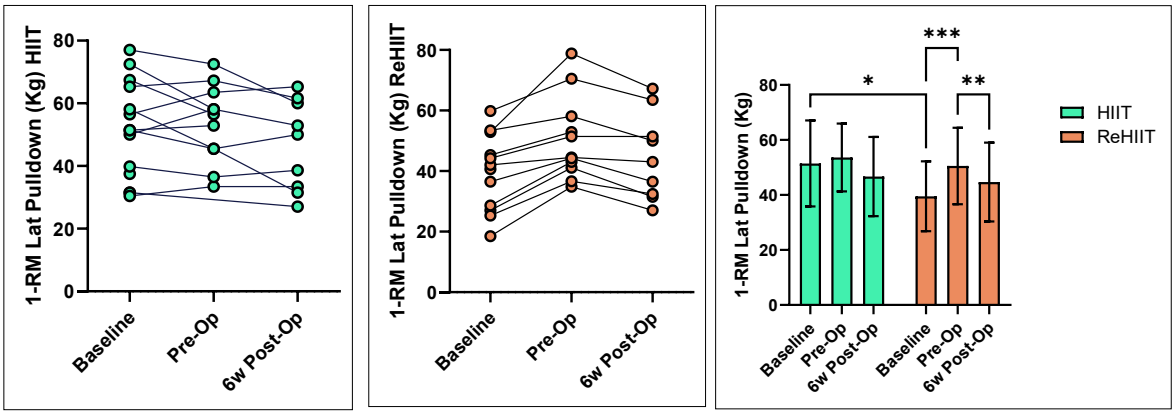


Figure 4.35- Individual changes in 1-RM (latissimus dorsi pulldown) for participants in the HIIT group; ReHIIT group and; mean difference in 1-RM (latissimus dorsi pulldown) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 66 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.4.1.3 Seated Row

Data were available for 26 participants with 12 missing values. There was a statistically significant difference in seated row 1-RM between HIIT and ReHIIT groups at baseline (MD: -11.99 Kg; CIs: -23.48 – -0.50; p=0.04). There was a significant increase in seated row 1-RM between baseline and preoperative assessment in the ReHIIT group (MD: 13.27 Kg; CIs: 2.87 – 23.7; p=0.01). There was a significant time (p=0.05) but no exercise group effect (p=0.43) (Figure 4.36).

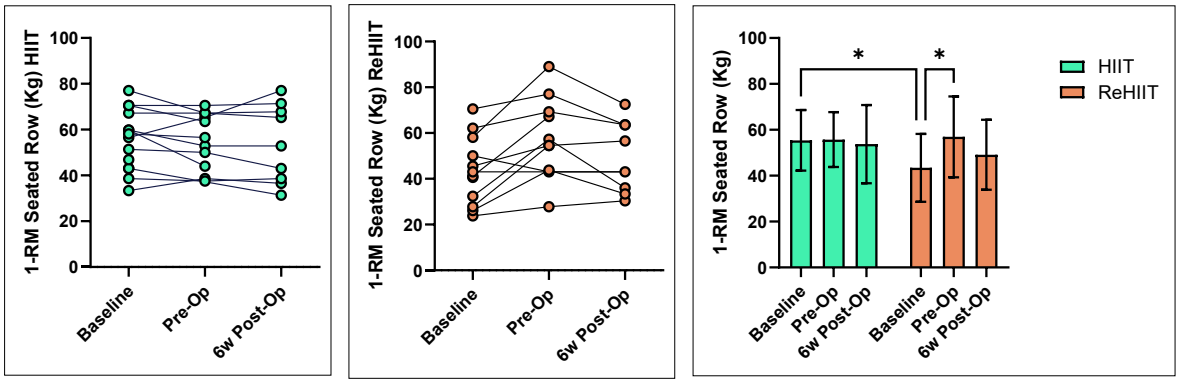


Figure 4.36- Individual changes in 1-RM (seated row) for participants in the HIIT group; ReHIIT group and; mean difference in 1-RM (seated row) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 66 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.4.1.4 Leg Extension

Data were available for 26 participants with 12 missing values. There was a statistically significant difference in leg extension 1-RM between HIIT and ReHIIT groups at baseline (MD: -21.32 Kg; CIs: -39.70 – -2.94; p=0.02). There was a significant increase in leg extension 1-RM between baseline and preoperative (MD: 22.87 Kg; CIs: 7.65 – 38.09; p=0.005), and between baseline and 6-week postoperative assessments (MD: 8.26 Kg; CIs: 0.80 – 15.71; p=0.03) in the ReHIIT group. There was a significant time (p=0.001) but no exercise group effect (p=0.53) (Figure 4.37).

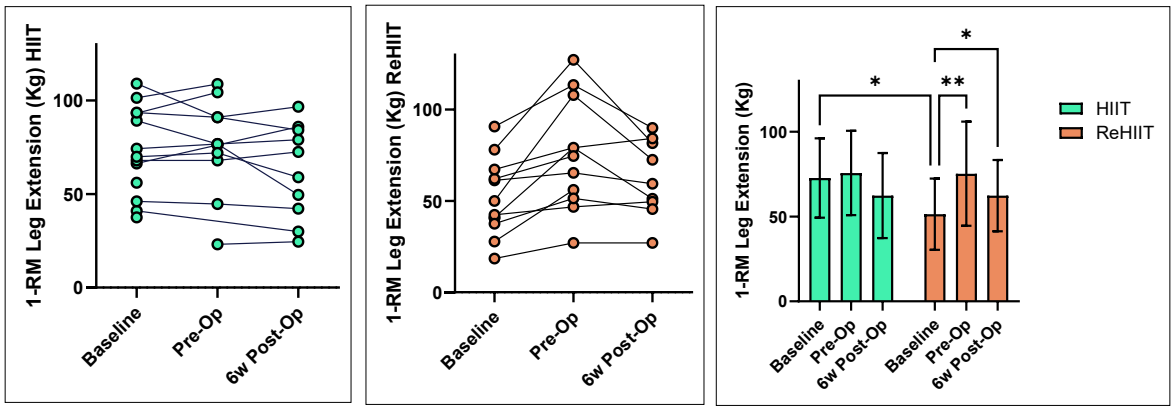


Figure 4.37- Individual changes in 1-RM (leg extension) for participants in the HIIT group; ReHIIT group and; mean difference in 1-RM (leg extension) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 66 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.4.1.5 Leg Press

Data were available for 26 participants with 11 missing values. There was no statistically significant difference in leg press 1-RM between HIIT and ReHIIT groups at baseline (MD: -12.44 Kg; CIs: -32.50 – 7.62; p=0.20). There was a significant increase in leg press 1-RM between baseline and preoperative assessments (MD: 30.15 Kg; CIs: 19.76 – 40.53; p<0.0001), and a significant decrease between preoperative and 6-week postoperative assessments (MD: -25.10 Kg; CIs: -39.19 – -11.01; p=0.002) in the ReHIIT group. There was a significant time (p=0.005) but no exercise group effect (p=0.61) (Figure 4.38).

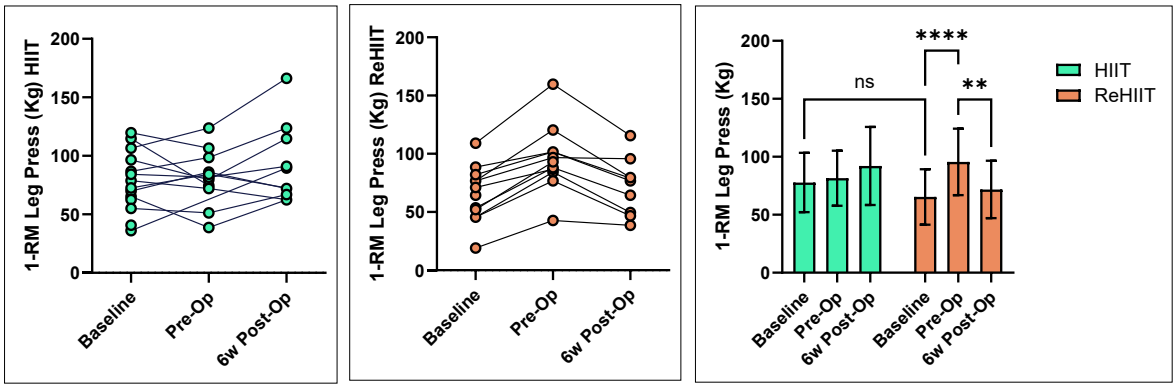


Figure 4.38- Individual changes in 1-RM (leg press) for participants in the HIIT group; ReHIIT group and; mean difference in 1-RM (leg press) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 67 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.4.1.6 Leg Curl

Data were available for 21 participants with 13 missing values. There was no statistically significant difference in leg curl 1-RM between HIIT and ReHIIT groups at baseline (MD: -2.72 Kg; CIs: -13.76 – 7.72; p=0.59). There was a significant decrease in leg curl 1-RM between preoperative and 6-week postoperative assessment in the ReHIIT group (MD: -9.10 Kg; CIs: -16.46 – -1.74; p=0.02). There was a significant time (p=0.04) but no exercise group effect (p=0.46) (Figure 4.39).

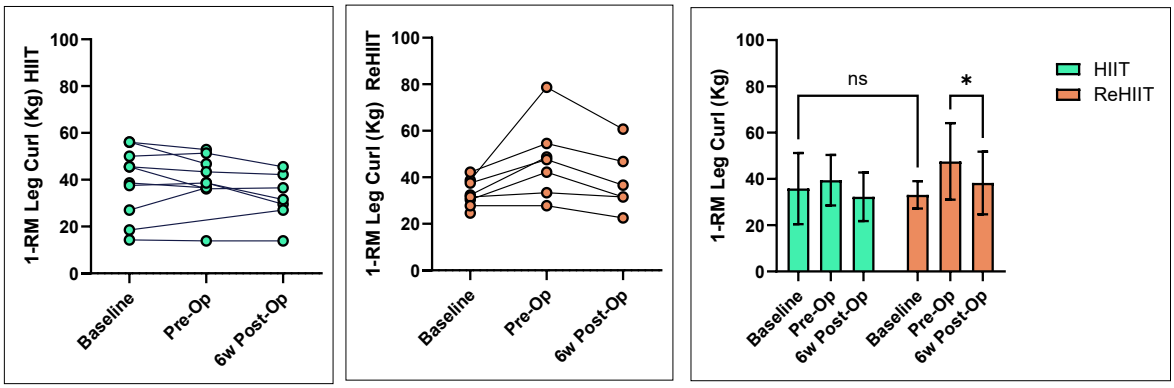


Figure 4.39- Individual changes in 1-RM (leg curl) for participants in the HIIT group; ReHIIT group and; mean difference in 1-RM (leg curl) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 50 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.5 Neuromuscular Function

4.4.5.1 Maximum Voluntary Isometric Contraction

Data were available for 26 participants with 11 missing values. There was no statistically significant difference in MVC between HIIT and ReHIIT groups at baseline (MD: -70 N; CIs: -163.5 – 22.76; p=0.13). There was a significant decrease in MVC between baseline and 6-week postoperative (MD: -35.7 N; CIs: -70.37 – -0.91; p=0.045) and preoperative and 6-week postoperative (MD: -35.5 N; CIs: -64.18 – -6.73; p=0.018) assessments in the HIIT group. There was a significant time (p=0.04) but no exercise group effect (p=0.15) (Figure 4.40).

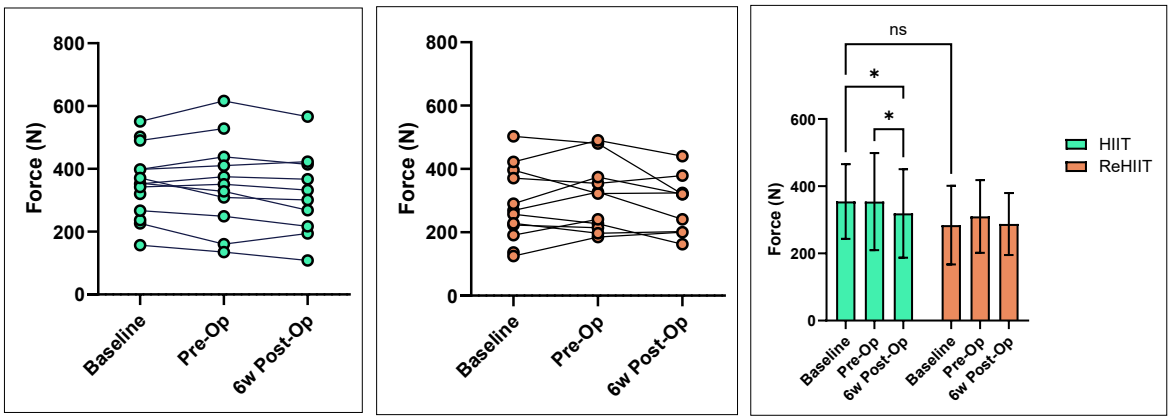


Figure 4.40- Individual changes in MVC for participants in the HIIT group; ReHIIT group and; mean difference in MVC for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 67 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.5.2 Force Steadiness

4.4.5.2.1 Coefficient of Variation at 10% Maximum Voluntary Isometric Contraction

Data were available for 26 participants with 14 missing values. There was no statistically significant difference in CoV at 10% of MVC between HIIT and ReHIIT groups at baseline (MD: 1.17 %; CIs: -0.70 – 3.04; p=0.22). There was no significant time (p=0.25) or exercise group (p=0.81) effect (Figure 4.41).

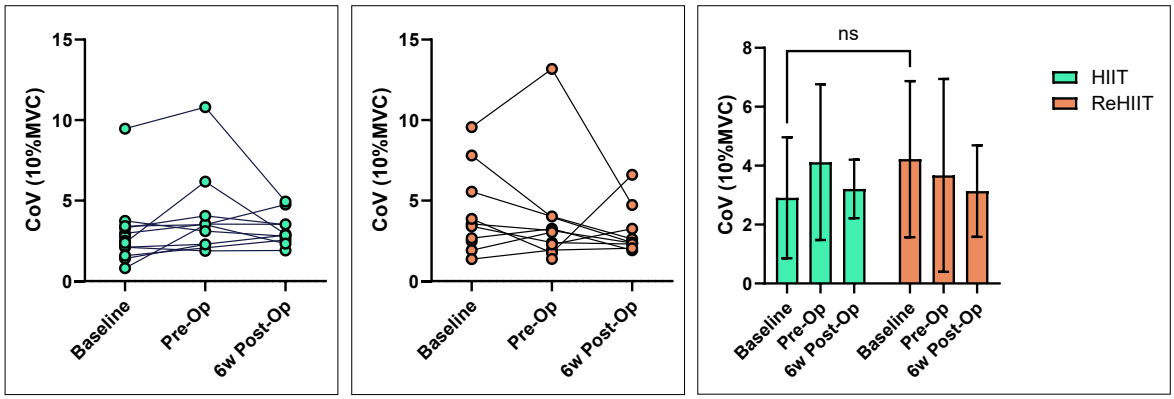


Figure 4.41- Individual changes in CoV at 10% of MVC for participants in the HIIT group; ReHIIT group and; mean difference in CoV at 10% of MVC for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 64 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.5.2.2 Coefficient of Variation at 25% Maximum Voluntary Isometric Contraction

Data were available for 26 participants with 14 missing values. There was no statistically significant difference in CoV at 25% of MVC between HIIT and ReHIIT groups at baseline (MD: 1.15 %; CIs: -0.03 – 2.34; p=0.056). There was a significant exercise group (p=0.02) but no time (p=0.14) effect (Figure 4.42).

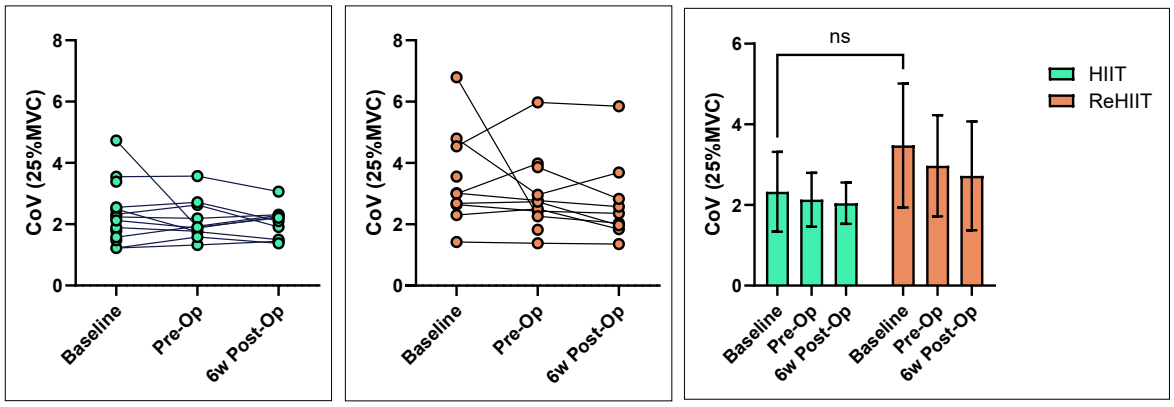


Figure 4.42- Individual changes in CoV at 25% of MVC for participants in the HIIT group; ReHIIT group and; mean difference in CoV at 25% of MVC for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 64 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.4.5.2.3 Coefficient of Variation at 40% Maximum Voluntary Isometric Contraction

Data were available for 26 participants with 14 missing values. There was a statistically significant difference in CoV at 40% of MVC between HIIT and ReHIIT groups at baseline (MD: 1.02 %; CIs: 0.23 – 1.81; p=0.02). There was a significant difference between 6-week postoperative assessments between the HIIT and ReHIIT groups (MD: 1.01 %; CIs: 0.15 – 1.97; p=0.026). There was a significant exercise group (p=0.005) but no time (p=0.98) effect (Figure 4.43).

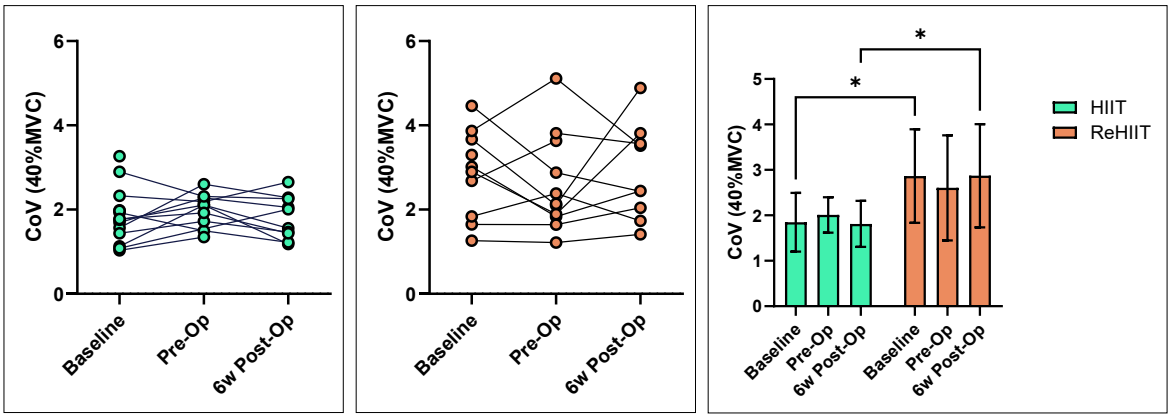


Figure 4.43- Individual changes in CoV at 40% of MVC for participants in the HIIT group; ReHIIT group and; mean difference in CoV at 40% of MVC for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 64 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

4.5 Discussion

All results must be interpreted with caution as this is an interim analysis of the EPiC study after 28 participants (target recruitment n=56). Though underpowered for the composite endpoint of change in AT and whole-body muscle mass early results from the EPiC study are positive.

Recruitment and retention to the study suggest that it is feasible to deliver this in the target population. Randomisation appears successful with no significant difference in baseline characteristics between the HIIT and ReHIIT groups with regard to age, sex, operative approach, postoperative histology, requirement for adjuvant chemotherapy or length of exercise period. With the exception of some measurements of 1-RM and neuromuscular function, baseline measurements of physiological parameters were not significantly different between the two groups. There was similar attrition in both groups which represented less than one in five participants, and the number of exercise sessions completed was similar between groups. No participants withdrew from the study due to the demands of the intervention.

Regarding CRF, both groups displayed a statistically significant increase in maximum wattage attained on CPET and corresponding VO_{2Peak} however there was no differences between the two groups at any timepoint. This suggests an increased ability to perform exercise to exhaustion in both groups, but familiarity with equipment and setting is likely to impact these results. AT, both absolute and adjusted for BW and LM were unchanged in the HIIT group and was significantly reduced at six weeks post-operation versus preoperatively in the ReHIIT group versus baseline. This is in keeping with previous work undertaken by the research group which showed that HIIT-alone did not improve AT in a similar population[212]. Reassuringly,

given the period over which the study was undertaken, there was no decrease in AT between baseline and 6-week postoperative assessment in either group which considering that this period consisted of a time where the individual had cancer, followed by an operation and the resultant stresses on the body, is remarkable considering AT often decreased immediately post cancer resection[357]. To further investigate this phenomenon, a control group would be required, though it is accepted that the presence of cancer, and the stress of surgery leads to a loss of CRF[358]. Both groups did display a numerical increase in AT between baseline and preoperative assessments, with the results more pronounced when adjusted for bodyweight but completion of the study is required to comment on significance and magnitude. Further, 'non-responder' status whereby individuals are genetically restricted in terms of exercise-induced gains in CRF is an accepted concept, but cohorts with CRC appear to have a larger proportion of non-responders, though this may be associated with the changes in MPS and anabolism [212,359]. This might mean that, though benefits in terms of improving CRF are possible for some individuals, on an 'all-comer' level, this improvement is not seen. One reading of these findings in CRC cohorts, considering exercise is known to reduce cancer risk[360], is that individuals who are genetically-determined to not be able to improve their CRF via exercise, thus do not exercise, thus are more prone to developing cancer.

In terms of body composition, both groups lost weight over the period of the study, though this appears to predominantly be a postoperative change as seen after any trauma including significant operative intervention. However, LM remained unchanged throughout for both groups, which may be an encouraging finding, notwithstanding this is an interim analysis. Some surgeons, especially for rectal cancers, encourage weight loss prior to an operation to make the procedure less technically challenging. A loss in %BF with a maintenance of LM would suggest that, in EPiC trial participants, the change in body composition was not

sarcopenic or cachectic-based and that participants were able to maintain muscle even whilst changing nutritional intake[361]. Other studies in CRC suggest that LM can be maintained with exercise[358], thought the addition of a RET component as in the EPiC trial may protect further against some of the effects of i) the adaptive blunting of changes in muscle mass seen with age and, ii) the pronounced reduction in MPS seen in CRC[128].

Changes in muscle architecture were either non-significant or small in magnitude. Again, this is not surprising given the reported difficulty in eliciting change in gross muscle architecture in a short timeframe[362,363], which are likely compounded by the effects of in situ neoplasia[14] and possible changes in nutritional intake.

Interestingly, as was also seen by Lee et al.[362] muscle function (1-RM) was improved by ReHIIT which elicited significant increases in 1-RM for chest press, lat pulldown, seated row, leg extension, leg press and the sum of these exercises. Conversely, no such similar improvement was seen with HIIT alone. Though these findings are promising, compounding factors such as equipment and exercise familiarity in the ReHIIT when compared with the HIIT group may explain some of this change. Neuromuscular function was broadly unchanged in the ReHIIT versus the HIIT group with the exception of 6 weeks postoperative results for CoV at 40% of MCV, though the significant difference in baseline values probably makes up for this difference.

Overall, the effects of HIIT-alone versus RET in addition to HIIT as prehabilitation in CRC on physiological reliance are mixed. Considering the definition of resilience as the ability to 'bounce back' the lack of a significant change between baseline and 6-week postoperative assessments in most measures of physiological reliance are positive. Measures which required some degree of psychological effort such as maximum wattage, VO_{2Peak} and 1-RMs

were unchanged over this period suggesting that participants at least felt they were able to push themselves back to where they were prior to starting the exercise period. Considering patients are told to abstain from vigorous exercise for approximately six weeks postoperatively[364], the ability to return to the state at which they were diagnosed is encouraging. Though not formally studied, when asked on the final assessment day, participants were overall very happy to have returned to their preoperative state.

Demographics on ethnicity were not recorded which may limit the analysis in terms of genetic and cultural factors which may affect outcomes. Though the results include a wide range of ages (38-77 years) and good sex distribution, with a younger minimum and average age versus other work on similar cohorts[98] perhaps being reflective of the increase in CRC in younger people seen worldwide in recent years[365]. 82% of participants completed the exercise intervention with five participants unable to do so, though two of these dropped out prior to starting exercise, and two dropped out after being offered an earlier operation date. Only a single participant was withdrawn during the exercise period, which was a medical decision, so overall the exercise intervention was very well tolerated, though clearly, only a select group of patients were willing to commit to the time and effort required and it is possible that they might not be representative of the larger cohort of patients with operable CRC. The EPiC study however was more demanding than just the intervention itself however, and required patients to travel to the exercise facilities in addition to assessment days. This further burden over and above the exercise may artificially reduce the number of willing participants versus an exercise regime only (i.e. and no assessment) and all EPiC participants were taken from a cohort in a setting in which other clinical trials were running, further reducing participation (Figure 4.18).

With the exception of muscle function (1-RM), where improvements in physiological resilience were seen, it was seen in both HIIT and ReHIIT groups. As alluded to, future results of the EPiC study may show a difference between the two groups, but the findings are not in keeping with previous work whereby participants undertook a similar HIIT regime yet were not able to increase their AT or VO_{2Peak} prior to an operation[98] despite similar baseline demographics. After adequate recruitment for the EPiC study is achieved, future work could add healthy matched controls to investigate if RET in addition to HIIT effects individuals with CRC differently from that of the general population. A further group of controls with CRC who do not undergo intervention would also be pertinent to observe, as considering the focus of prehabilitation is to optimise an individual for an insult, there may be a difference six weeks postoperatively between prehabilitated (with ReHIIT) and non-prehabilitated individuals.

5. High-Intensity Interval Training (HIIT) Alone Versus HIIT Plus Resistance Exercise Training (ReHIIT) as Prehabilitation for Operable Colorectal Cancer: A Focus on Functional & Clinical Outcomes

5.1 Introduction

'Function' is a difficult concept to define, and a complex interplay exists between physical measures of function, an individual's perception of what they are capable of, and how that effects their life. The *intrinsic capacity* of an individual can be thought of as a composite of their physical and mental capacities and perhaps function is best described as the outcome that is measured when an individual's intrinsic capacity is tested[366,367]. Function is an essential component of the health of an older person or cancer survivor, and may include physical activities such as performing ADLs, exercising, undertaking normal habitual activity and attending social events or, as neuropsychological function such as QoL, self-image and mood[367]. Many individuals, especially as they age, consider their QoL to be paramount and will often make decisions to maximise quality, over length of life[368], but fortunately, CRC survivors display a relatively high QoL in the long-term[369].

Clinical outcomes are also important to an individual, but also to a health system. The median LOS after major resection for CRC in the UK is six days (IQR 4-10)[370], which has significantly improved in recent years[371], at least in part due to the widespread implementation of ERAS protocols[372]. Mortality in the early postoperative period (90 days) is relatively rare (2.7%)[370], yet complications are relatively common (~27%[373,374]). Perhaps unsurprisingly, postoperative complications effect the short- and long-term outcomes after CRC resection with increased five-year mortality and poorer oncological outcomes[373]. Postoperative complications also have an adverse effect on QoL in the long-term and thus are an important component of the

patient journey and consent process[375]. If psychological resilience can be thought of as the '*how'* a patient can recover after CRC resection, the functional and clinical outcomes can be thought of as the '*why'*.

5.2 Aims

The aims of the chapter are to investigate the effects of adding RET to HIIT prehabilitation in patients with CRC scheduled for curative intent on functional and clinical outcomes.

5.3 Methods

5.3.1 Functional Impacts of Exercise

Individuals with cancer often prioritise functional outcome over much else[376] with QoL and independence often cited as two of the most important outcomes in patients who have surgery for cancer[377].

Functional ability can be thought of as the degree to which an individual can perform ADLs, enjoy an acceptable QoL and participate in society to the degree to which they desire. Functional outcomes are difficult to measure without bias in that they are, at least to some degree, subjective. Though measures such as the *6MWT*, HGS and *Short Physical Performance Battery Test* (SPPBT) can report objective outcomes, they still require a larger degree of individual participation compared to outcomes such as mortality or AT. For example, Williams et al., showed that after tumour resection, individuals with CRC tend towards a normal AT, but self-reported measures of activity do not mirror this objective change[14]. Other functional outcomes such as QoL as defined by self-reported questionnaires are clearly more subjective but so to is the nature of the variable.

5.3.1.1 Functional Capacity

Functional capacity was assessed via the 6MWT[378], *Timed Up & Go* (TUG)[379], SPPBT[380], balance and respirometry. Measures of each were taken at each assessment day with participants blinded to previous results.

5.3.1.1.1 Six-Minute Walk Test

The 6MWT is a simple test of functional CRF that requires a small amount of inexpensive and readily available equipment to undertake. The test is undertaken by measuring the distance a participant can walk, in increments of 30 meters, on a flat surface in six minutes. Measures

of actual versus predicted 6MWT can help risk stratify individuals prior to an operation, with those with relatively diminished results having a higher incidence of postoperative complications. Limitations include underreporting of true CRF in participants who have neurological or muscular impairment[378].

The 6MWT has been validated for use in measuring recovery after elective colonic resection[381] and has been shown to correlate well with AT in individuals undergoing major noncardiac surgery[382], and with VO_{2Peak} in individuals with cancer[383]. Thresholds have been suggested for forgoing further measures of CRF such as CPET testing based on an individual's 6MWT distance alone[382].

Studies of preoperative exercise in individuals with CRC have shown mixed result regarding improving participant's 6MWT distances, but most studies showed a positive correlation[96].

5.3.1.1.2 Six-Minute Walk Test Methodology

The 6MWT was performed in line with standardised protocols[384] (Figure 5.1). Participants were asked to walk 30 meters along a flat track for as many repetitions as possible in six minutes. A member of the research team demonstrated the task, checked understanding and manually recorded the number of repetitions whilst informing the participant of the time left on the task. To accurately assess distance covered, participants wore an inertial motion sensor (G-Sensor 2; BTS Bioengineering Corp., Milan, Italy; Figure 5.2) on the back at the level of S2. Captured data was transferred via Bluetooth to a computer for analysis and interpreted on G-Studio (BTS Bioengineering Corp.) after verification via comparison with the manual estimate. Failed tests, for example due to hardware error, were repeated after a period of rest to ensure an accurate result.

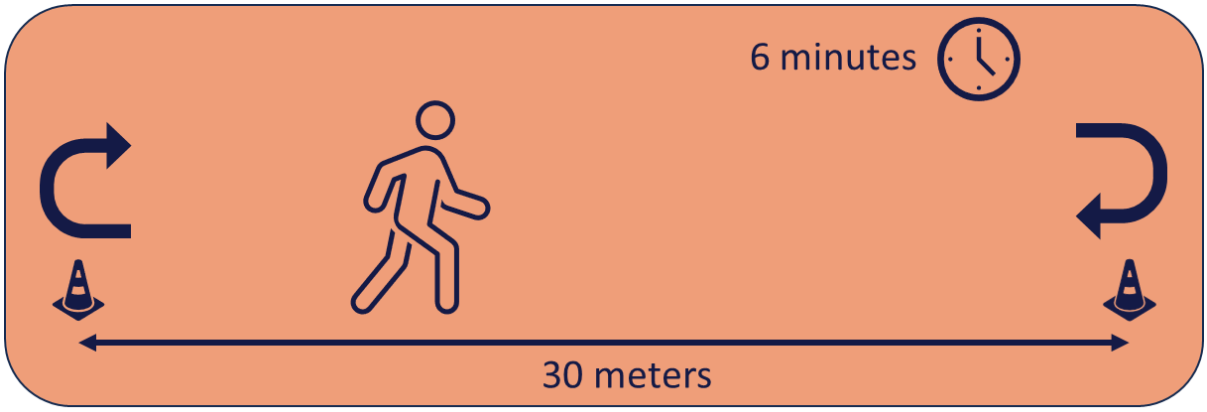


Figure 5.1- A schematic representation of the Six-Minute Walk Test (6MWT)

Figure 5.2- An example of the G-Sensor 2 placement. Image taken from Ruben et al[385]

5.3.1.1.3 Timed Up-and-Go

TUG is a test to assess physical mobility and functional capacity. Modified from the 'Up & Go' test[386], the TUG adds a time element which in a population of community-dwelling older adults reliably assesses physical mobility and an objective measure of change over time[387]. The test is easy and cheap to perform and is linked with functional ability including muscular strength, aerobic capacity and walking endurance[388].

In cancer, an impaired (<12) score achieved on TUG is a strong predictor of mortality in oncology patients, but does not seem to influence the occurrence of postoperative complications[389].

5.3.1.1.4 Timed Up-and-Go Methodology

TUG was performed in line with standardised protocols[390] (Figure 5.3). Participants were seated in a chair and asked to stand, without aid, walk three meters, turn on the spot, walk back, and sit down. Participants were given a demonstration and understanding of the task was ensured. The time taken to perform this was recorded using an inertial sensor (G-Sensor 2; BTS Bioengineering Corp.) placed on the back and secured at the level of L1 and data transferred to G-Studio (BTS Bioengineering Corp.). The test was repeated three times on each assessment day with the best (fastest) recorded.

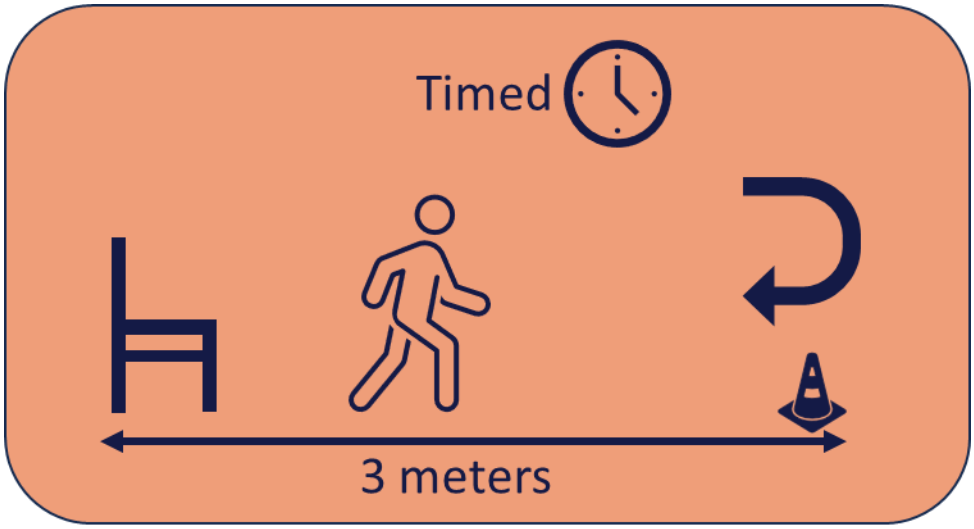


Figure 5.3- A schematic of the timed up-and-go test

5.3.1.1.5 Counter Movement Jumps

Countermovement jumps (CMJs) are jumps involving a downward, followed by an upward motion. It is a simple test that tests neuromuscular capacity in the lower limbs and is commonly assessed in athletes[391]. Take-off speed (TOS) and height, amongst other values can be measured during the test. TOS is the speed at which the body is moving at the moment of 'toe off'. Height is the height an individual can jump from the floor[391]. There is some evidence that in older adults, CMJ parameters are improved in those who perform regular exercise, and as such might be useful as a surrogate for strength and fitness[392]. Measures derived from CMJs have been shown to improve in older adults after strength training suggesting the test is reliable in assessing response to exercise[393].

5.3.1.1.6 Counter Movement Jumps Methodology

The CMJ test was performed using standardised protocols[394]. Participants were asked with their feet shoulder's width apart and without the use of aids such as arms, to bend their knees to 90° and jump as high as they can. The test was demonstrated to participants, and their understanding was ensured by a member of the research team. During the test, the

participants wore an inertial sensor (G-Sensor 2; BTS Bioengineering Corp.) secured to their back at the level of the S2 vertebra and data were transferred to G-Studio (BTS Bioengineering Corp.). Participants were asked to repeat the test three times, with the best values for each of *height*, and *TOS* recorded.

5.3.1.1.1 Short Physical Performance Battery Test

The SPPBT assesses balance, strength, and gait in a functional assessment of lower limb and associated neuromuscular group performance. Though simple to perform for most healthy adults, the SPPBT requires coordination and strength of differing muscle groups, all coordinated centrally, thus testing several systems. The test is undertaken in three parts, testing balance, gait speed and standing from a seated position[395]. The test is inexpensive, reliable, valid and sensitive[396] and performance on the SPPBT is predictive of all-cause mortality, with suggestions that its use should be implemented into clinical practice to aid prognostication[397].

In individuals with cancer, physical performance scores show a significant correlation with survival, with a less explicit correlation for treatment-related complications and functional decline[398]. This is reflected in a 2022 study which found that, in individuals with CRC, a low SPPBT score in conjunction with low HGS was associated with higher risk of postoperative complications. Those with a low SPPBT score, regardless of HGS, had a significantly increased in-hospital, one-month and six-month mortality[399].

5.3.1.1.2 Short Physical Performance Battery Test Methodology

The SPPBT (Figure 5.4) was undertaken by assigning an individual score to three measures:

- The time taken to perform five repetitions of rising from, and returning to sitting in a chair without the use of aids:

    - Unable or able but in >60 seconds (0 points)
    - 16.7-60 seconds (1 point)
    - 13.7-16.69 seconds (2 points)
    - 11.2-13.69 seconds (3 points)
    - <11.19 seconds (4 points)
- The ability to balance, without aids, with feet together side-by side for 10 seconds (1 point), semi-tandem for 10 seconds (1 point) and full-tandem for 10 seconds (2 points) (Figure 5.4)
- The time taken to walk 4 meters from standing:
    - Unable (0 points)
    - Able but in >8.7 seconds (1 point)
    - 6.21-8.7 seconds (2 points)
    - 4.82-6.2 seconds (3 points)
    - <4.82 seconds (4 points)

Participants had each task demonstrated to them and their understanding was ensured. Each aspect of the test was repeated three times, unless a participant achieved maximum points with the initial or second attempt. The points corresponding to the best result from each aspect of the test were then summated and recorded out of 12. For example, a participant who was able to stand from and sit back into a chair five times in 11.5 seconds (3 points) balance with their feet together side-by-side (1 point), in semi-tandem (1 point) and in full-tandem for 10 seconds (2 points) each, and was able to walk 4 meters in 6.23 seconds (2 points) would receive a score of 3+1+1+2+2= 9 out of 12.

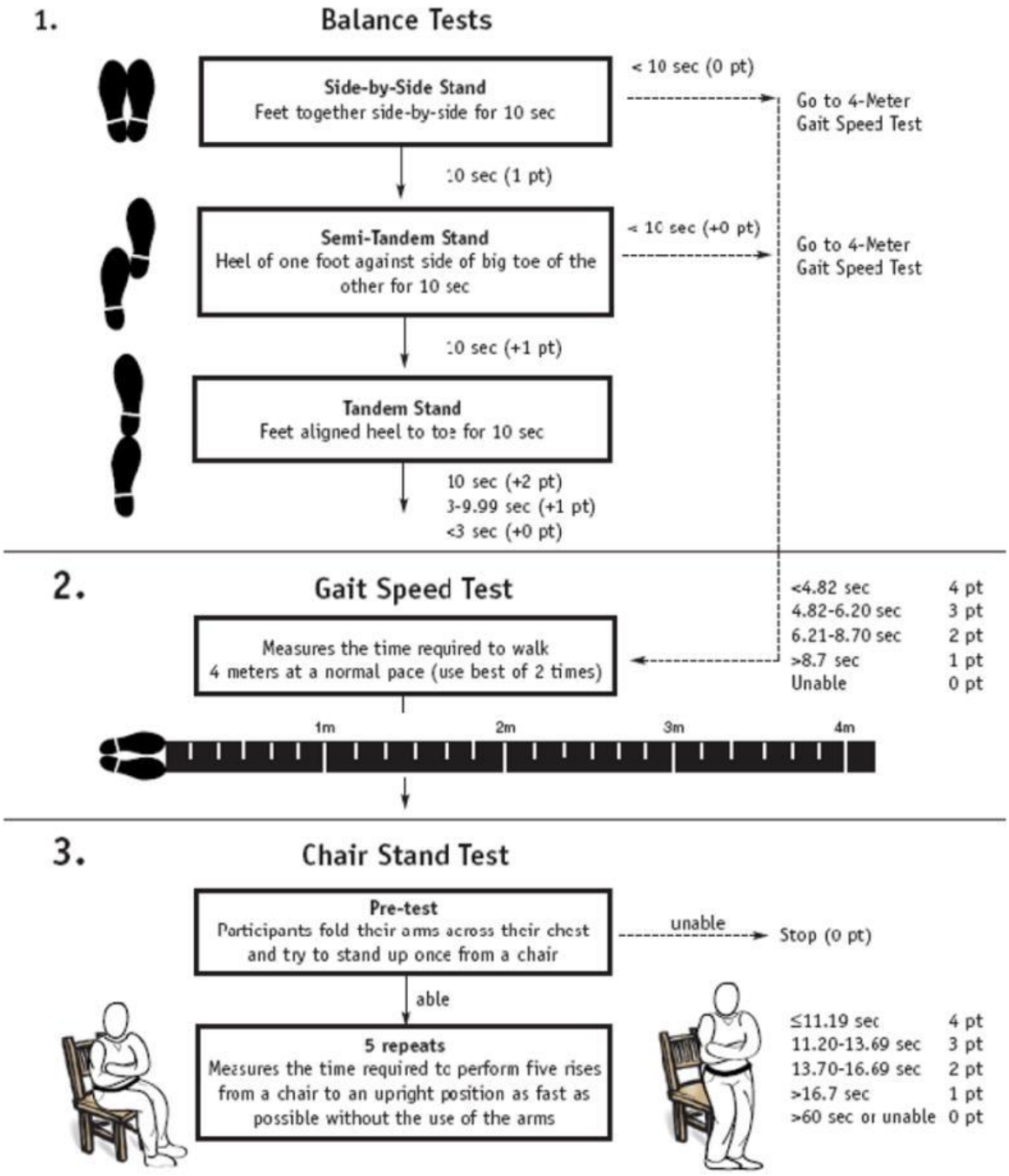


Figure 5.4- Scoring of the short physical performance battery test. Taken from Riskowski et al[400].

5.3.1.1.1 Handgrip Strength

HGS is the ability of the muscle groups responsible for grip to perform maximum contractile strength against resistance and is important functionally as it is required for many ADLs. It is also a useful measure of overall fitness; is easy to perform and measure; and is inexpensive and reproducible. Testing HGS involves a participant squeezing their hand onto a dynamometer which can measure the force applied[401,402].

HGS can act as a surrogate for muscular mass and function and low HGS has been shown to be associated with mortality in individuals with cancer[403]; and in all-cause-, cancer- and cardiovascular- mortality in adults[404]. Specifically in CRC however, a 2020 study investigating preoperative HGS in individuals who had surgery concluded that HGS is not associated with complications or health-related QoL[405].

5.3.1.1.2 Handgrip Strength Methodology

Participants were asked to squeeze each hand in turn with as much force as possible onto a digital dynamometer (Takei T.K.K. 5401; Takei Scientific Instruments Co., Ltd., Japan). Participants were supervised by a member of the research team and asked to stand with feet shoulder's width apart and their arms by their side. Participants were encouraged verbally, and the measurements were repeated three times with each hand with a minute between. The best (largest force) reading from the six attempts was recorded.

5.3.1.2 Quality-of-Life

QoL is difficult to define and measure and must be subjective and individual dependant. It can be affected disproportionately by objectively small insults and remain constant through objectively severe changes in an individual's life. A wide and long-standing literature exists regarding QoL in individuals with cancer and, with improvements in cancer treatment over

the last century, there has been a growing measurement of long-term QoL as opposed to specifically the QoL of those living with cancer[406]. HR-QoL acts to bridge this gap, with many tools designed to ascertain the subjective perceptions of an individual with a specific disease such as cancer. The tools aim to collect information on the positive and negative consequences of a disease and its treatment including physical, emotional, social, and cognitive functions[407].

QoL in individuals with CRC is unsurprisingly linked with a poorer QoL than those without such disease-burden. Individuals with CRC have a significantly higher prevalence of distress, depression, and anxiety than the general population[408]. Surgery too can influence an individual's QoL. Psychological concern over the intervention may be compounded by being the unfamiliar environment, pain, change in body image, loss of mobility and loss of control associated with surgery[408]. In CRC surgery more specifically, QoL can be negatively affected by factors such as changes in bowel habits or living with a stoma[408]. Postoperative complications, which are common in individual undergoing surgery for CRC, are also significantly associated with long-term reduced HR-QoL in domains such as physical and social function and body image when compared to those without complications[409]. Regarding exercise, HR-QoL is associated with levels of habitual activity[410], and both home-based and supervised exercise interventions are effective in improving the QoL of individual with CRC[411].

Various questionnaires have been developed to consider HR-QoL in individuals with cancer and specific cancer types[407]. The *European Organisation for Research and Treatment of Cancer* (EORTC) have developed the *Core Quality of Life Questionnaire* (EORTC QLQ-C30) which comprises of 30 questions and can be used in conjunction with various cancer-type

specific modules. It has been continuously developed and validated, with the most recent version being the third major revision (version 3.0)[412].

5.3.1.3 Self-Reported Quality-of-Life, Functional Status, Symptom Burden & Activity Status Methodology

The EORTC QLQ-C30 (version 3[412]) was completed by each participant at each assessment day. The scores are reported as per the *EORTC QLQ-C30 Scoring Manual*[413]. For the domains of *Global Health Status/QoL*, and *Physical/Role/Emotional/Cognitive/Social functioning*, a higher score related to a '*better*' level of functioning. For symptom scores (*Fatigue, Nausea & Vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea and Financial Difficulties*), a lower score related to a '*better*' symptoms.

The Duke Activity Status Index (DASI) questionnaire[414] was also completed by each participant at each assessment day. Estimated VO_{2Peak} and Metabolic Equivalent of Tasks (METs; a ratio of working versus resting metabolic rate measured in $mlO_2/Kg/min$[415]) were calculated as per the DASI instructions and owing to the design of the questionnaire, incomplete questionnaires were excluded from analysis.

Participants completed the questionnaires in private, with no time limit and could not see previously completed questionnaires.

5.3.1.4 Habitual Activity

Habitual activity is the amount of activity an individual will undertake without intervention. Monitoring habitual activity can be challenging as methods for data collection may include self-reported outcomes which have limited reliability, or via wearable devices which whilst accurate, may change an individual's habits[416].

Large cross-sectional studies have suggested that the overall physical and mental health of older people is associated with average daily step count and the average daily duration of physical activity undertaken at >3 METs[417]. In older English adults, higher moderate-vigorous physical activity and lower sedentary time has been shown to be associated with better QoL. Moreover, declines in activity were associated with worse HR-QoL, as were increases in sedentary behaviour[410]. In terms of mortality and morbidity, a large UK-based study found that an increase in average daily step count was associated with reduced mortality, cancer and cardiovascular disease with the effects plateauing after 10,000 steps. There was also a clear association between peak cadence and improved morbidity and mortality rates[418].

Sit-to-stand (STS) is an important component of everyday mobility, with healthy individuals performing the manoeuvre on average 45 times a day[419]. This is reduced in diseased states, and the reduction in STS may be a result of, and perpetuate, muscle weakness and limited activity. Though STS count is likely to reduced immediately postoperatively, most ERAS protocols encourage early mobilisation with initially aided, and later unaided standing from a sitting position[420].

In individuals who have elective surgery for CRC, self-assessed levels of habitual physical activity have been shown to be positively associated with fewer postoperative complications with the effect demonstrating a dose-response relationship[421].

Habitual activity can be measured using validated self-administered questionnaires such as the DASI questionnaire[414] or, via the wearing of small personal devices such as the activPAL™ monitor[422]. The DASI questionnaire, has been shown to be useful in assessing postoperative recovery of functional capacity after colorectal surgery[423].

5.3.1.5 Habitual Activity Methodology

Measurement of physical activity was performed using an activPAL™ physical activity monitor (PAL Technologies, Glasgow, UK). Participants wore the monitor on the right thigh for four days, repeated at four time points: after screening but prior to starting exercise (A1); during the exercise intervention (A2); immediately postoperatively (A3) and approximately three to four weeks postoperatively (A4). The monitors were set to record using PALconnect software (PAL Technologies), and data were recorded and interpreted using PALanalysis (PAL Technologies). Daily step count, daily STS and MET hours (MET.h) were captured for analysis. Data is reported as an average over each period. For v3, there is an expected reduction in habitual activity in the immediate postoperative period and as such, results were only included if recording for this day were included (i.e. missing data from postoperative day 1 would exclude analysis of all V3 data).

5.3.1.1 Return to Normal Activities

Returning to a state of 'normality' may not be possible after a diagnosis of cancer and or the effects of its treatment. The psychological and physical effects are compounded by the population in which cancer most commonly occurs. Cancer, its treatment and follow-up are commonly in the order of multiple years or in some instances, decades and thus, with the collective deleterious effects of ageing over time, few if any individuals return to a pre-diagnosis 'normal'. Accepting this, a '*new normal*' may be achieved by some and this must be defined by the individual. A new normal can encompass, but is not limited to i) being able to participate in activities they could prior to diagnosis; ii) live without pain or discomfort and; iii) work, earn money and support their family[424].

Cancer and its treatment may hamper some of these aims due to persistent symptoms and fear of cancer returning, but also in some more concrete ways such as the inability to exercise strenuously or fly immediately after an abdominal operation. Specifically in CRC[27], but also in other cancers[425], a high proportion of individuals fail to return to work or return to work and subsequently lose employment. Physical activity can improve the proportion of individuals returning to work post cancer diagnosis in addition to improving QoL and fatigue[426].

Though return to normal activity per se is not reported in this thesis, the overall results of clinical and functional outcomes six weeks postoperatively may be used as a surrogate to evaluate a trend towards 'normality'.

5.3.2 Clinical Impacts of Exercise

Clinical outcomes are important to individuals in terms of returning to 'normal life' as soon as possible after an insult, but also in the ability to progress with therapy or engage in meaningful ADLs. In cancer cohorts, certain poor clinical outcomes for example after cancer surgery, may lead to a delay in initiating adjuvant therapy, this in turn can lead to a higher rate of cancer recurrence and the associated morbidity and mortality. Outside the scope of the clinical environment, less-then-optimal clinical outcomes may lead to a protracted hospital LOS, debilitating injuries, or psychological trauma, which in turn affects QoL, ability to engage in pleasurable activities and depression of mental state.

5.3.2.1 Length-of-Stay

Between 1998 and 2010 the median LOS for individuals who had major resections for CRC was 10 days (IQR 7-14 days) but with a clear trend in later years towards a shorter LOS (median LOS 1998: 11; 2010: 7)[427]. The widespread adoption of laparoscopic surgery as the primary operating modality has partially led to this reduction and individuals undergoing

robotic surgery for CRC appear to have a similar LOS to those undergoing laparoscopic surgery[428]. The drive to reduce LOS is both to the benefit of the individual returning to 'normal' activity, but also in financial terms to the individual or healthcare institution; an overnight inpatient stay on a general ward costs £586.59, a stay on the intensive care unit (ICU), £1621.16 (2016/17 prices)[429].

Owing to the personal and financial costs of LOS, combined with the ease at which this metric can be captured, much work has studied the effects of prehabilitation on LOS in individuals with cancer. Multi-modal prehabilitation regimes have been consistently shown to reduce LOS and healthcare associated costs[430] in individuals with cancer, and prehabilitation with exercise alone has mirrored this finding in cohorts which include individuals with cancer[179,431,432].

5.3.2.2 Mortality

As with LOS, mortality statistics are easy to find and are robust in nature, with a clear binary outcome. Clearly mortality is an important outcome for an individual and their support networks, but in health economic terms, needs to be weighed against the risk of non-intervention, that is, mortality in non-operated on individuals.

A 2022 systematic review and meta-analysis included 13 observational studies representing 19,135 patients, concluding that exercise was associated with an increased overall survival after resection for CRC. Of note, the review was observational in nature, leading to possible biases about participant selection and the self-reporting of key variables also raises questions about the validity of the claims[433]. Perhaps fitter individuals were the ones who were able to exercise, with exercise being a consequence of inherent fitness rather than a driver; there is likely some degree of both. This hypothesis is supported by a 2021 meta-analysis of

interventional studies, suggesting no effect of prehabilitation on mortality amongst other outcomes[179].

5.3.2.3 Postoperative Complications

A 'non-perfect' recovery after surgery is common[434] and one in three individuals who have surgery for CRC experience a complication[409]. This is not surprising given the insult of surgery, the cohort in which surgery takes place and the spectrum of what is considered a 'complication', but nonetheless, postoperative complications have adverse effects on long-term QoL and should be weighed-up against risks of non-operative intervention as part of the consent process[409].

Postoperative complications are usually defined by the Clavien-Dindo classification system developed in 2004 (Table 5.1). The system groups postoperative complications in a five-point scale (with additional subsections; not considered here) which are correlated with complexity of surgery and LOS. Complications range from grade *I* defined as '*any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions*' to grade *V*- death[236].

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimes include: antiemetics, analgesics, electrolytes etc.
II	Requiring pharmacological treatment with drugs other than such allowed for grade *I* complications
III	Requiring surgical, endoscopic or radiological intervention
IV	Life-threatening complications requiring ICU management
V	Death

Table 5.1- Clavien-Dindo classification of surgical complications. Adapted from Dindo et al[236].

Though less so than LOS or mortality, postoperative complications are clearly defined endpoints that are relatively easy to collate data regarding, they are also an important

outcome for individuals and for healthcare systems, both to audit performance and to change practice where appropriate. Preoperative exercise has been shown reduce postoperative complications in individuals with lung cancer who have surgery[435], the results do not seem to translate to gastrointestinal surgery at large[278], and specifically not after CRC surgery[96].

5.3.3 Statistical Analysis

Statistical analysis was performed using the methods described in chapter 4.

5.4 Results

5.4.1 Participant Demographics

Basic demographics for the study population are described in chapter 4.

5.4.2 Functional Capacity

5.4.2.1 Six-Minute Walk Test

Data were available for 25 participants with 14 missing values. There was no statistically significant difference in 6MWT between HIIT and ReHIIT groups at baseline (MD: 2.82 meters; CIs: -57.01 – 62.64; p=0.92). There was no significant time (p=0.36) or exercise group (p=0.98) effect (Figure 5.5).

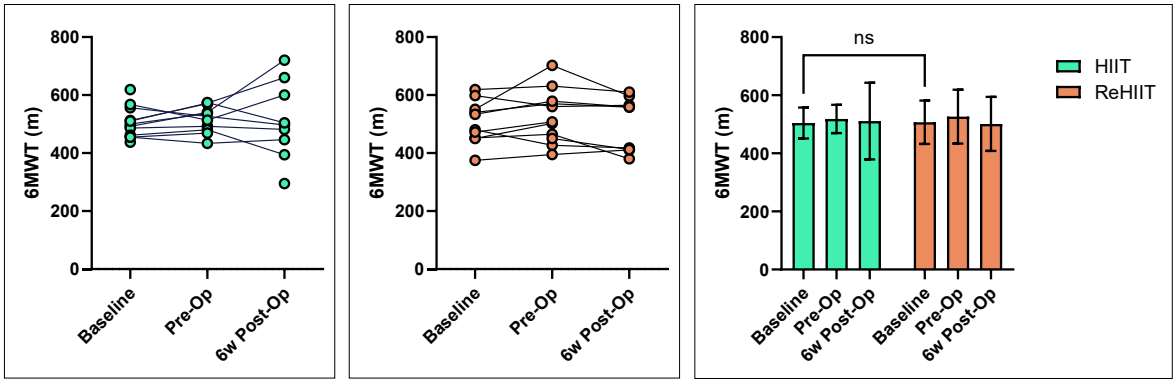


Figure 5.5- Individual changes in six minute walk test distance for participants in the HIIT group; ReHIIT group and; mean difference in six minute walk test distance for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 61 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.2.2 Timed Up-and-Go

Data were available for 26 participants with 11 missing values. There was no statistically significant difference in TUG between HIIT and ReHIIT groups at baseline (MD: 0.57 seconds; CIs: -0.89 – 2.02; p=0.42). There was no significant time (p=0.17) or exercise group (p=0.80) effect (Figure 5.6).

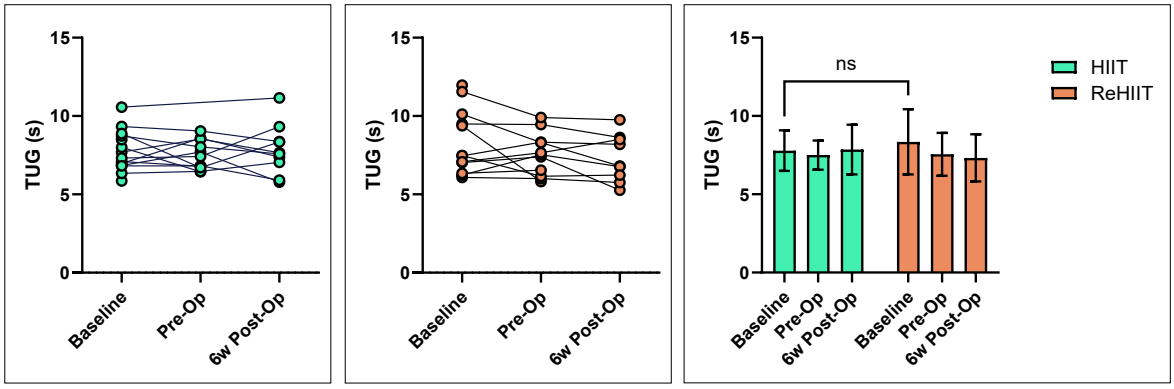


Figure 5.6- Individual changes in timed up-and-go time for participants in the HIIT group; ReHIIT group and; mean difference in timed up-and-go time for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 67 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.2.3 Counter Movement Jumps

5.4.2.3.1 Maximum Jump Height

Data were available for 26 participants with 11 missing values. There was no statistically significant difference in jump height between HIIT and ReHIIT groups at baseline (MD: -0.74 cm; CIs: -4.64 – 3.17; p=0.74). There was a significant increase in jump height between baseline and preoperative assessments (MD: 1.13cm; CIs: 0.10 – 2.15; p=0.03) in the HIIT group. There was no significant time (p=0.09) or exercise group (p=0.56) effect (Figure 5.7).

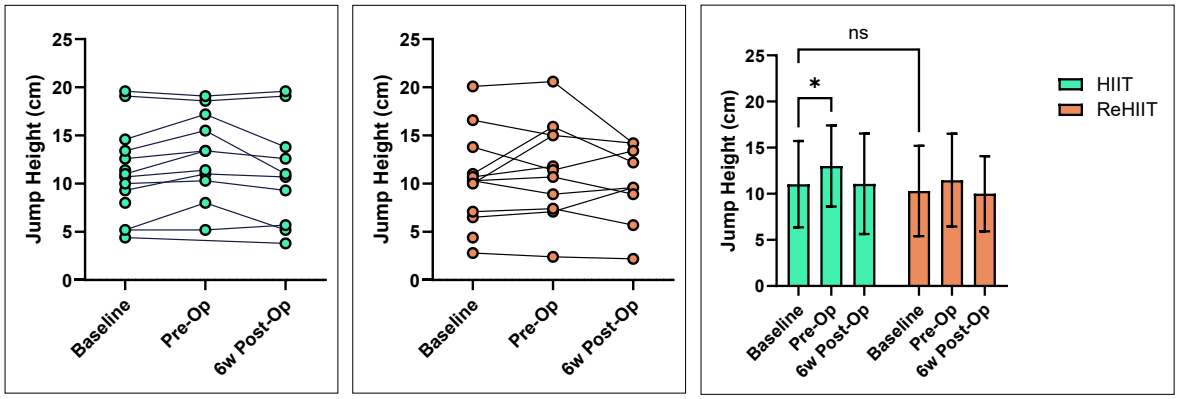


Figure 5.7- Individual changes in jump height for participants in the HIIT group; ReHIIT group and; mean difference in jump height for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 67 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.2.3.2 Maximum Power

Data were available for 26 participants with 11 missing values. There was no statistically significant difference in jump maximum power between HIIT and ReHIIT groups at baseline (MD: -0.02 kW; CIs: -0.62 – 0.57; p=0.93). There was no significant time (p=0.22) or exercise group (p=0.56) effect (Figure 5.8).

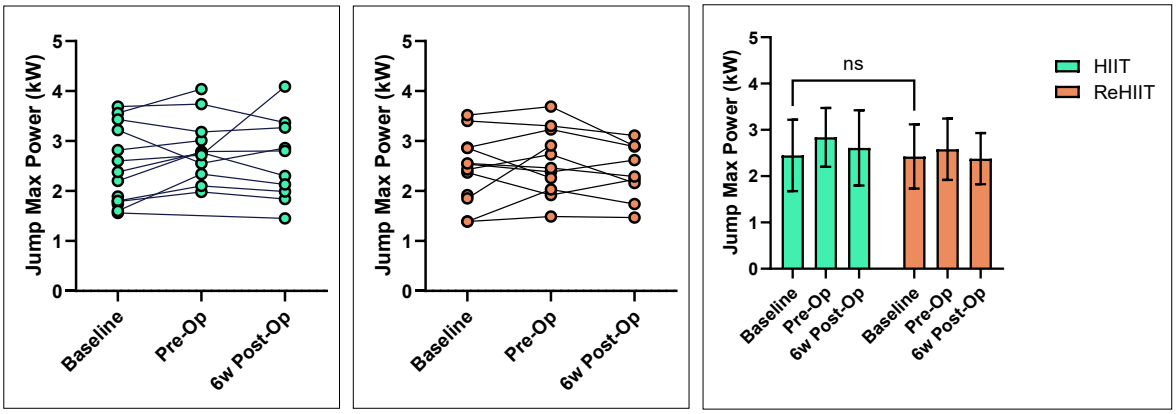


Figure 5.8- Individual changes in jump maximum power for participants in the HIIT group; ReHIIT group and; mean difference in jump maximum power for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 67 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.2.3.3 Take-Off Speed

Data were available for 26 participants with 11 missing values. There was no statistically significant difference in jump TOS between HIIT and ReHIIT groups at baseline (MD: -0.13 m/s; CIs: -0.47 – 0.20; p=0.41). There was no significant time (p=0.06) or exercise group (p=0.34) effect (Figure 5.9).

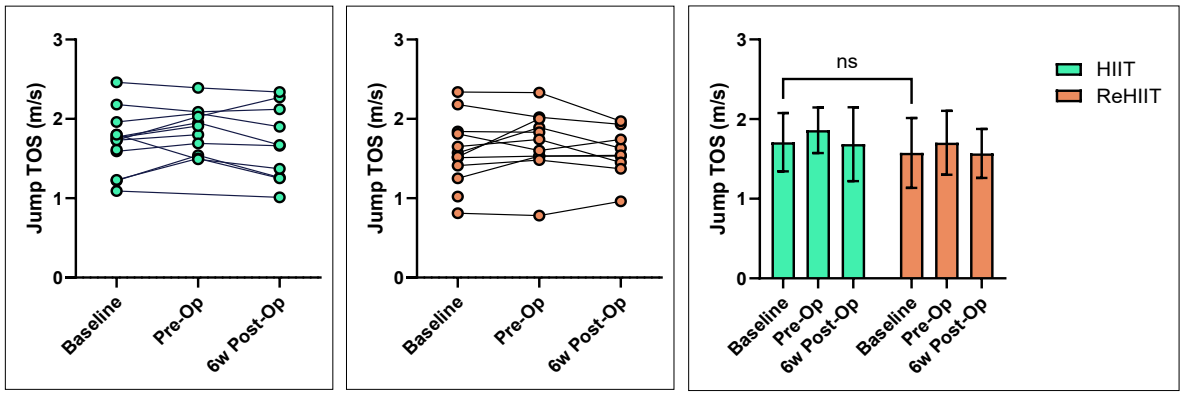


Figure 5.9- Individual changes in jump take-off speed for participants in the HIIT group; ReHIIT group and; mean difference in jump take-off speed for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 67 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.2.4 Short Performance Physical Battery Test

Data were available for 26 participants with 11 missing values. There was no statistically significant difference in SPPBT scores between HIIT and ReHIIT groups at baseline (MD: 0.29 points; CIs: -0.61 – 1.19; p=0.52). There was a significant time (p=0.02) but no exercise group (p=0.12) effect (Figure 5.10).

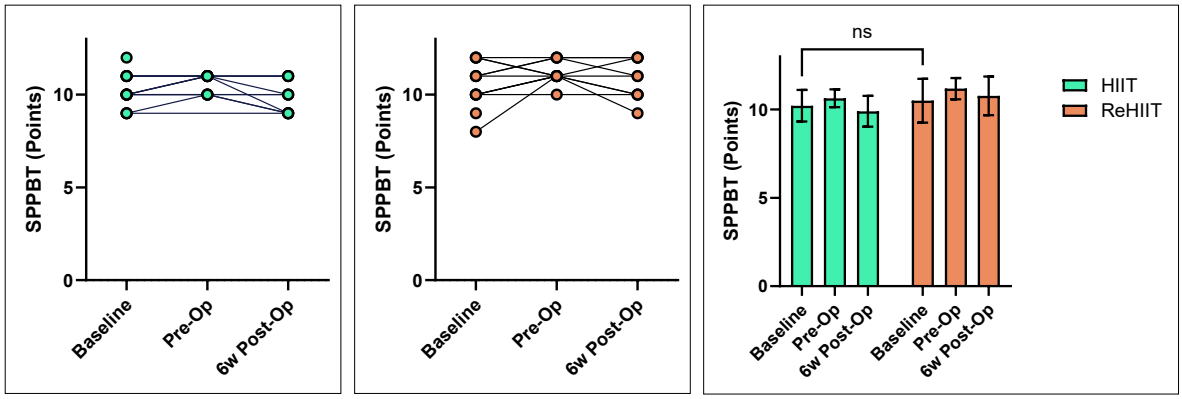


Figure 5.10- Individual changes in short physical performance battery test score for participants in the HIIT group; ReHIIT group and; mean difference in short physical performance battery test score for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 67 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.2.1 Handgrip Strength

Data were available for 26 participants with 11 missing values. There was no statistically significant difference in HGS between HIIT and ReHIIT groups at baseline (MD: -6.48 Kg; CIs: -13.88 – 0.93; p=0.08). There was a significant decrease in HGS between preoperative and 6-week postoperative assessments (MD: -1.9 Kg; CIs: -3.71 – -0.16; p=0.03) in the ReHIIT group. There was a significant time (p=0.04) but no exercise group (p=0.09) effect (Figure 5.11).

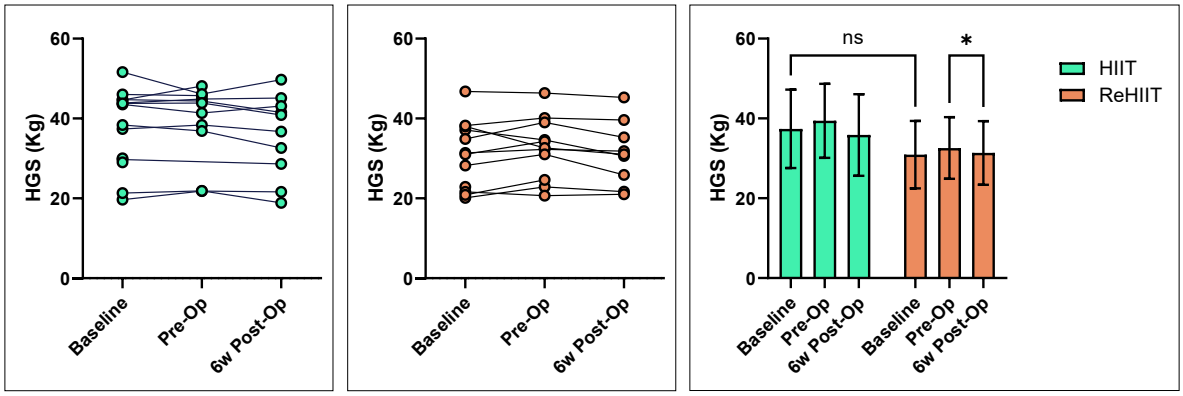


Figure 5.11- Individual changes in handgrip strength for participants in the HIIT group; ReHIIT group and; mean difference in handgrip strength for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 67 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.3 Self-Reported Quality-of-Life, Functional Status & Symptom Burden

QoL, functional and symptom scales were self-reported/ recorded by participants using the EORTC QLQ-C30. For QoL and functional scales, a higher score is associated with a subjective '*better*' QoL and functional status; for symptom scores, a higher score equates with subjectively '*worse*' symptoms. A maximum score on any single metric is 100.

5.4.3.1 Quality-of-Life/ Global Health Status

Data were available for 27 participants with 12 missing values. There was no statistically significant difference in QoL/ *Global Health Status* between HIIT and ReHIIT groups at baseline (MD: 2.36; CIs: -10.36 – 15.08; p=0.70). There was a significant decrease in QoL/ *Global Health Status* between baseline and 6-week postoperative (MD: -8.80; CIs: -17.32 – -0.27; p=0.04) and preoperative and 6-week postoperative assessments (MD: -18.06; CIs: -32.64 – -3.47; p=0.02) in the ReHIIT group. There was significant time (p=0.0004) but no exercise group (p=0.69) effect (Figure 5.12).

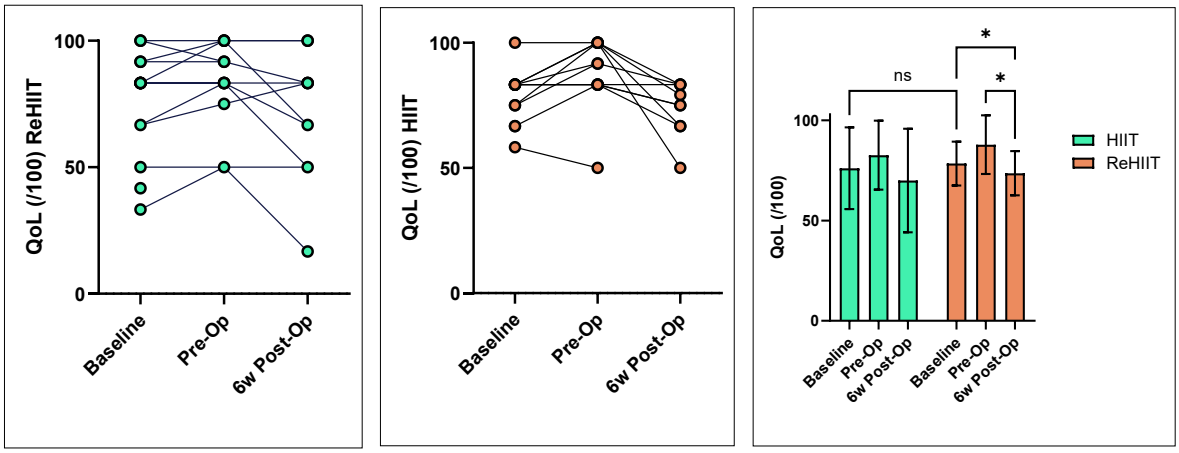


Figure 5.12- Individual changes in quality-of-life score (as measured by EORTC QLQ-C30) for participants in the HIIT group; ReHIIT group and; mean difference in Quality of Life score for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 69 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.3.2 Functional Status

Data availability and baseline comparison are detailed in Table 5.2 and displayed graphically in Figure 5.13.

Functioning Domain (EORTC)	Data Availability (n Participants)	Missing Data (n)	p-value at Baseline (HIIT vs ReHIIT)
Physical	27	12	0.40
Emotional	27	12	0.29
Social	27	12	0.51
Role	27	12	0.37
Cognitive	27	12	0.74

Table 5.2- Baseline comparative statistics between HIIT and ReHIIT groups for EORTC functional domains. Analysis via mixed-effects analysis.

There was no statistically significant change in any self-reported functional domain in the HIIT group. The only significant between group difference was in role functioning where the HIIT group showed increased role functioning (/100) compared to the ReHIIT group at 6-week postoperative assessment (MD: 22.41; CIs: 2.842 – 41.97; p=0.03). Significant changes in self-reported functional status in the ReHIIT group are detailed in Table 5.3.

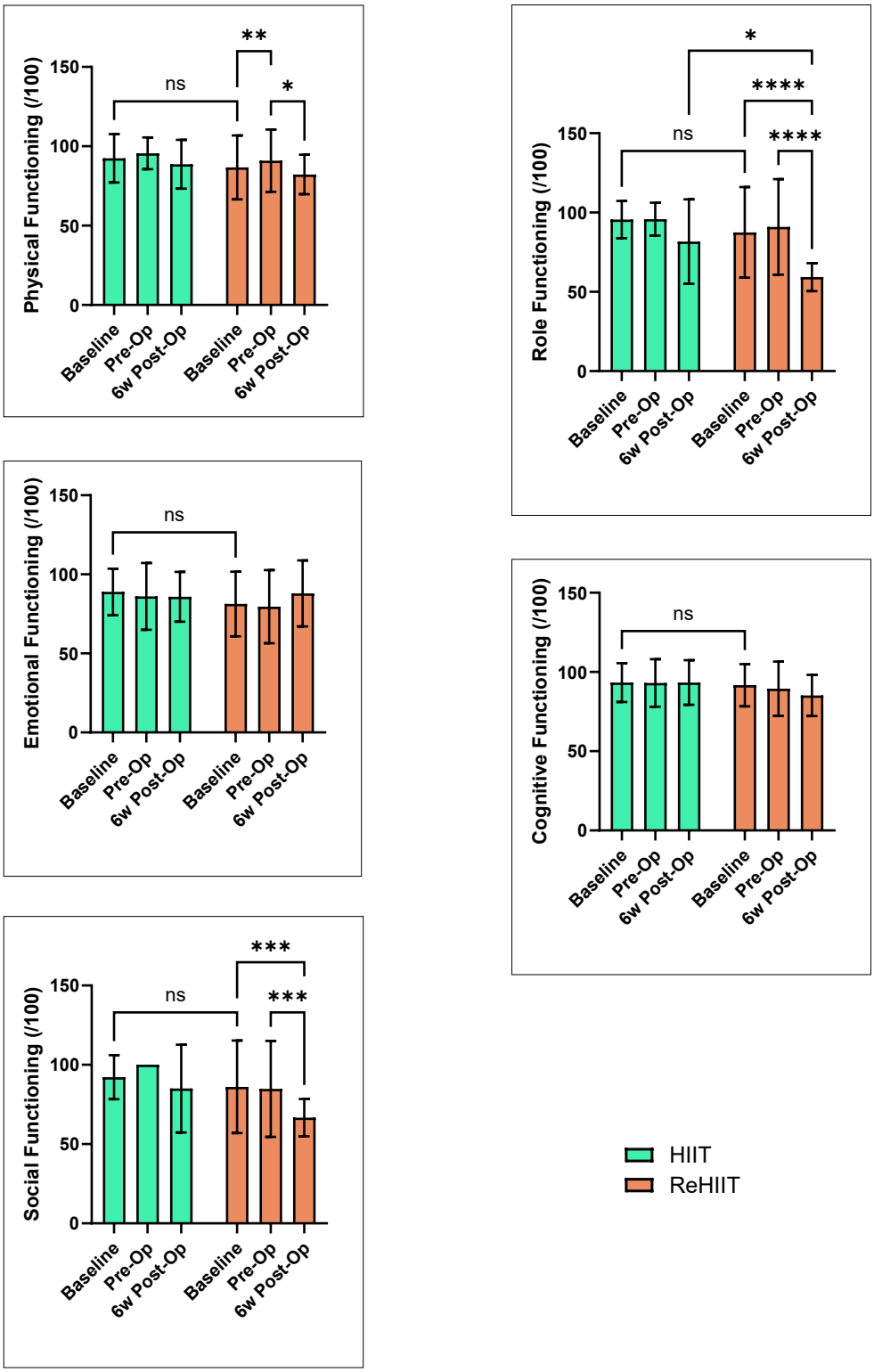


Figure 5.13- Mean difference in functional domains (EORTC) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 69 datapoints. Analysis via mixed-effects analysis.

	Assessment Comparisons (ReHIIT)		
Functioning Domain (EORTC)	**Baseline to Preoperative (V1-V2)**	**Baseline to 6-Week Postoperative (V1-V3)**	**Preoperative to 6-Week Postoperative (V2-V3)**
Physical	Increase (MD: 4.24; CIs: 1.46 – 7.02; p=0.005)	Non-Sig	Decrease (MD: -14.07; CIs: -25.27 – -2.87; p=0.02)
Emotional	Non-Sig	Non-Sig	Non Sig
Social	Non-Sig	Decrease (MD: -25.93; CIs: -37.46 – -14.39; p=0.0005)	Decrease (MD: -27.78; CIs: -39.00 – -16.55; p=0.0003)
Role	Non-Sig	Decrease (MD: -35.19; CIs: -44.72 – -25.65; p<0.0001)	Decrease (MD: -40.74; CIs: -49.11 – -32.37; p<0.0001)
Cognitive	Non-Sig	Non-Sig	Non-Sig

Table 5.3- Comparative statistics for functional domain outcomes (EORTC) for the ReHIIT group between baseline (V1), preoperative (V2) and 6-week postoperative (V3) assessments. Analysis via mixed-effects analysis. Green signifies a statistically significant increase (improvement); red signifies a statistically significant decrease (worsening) and yellow signifies no statistically significant change.

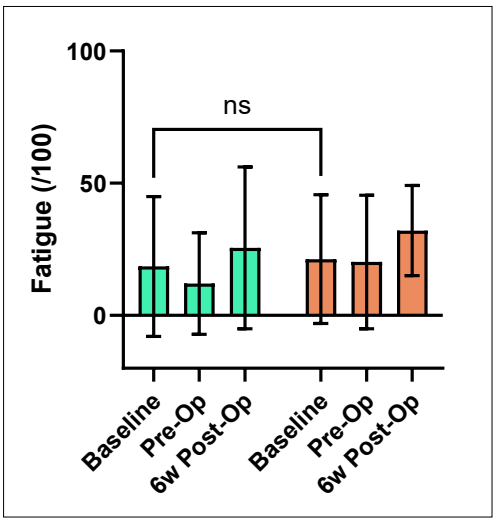
5.4.3.3 Symptom Burden

Data availability and baseline comparison are detailed in Table 5.4 and displayed graphically in Figure 5.14.

Symptom Domain (EORTC)	Data Availability (n Participants)	Missing Data (n)	p-value at Baseline (HIIT vs ReHIIT)
Fatigue	27	12	0.78
Nausea & Vomiting	27	12	0.63
Pain	27	12	0.08
Dyspnoea	27	12	0.76
Insomnia	27	12	0.73
Appetite Loss	27	12	0.77
Constipation	27	12	0.56
Diarrhoea	27	12	0.56
Financial Difficulties	27	12	>0.99

Table 5.4- Baseline comparative statistics between HIIT and ReHIIT groups for EORTC symptom domains. Analysis via mixed-effects analysis.

There was no statistically significant change in any self-reported symptom domain in the either group. With the exception of fatigue, where there was a time effect (p=0.005), there was no significant time, exercise group or time x exercise group effect in any of the symptom domains.


Fatigue (/100)
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0
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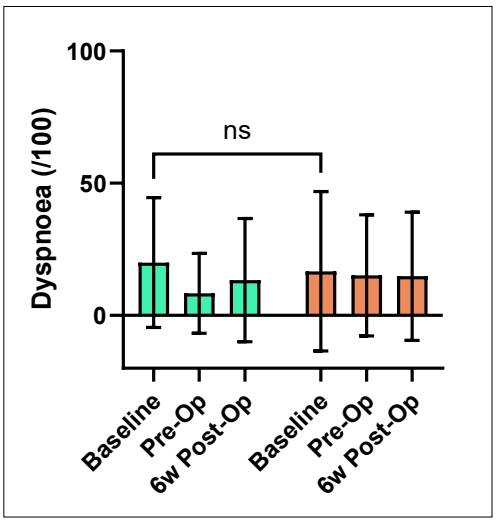
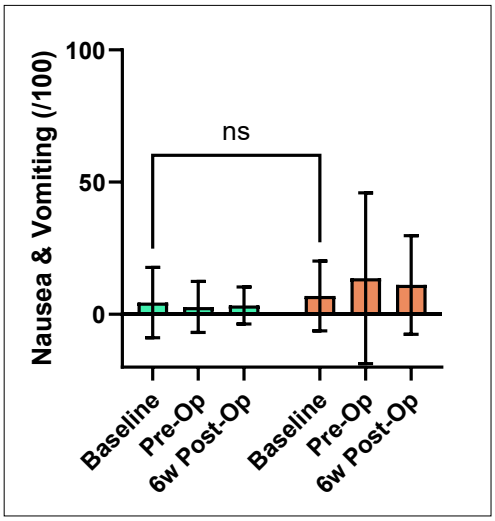
Baseline
Pre-Op
6w Post-Op
Baseline
Pre-Op
6w Post-Op


Dyspnoea (/100)
100
50
0
ns
Baseline
Pre-Op
6w Post-Op
Baseline
Pre-Op
6w Post-Op


Nausea & Vomiting (/100)
100
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0
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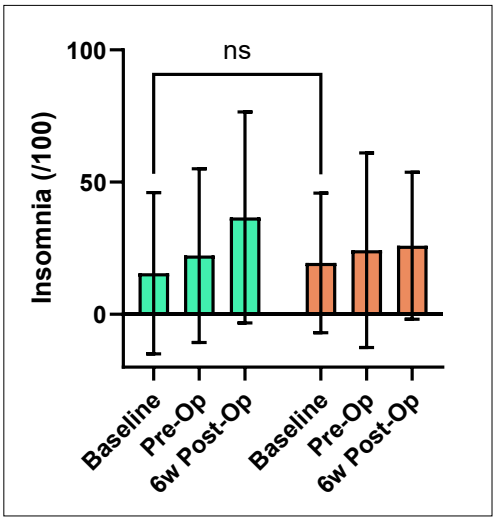
Baseline
Pre-Op
6w Post-Op
Baseline
Pre-Op
6w Post-Op


Insomnia (/100)
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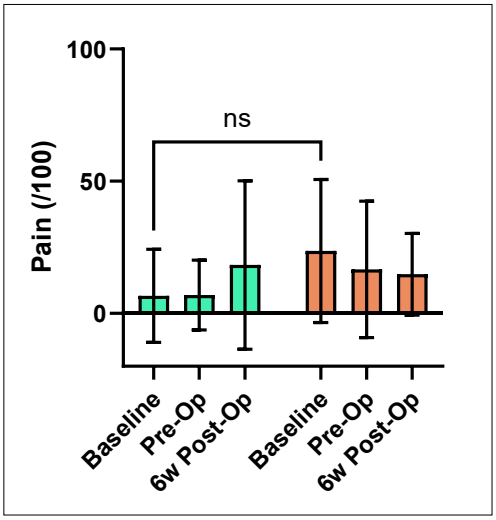
Baseline
Pre-Op
6w Post-Op
Baseline
Pre-Op
6w Post-Op


Pain (/100)
100
50
0
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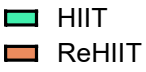
Baseline
Pre-Op
6w Post-Op
Baseline
Pre-Op
6w Post-Op


HIIT
ReHIIT

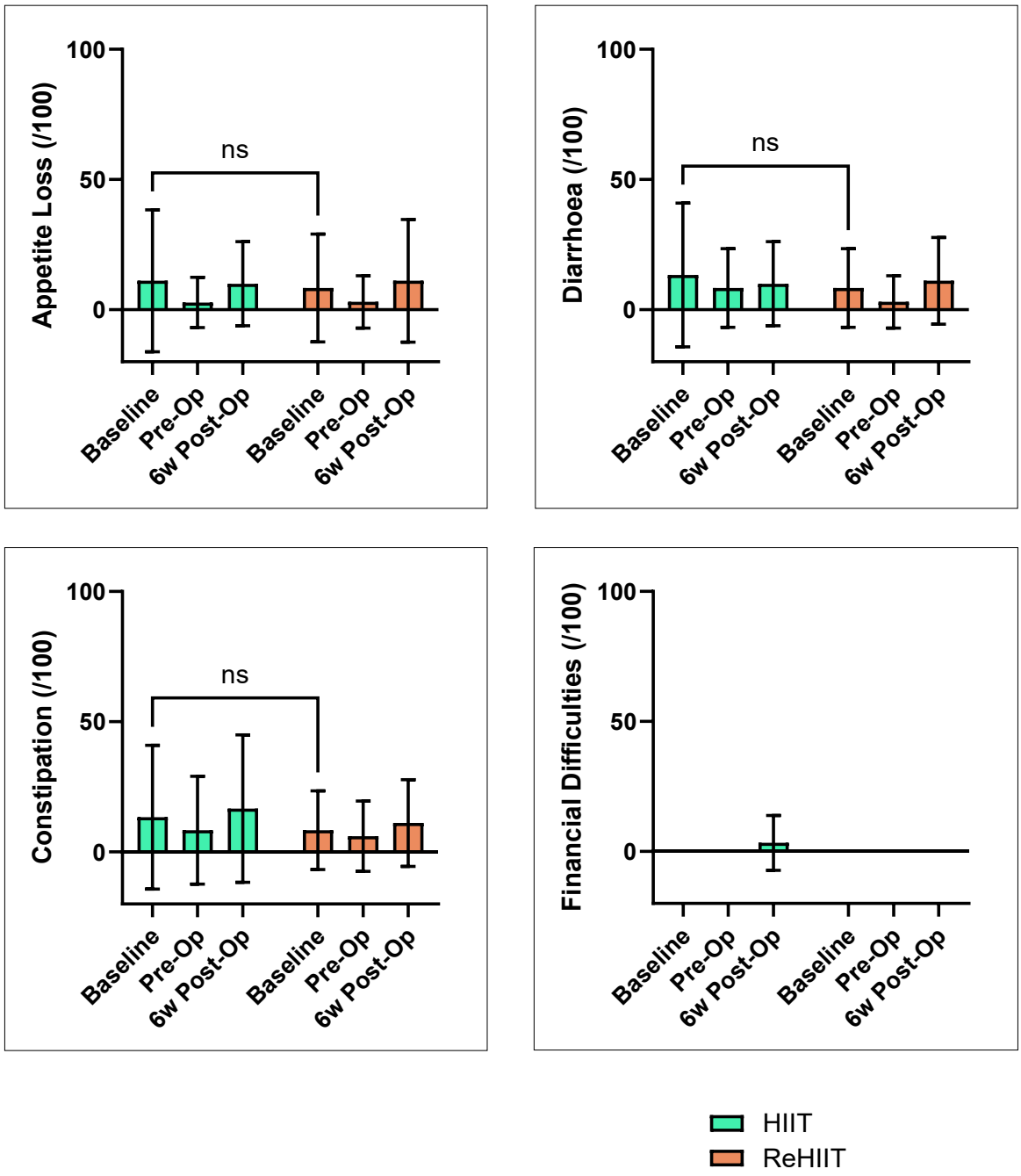


Figure 5.14- Mean difference in symptom domains (EORTC) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 69 datapoints. Analysis via mixed-effects analysis.

5.4.4 Self-Reported Activity Status

Self-reported activity status was self-reported/ recorded via the DASI questionnaire.

5.4.4.1 Self-Reported VO_{2Peak} Estimate

Data were available for 25 participants with 13 missing values. There was no statistically significant difference in self-reported VO_{2Peak} estimate between HIIT and ReHIIT groups at baseline (MD: -2.94 mL/min; CIs: -7.61 – 1.73; p=0.20). There was a significant decrease in self-reported VO_{2Peak} estimate between baseline and 6-week postoperative (MD: -7.07 mL/min; CIs: -11.29 – -2.85; p=0.004), preoperative and 6-week postoperative assessments (MD: -8.01mL/min; CIs: -12.87 – -3.16; p=0.005) in the HIIT group. There was a significant time (p<0.0001), but no exercise group (p=0.45) effect (Figure 5.15).

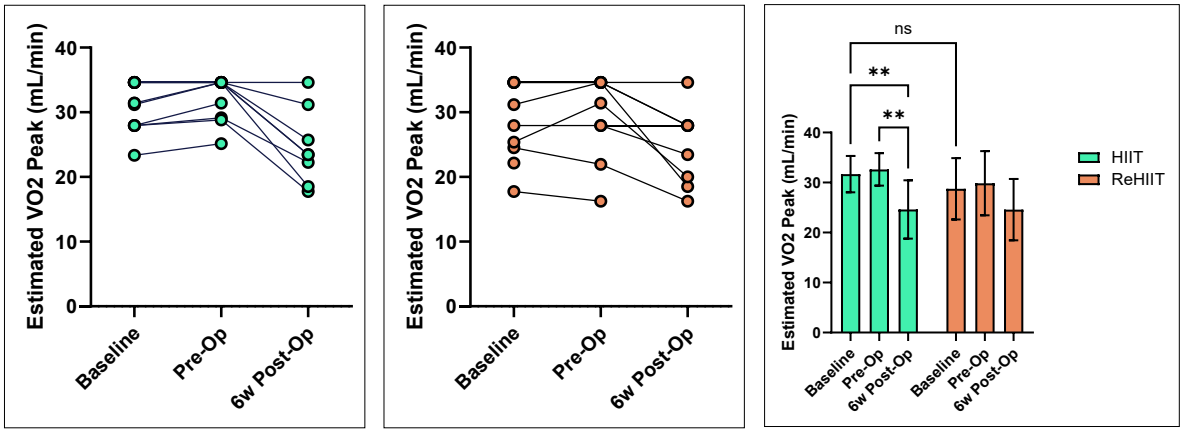


Figure 5.15- Individual changes in estimated VO_{2Peak} (DASI) for participants in the HIIT group; ReHIIT group and; mean difference in VO_{2Peak} (DASI) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 62 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.4.2 Self-Reported Metabolic Equivalent of Tasks Estimate

Data were available for 25 participants with 13 missing values. There was no statistically significant difference in self-reported METs estimate between HIIT and ReHIIT groups at baseline (MD: -0.84 METs; CIs: -2.17 – 0.49; p=0.20). There was a significant decrease in self-reported METs estimate between baseline and 6-week postoperative (MD: -2.02 METs; CIs: --3.23 – -0.82; p=0.004), preoperative and 6-week postoperative assessments (MD: -2.29 METs; CIs: -3.68 – -0.82; p=0.005) in the HIIT group. There was significant time (p<0.0001), but no exercise group (p=0.45) effect (Figure 5.16).

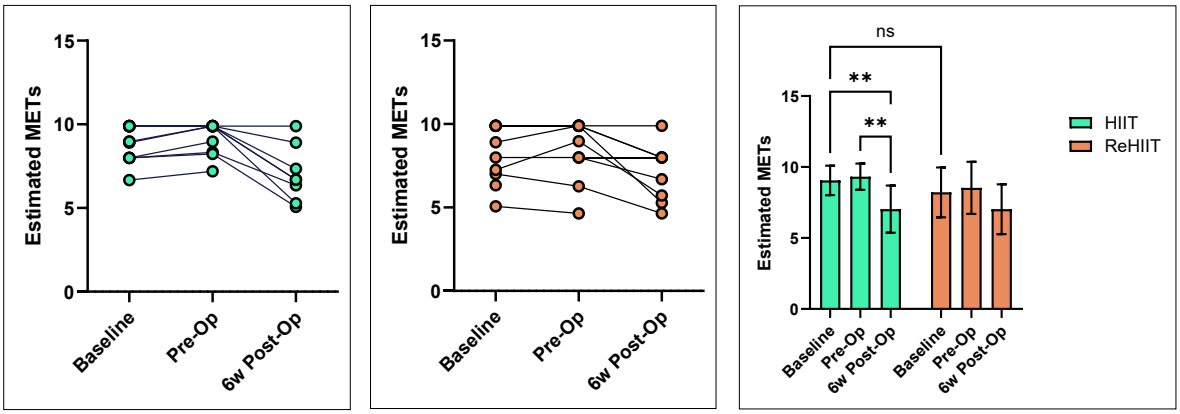


Figure 5.16- Individual changes in estimated METs (DASI) for participants in the HIIT group; ReHIIT group and; mean difference in METs (DASI) for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 62 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.5 Habitual Activity

Data availability and baseline comparison are detailed in Table 5.5.

Habitual Activity Domain	Data Availability (n Participants)	Missing Data (n)	p-value at Baseline (HIIT vs ReHIIT)
Steps/ Day	27	19	0.20
STS/ Day	27	19	0.99
MET.h/ Day	27	23	0.16

Table 5.5- Baseline comparative statistics between HIIT and ReHIIT groups for habitual activity. Analysis via mixed-effects analysis.

5.4.5.1 Steps per Day

There was no statistically significant difference in steps/day between HIIT and ReHIIT groups at baseline (MD: 1,867 steps; CIs: -1048 – 4783; p=0.20). There was a significant time (p<0.0001) but no exercise group (p=0.49) effect (Figure 5.17). Of note, there was no significant difference in values of steps/day between groups at any matched timepoint.

Significant changes in steps/day in the HIIT and ReHIIT group are detailed in Table 5.6.

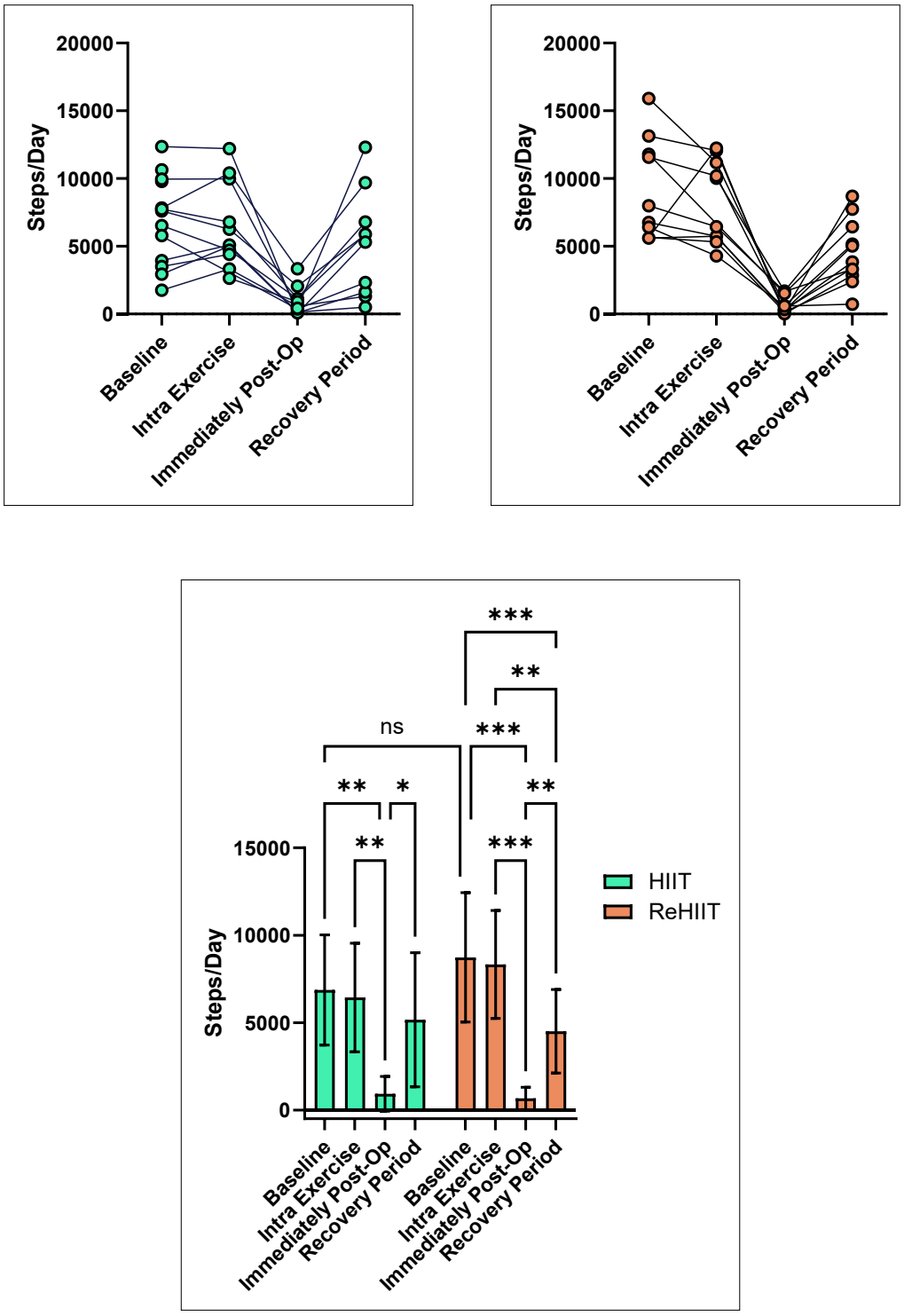


Figure 5.17- Individual changes in steps/day for participants in the HIIT group; ReHIIT group and; mean difference in steps/day for HIIT & ReHIIT groups between baseline, preoperative

and 6-week postoperative assessments. A total of 62 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.5.2 Sit-To-Stands per Day

There was no statistically significant difference in STS/day between HIIT and ReHIIT groups at baseline (MD: -0.07 STSs; CIs: -10.65 – 10.51; p=0.99). There was a significant time (p<0.0001); but no but no exercise group (p=0.49) effect (Figure 5.18). Of note, there was no significant difference in values of STS/day between groups at any matched timepoint.

Significant changes in STS/day in the HIIT and ReHIIT group are detailed in Table 5.6.

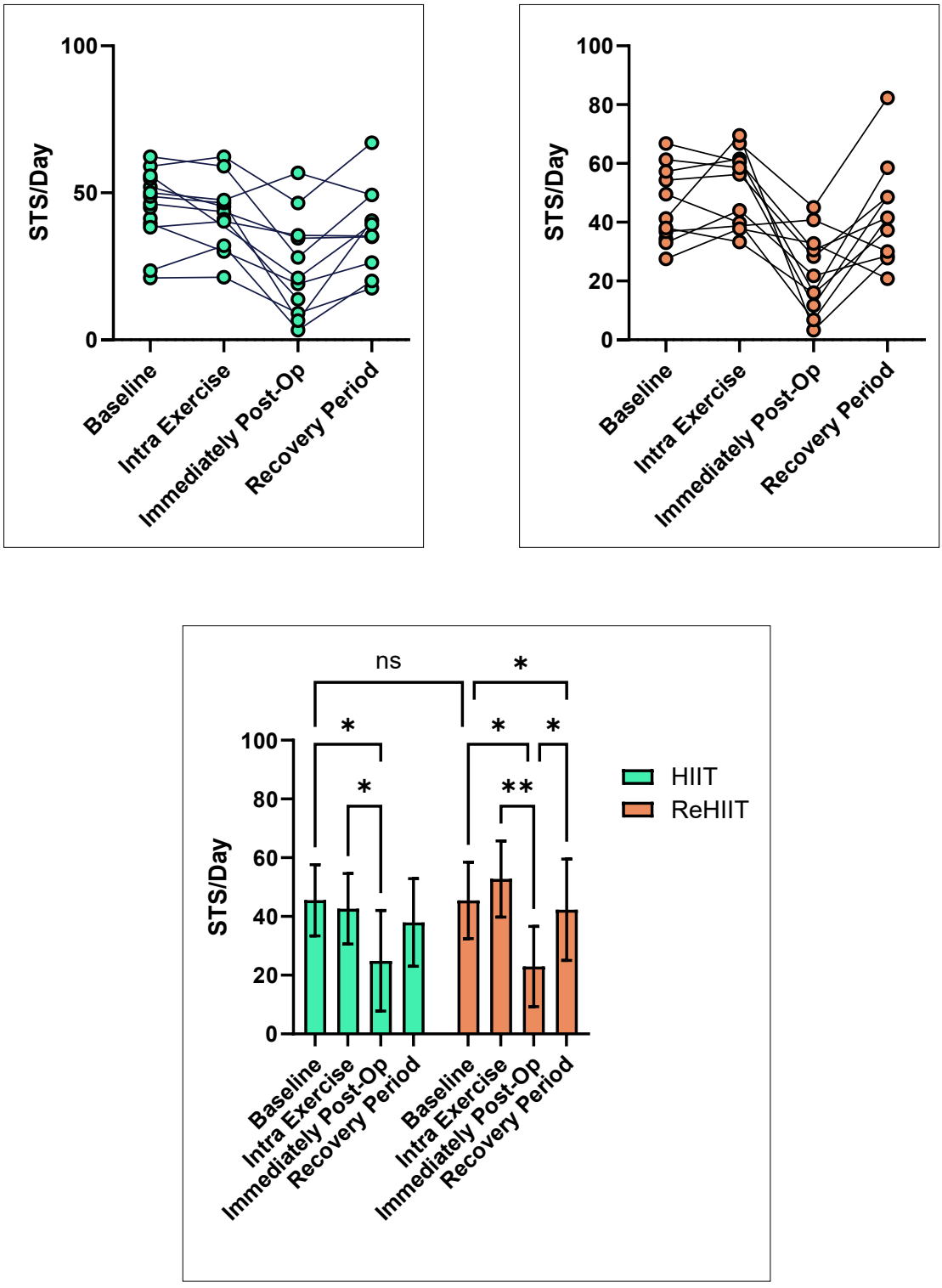


Figure 5.18- Individual changes in sit-to-stands/day for participants in the HIIT group; ReHIIT group and; mean difference in sit-to-stands/day for HIIT & ReHIIT groups between baseline,

preoperative and 6-week postoperative assessments. A total of 62 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.5.1 Metabolic Equivalent Hours per Day

There was no statistically significant difference in MET.h/Day between HIIT and ReHIIT groups at baseline (MD: 0.85 MET.h/day; CIs: -0.37 – 2.07; p=0.16). There was a significant time (p<0.0001) but no exercise group (p=0.47) effect (Figure 5.19). Of note, there was no significant difference in values of MET.h/Day between groups at any matched timepoint.

Significant changes in MET.h/day in the HIIT and ReHIIT group are detailed in Table 5.6.

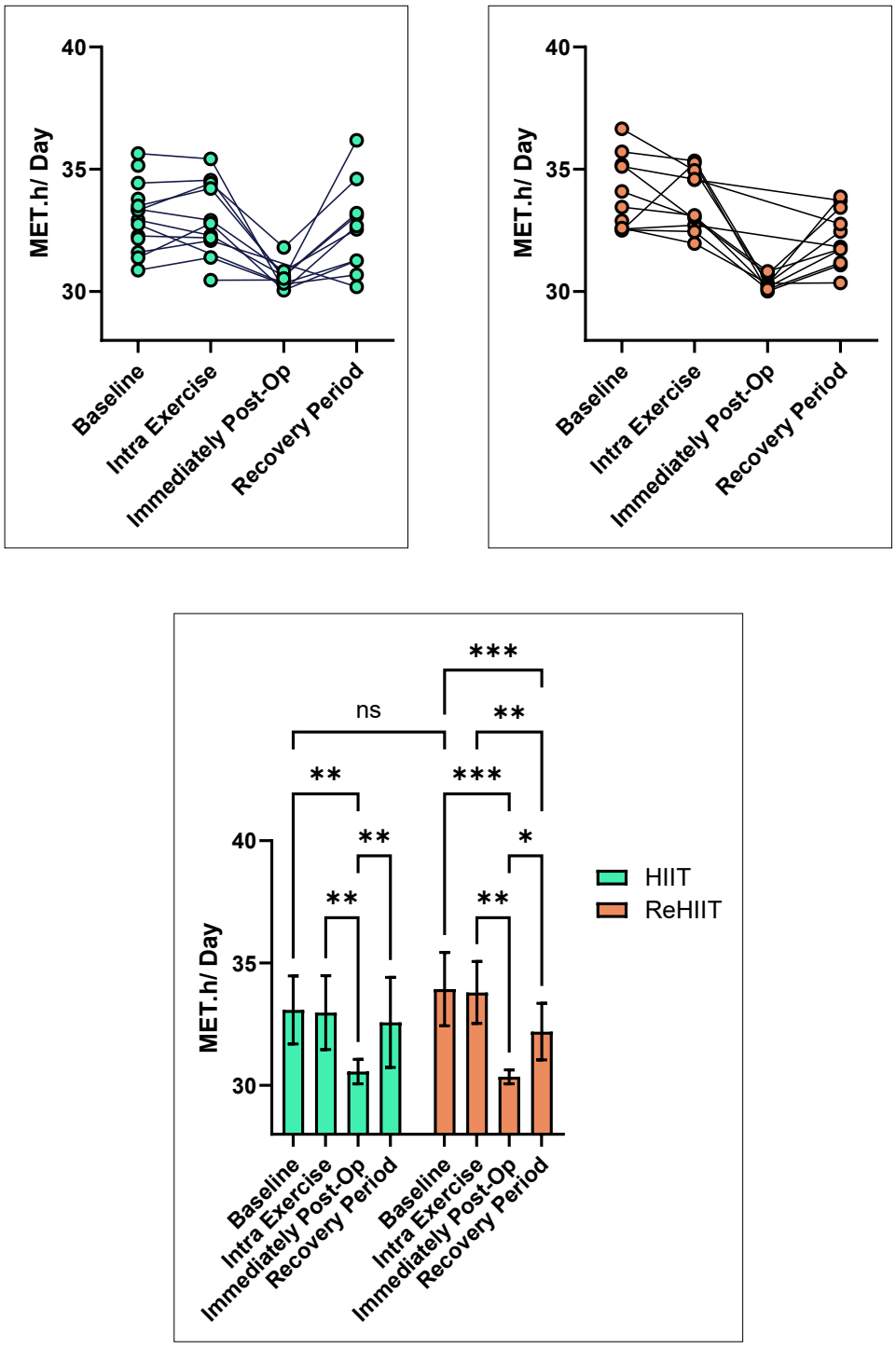


Figure 5.19- Individual changes in metabolic equivalent hours/day for participants in the HIIT group; ReHIIT group and; metabolic equivalent hours /day for HIIT & ReHIIT groups between baseline, preoperative and 6-week postoperative assessments. A total of 58 datapoints; datapoints may appear stacked. Analysis via mixed-effects analysis.

5.4.5.2 Habitual Activity Significant Values Summary

Habitual Activity Domain	Assessment Period Comparisons					
	Baseline to Intra-Exercise (A1-A2)	Baseline to Immediately Postoperatively (A1-A3)	Baseline to Recovery (A1-A4)	Intra Exercise to Immediately Postoperatively (A2-A3)	Intra-Exercise to Recovery (A2-A4)	Immediately Postoperatively to Recovery (A3-A4)
	HIIT					
Steps/ Day	Non Sig	Decrease (MD: -5710; CIs: -8886 – -2533; p=0.002)	Non-Sig	Decrease (MD: -5657; CIs: -8793 – -2520; p=0.002)	Non-Sig	Increase (MD: -4232; CIs: -839 – -7625; p=0.02)
STS/ Day	Non-Sig	Decrease (MD: -18.43; CIs: -33.48 – -3.37; p=0.02)	Non-Sig	Decrease (MD: -17.07; CIs: -31.52 – -2.61; p=0.02)	Non-Sig	Non-Sig
MET.h/ Day	Non-Sig	Decrease (MD: -2.56; CIs: -4.14 – -0.97; p=0.004)	Non-Sig	Decrease (MD: -2.57; CIs: -4.30 – -0.85; p=0.006)	Non-Sig	Increase (MD: 2.26; CIs: 0.63 – 3.90; p=0.009)
	ReHIIT					
Steps/ Day	Non-Sig	Decrease (MD: -8485; CIs: -12101 – -4869; p=0.0002)	Decrease (MD: -4865; CIs: -7355 – -2375; p=0.008)	Decrease (MD: -7748; CIs: -10915 – -4581; p=0.0002)	Decrease (MD: -4015; CIs: -6272 – -1758; p=0.002)	Increase (MD: 3840; CIs: 1735 – 5946; p=0.001)
STS/ Day	Non-Sig	Decrease (MD: -25.82; CIs: -45.08 – -6.55; p=0.01)	Decrease (MD: -8.28; CIs: -15.71 – -0.84; p=0.03)	Decrease (MD: -31.61; CIs: -48.82 – -14.40; p=0.001)	Non-Sig	Increase (MD: 19.33; CIs: 1.96 – 36.71; p=0.03)
MET.h/ Day	Non-Sig	Decrease (MD: -3.74; CIs: -5.50 – -1.97; p=0.0009)	Decrease (MD: -2.00; CIs: -2.91 – -1.08; p=0.0004)	Decrease (MD: -3.43; CIs: -5.39 – -1.47; p=0.004)	Decrease (MD: -1.73; CIs: -2.69 – -0.76; p=0.002)	Increase (MD: 1.63; CIs: 0.31 – 2.95; p=0.02)

Table 5.6- Comparative statistics for habitual activity for the HIIT and ReHIIT group between baseline (A1), intra-exercise (A2), immediately postoperative (A3) and recovery periods (A4). Analysis via mixed-effects analysis. Green signifies a statistically significant increase (improvement); red signifies a statistically significant decrease (worsening) and yellow signifies no statistically significant change.

5.4.6 Clinical Outcomes

5.4.6.1 Length-Of-Stay

Data were available for 27 participants. There was no statistically significant difference in LOS between HIIT and ReHIIT groups (p=0.417) (Figure 5.2). The HIIT group had a median LOS of 6 days (IQR 4-10). The ReHIIT group had a median LOS of 6 days (IQR 3-8).

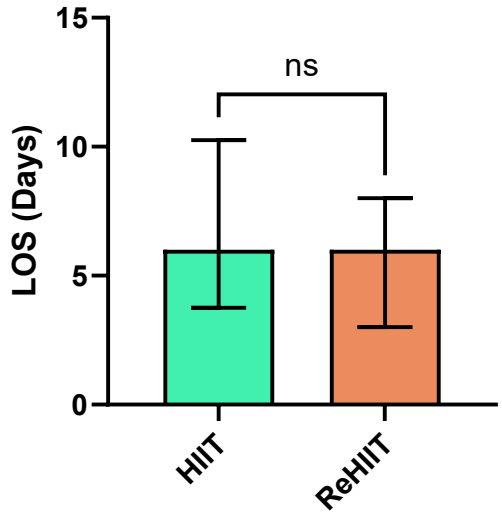


Figure 5.20- Median difference (error bars= IQR) in length-of-stay for HIIT & ReHIIT groups. A total of 27 datapoints. Analysis via Mann-Whitney U test.

5.4.6.2 30-Day Mortality

Data were available for 27 participants. There was no death in either group at 30-days (p>0.9999).

5.4.6.3 Postoperative Complications

Data were available for 27 participants and results are detailed in Table 5.7. There was no statistically difference in number (Pearson's chi-squared test; p=0.84) or severity (Clavien-Dindo grade; Fisher's exact test p=0.40) of postoperative complications between the HIIT and ReHIIT groups.

Postoperative Complications	HIIT	ReHIIT
Yes	7	7
No	7	6
Clavien-Dindo Grade		
N/A	7	7
I	3	1
II	4	2
III	0	2
IV	0	1

Table 5.7-Descriptive statistics of postoperative complications. Absolute and stratified by Clavien-Dindo grade[236].

5.5 Discussion

As discussed in chapter 4, results from the first 28 participants enrolled into the EPiC study make up the results discussed here and should be interpreted with caution as they represent the halfway point of the total aimed recruitment of the EPiC study.

Regarding functional and clinical outcomes, randomisation appears to have been successful, with no significant difference in baseline values for any of the functional or clinical outcomes.

Changes in measures of objectively measured functional capacity were broadly unremarkable. There were no significant changes in 6MWT distance in either group, nor in TUG speed, or SPPBT score. There was a small but significant increase in jump height between baseline and preoperative assessment in the HIIT group and a similar small but significant decrease in HGS between preoperative and 6-week postoperative assessment in the ReHIIT group, but the clinical and functional ramifications are unlikely significant, and the results are likely a result of chance alone given the number of measurements reported.

Self-reported QoL suggested a high QoL for both groups at baseline. There was a small but significant decrease in QoL in the ReHIIT group between baseline/ preoperatively and six weeks post-operation with a similar, but non-significant trend in the HIIT group. This might be related to expected recovery projections or postoperative complications but also coincides with the time where some patients will be about to start adjuvant chemotherapy which is likely to influence QoL. These findings were also mirrored in self-reported functional status, with significant decreases in many functional domains in the ReHIIT group over the length of the study, though there was an increase in self-assessment of physical function between baseline and preoperative assessments, which suggest that the ReHIIT exercise intervention made participants feel 'fitter'. Again, no significant changes were noted in the HIIT group, nor

were there any significant changes in symptom burden in either group, though absolute burden was very low.

Estimates of VO_{2Peak} via the DASI questionnaire significantly reduced in the HIIT group at six weeks post-operation versus baseline and preoperatively with the METs estimate displaying the same change. Both groups self-reported lower values at six weeks post-operation than at baseline and preoperatively, but results did not reach significance in the ReHIIT group which could be due to chance, no effect, or the underpowered nature of the data.

Unsurprisingly, there was a significant reduction in steps/day, STS/day and MET.h/ day immediately postoperatively compared with all other timepoints in both groups. Neither group displayed an increase in any measure of habitual activity between baseline and the intra-exercise period, but the ReHIIT group displayed a global reduction in habitual activity between baseline and recovery periods which was not found in the HIIT group. This may suggest a delayed return to habitual activity in the ReHIIT group, but given the low n, a small number of outliers may affect this result and full reporting from the EPiC study is required prior to assigning weight to this finding.

There was no difference in the clinical outcome of 30-day mortality, LOS or postoperative complications between the groups. Though the complication burden was relatively high (52%) for the 27 participants who had an operation, these were predominantly minor complications and unlikely to skew the results given the expected postoperative complication burden seen in CRC resection.

Overall, though there were some differences between the HIIT and ReHIIT groups regarding functional and clinical outcomes, these were minor, unlikely of clinical significance and underpowered. A positive to be taken, is that for the majority of measures, both groups were

performing equally well at baseline as they were six weeks postoperatively. QoL indicators, symptom burden and habitual activity were all relatively 'good' at baseline which, given the population had already been deemed fit for operative intervention, is not surprising.

Clinical outcomes such as LOS and mortality are likely difficult to affect given the short LOS and the rarity of mortality in this population and much larger studies would be required to tease out any effect.

It does not appear that the addition of RET to HIIT as prehabilitation in patients with CRC scheduled for surgery with curative intent has a significant effect on functional or clinical outcomes. Future work will focus on completion of the EPiC cohort, with a potential addition of healthy volunteers and those with CRC who do not undergo intervention to further delineate any effect of these exercise regimes.

6. General Discussion

6.1 Introduction

To contextualise this discussion and define the premise of this thesis, it is worth revising the current situation regarding exercised-based prehabilitation as monotherapy in patients with CRC scheduled for surgery with curative intent. Prehabilitation in CRC cohorts can only take place in those with CRC. Unlike other cancers[134], HIIT-based regimes in CRC do not appear to improve CRF and only have a marginal effect (if any) on functional and clinical outcomes[98]. Owing to government targets, the timeframe in which to prehabilitate patients with CRC awaiting surgery is short (≤31 days[9]), but despite HIIT-induced improvements being feasible in this timeframe, even amongst athletes[436], it appears that the condition of CRC may directly inhibit one's ability to improve CRF owing to an inability to upregulate MPS whilst CRC is in-situ[128]. Translational research has demonstrated that RET stimulates MPS[437] and thus the question: *does the addition of RET to HIIT as prehabilitation improve CRF and functional and clinical outcomes in patients with CRC scheduled for surgery with curative intent*?

The first aim of this thesis was to review the published literature on RET-based prehabilitation in individuals with CRC with a focus on clinical and functional outcomes. Chapter 2 delineates the current work in this space. Initially the systematic review and meta-analysis described was intended to find studies which employed combined HIIT and RET as exercise prehabilitation monotherapy in patients with CRC, a main aim of the *EPiC* study. The search revealed that no work currently exists answering this questions and thus a broader search of RET-based prehabilitation in this same cohort acted to consider what RET-based therapy could offer in terms of functional and clinical outcomes. A small but significant increase in 6MWT was

discovered which furthered the theory that RET can improve CRF and functional outcomes. Clinical outcomes (LOS and postoperative complication rates) were unchanged.

The second aim of this thesis was to explore the recent literature on nutritional interventions in cancer prehabilitation. Chapter 3 discusses the use of nutritional intervention in cancer prehabilitation, both alone, and in combination with other prehabilitation modalities. Though the focus of this thesis is on exercise monotherapy, much of the literature surrounding prehabilitation in CRC is multi-modal; nutritional therapy a common concomitant intervention. In health, MPS stimulated by RET, requires adequate substrate and thus, nutrition, and in particular malnutrition given a population with CRC must be considered when aiming to increase physiological resilience and thus potentially clinical and functional outcomes[129]. RET is the stimulation, nutrition allows change at a cellular level which in turn increases physiological resilience and thus effects change in functional and clinical domains. Chapter 3 also discusses the current state of prehabilitation research in cancer and argues that, owing to multimodal therapies, it is difficult to tease out specific effects of each individual therapy, or if there is a complex synergy between say nutrition *and* exercise. Further, the chapter speaks to the complexities in outcome measures, again making it hard to draw conclusion from not only individual studies, but from the body of literature as a whole.

The third aim of this thesis was to investigate if combined RET and HIIT prehabilitation in individuals with CRC is feasible in a timeframe in keeping with that between diagnosis and intervention. Chapter 4 represents the first experimental chapter of this thesis and introduces the *EPiC* study. In it, the feasibility of combining RET and HIIT as prehabilitation in CRC was shown to be acceptable to the target population. Much of the earlier work on the set-up of

the study is alluded to, with further information included as appendices. The results of chapter 4, which represent only the partial (and thus underpowered) results from the *EPiC* study are reassuring from a trial management perspective. Randomisation appears successful and recruitment is ahead of target. Both the HIIT and the ReHIIT group displayed changes in partially subjective measures of CRF such as maximum wattage (CPET) and VO_{2Peak} which increased from baseline to preoperative assessments in both groups. AT was unchanged in both groups between baseline and preoperatively and was significantly decreased between preoperative and 6-week postoperative assessments in the ReHIIT group with this effect remaining after correction for body weight and lean mass. Many measures of physiological resilience were increased post-intervention in both groups, but it does not appear that the addition of RET to HIIT in a prehabilitation programme for individuals with CRC scheduled for surgery with curative intent impacts physiological adaptation, nor clinical or functional outcomes.

Chapter 5 discussed functional and clinical outcomes in the cohort described in the previous chapter. Again, both groups displayed improvements in some domains but not to statistical significance. This is not surprising given the underpowering of the results here, which represent the first 28 participants recruited to the EPiC study which aims to recruit n=56. Chapters 4 and 5 further displayed the feasibility of EPiC as a study, and the acceptability of the intervention to the intended population. On average, each participant spent approximately 30 hours undertaking the study, with the majority (~33%) of this time dedicated to the intervention.

Further positives to take away from the results demonstrated in the experimental portion of this thesis include a low rate of participant drop out, anecdotal reports of satisfaction with

study involvement and a return to baseline in most metrics at 6-week postoperative assessment. If ReHIIT prehabilitation was to be considered on a national scale, the short length of exercise period (<26 days), small number of completed sessions (<10) and the standardised equipment used would all demonstrate feasibility within existing DTT targets and common gymnasium infrastructure.

On a personal level and perhaps over and above the training intervention, participants reported enjoying their time in the study. Reasons for involvement included wanting to regain some degree of autonomy, wanting to '*give back'*, wanting to familiarise themselves with the hospital environment and for the one-on-one time with doctors and researchers. Though not formally studied, this enjoyment is apparent in the interactions from participants, from the many cards, emails and gifts received by the research team to local press involvement, with least three of the 28 participants being interviewed for local articles shared by on UHDB social media and the British Broadcasting Corporation (BBC)[438]. Further highlights included study visits from *The Right Honourable* Wes Streeting MP (then Shadow Secretary of State for Health and Social Care) and Mr Tim Mitchell (President, Royal College of Surgeons of England).

6.2 Strengths

Reflecting on the body of work that makes up this thesis, there are many strengths and achievements. Firstly, Chapter 2 is a strong meta-analysis of the current state of RET-based prehabilitation in operable CRC. It is the first meta-analysis of it's kind and has been published in *JCSM Communications*[158]. Chapter 3, a narrative review regarding the effects of nutritional prehabilitation has also been published, and cited by multiple other paper[165].

Perhaps the biggest strength of this thesis is the setting up and undertaking of, the EPiC study. The study is a complex interventional trial which required hundreds of hours of work to

progress to this stage. The drop-out rate, especially due to the intervention, is low, and recruitment is ahead of target. Despite the issues with powering due to the incomplete nature of the data presented here, the results, once powering is reached are expected to be robust in that the systems in place for data collection are working well.

6.3 Limitations

Perhaps the clearest limitation that should be considered before drawing conclusions from the work described here is underpowering. The EPiC study powering is designed on a composite endpoint (change in AT and whole-body muscle mass) based on the assumption that expected effect sizes in either domain would not be apparent with the planned n=56. The results of this thesis are not only a sub-category (n=28) of the larger *EPiC* study, but are also based on single endpoints. As previously described, perhaps it is fairer to see the experimental results detailed here as the initial results of a larger study.

Other limitations include participant selection. Only 18% of patients approached to be in the study accepted (Figure 4.18). Though the main reasons for not wanting to be involved included the experimental burden, in particular muscle biopsies, this means that it was likely an especially motivated 10-20% of 'allcomers' who are described in the results and might not be representative of most patients with CRC scheduled for surgery with curative intent. Many approached patients specified time as one of the main barriers to study/ intervention involvement and considering the increasing incidence in early-onset CRC, perhaps this would be seen more commonly in a younger population who may have more regular work or family commitments[365]. Further, only patients scheduled for surgery were considered. Those who were deemed on a clinical basis to not be fit for an operation were not approached, despite

one stated aim of prehabilitation to make people fit for an operation; this thesis only examines improvements in those already deemed 'fit for an operation'.

Though validated questionnaires were used to capture QoL, no formal interviews were conducted and despite positive interactions with participants, perhaps more insight would be captured with qualitative techniques which could aid recruitment in further works; or further explore opinions from individuals who did not want to be involved with research.

Specifically to activity tracking, the use of ActivPAL monitors was suboptimal. Owing to such minimal activity the first postoperative day, many of the monitors did not start tracking movements, rendering MET.h impossible to interpret. Further, the four-day period selected as to not delay the intervention phase and allow more patients to be eligible for the study may give false readings as ideally five days (including a weekend) should be tracked[439]. However, pragmatic concessions are to be expected in the context of human studies.

Regarding clinical outcomes, no long-term data were captured for example on the incidence of hernias, delayed return to work etc. Some of the studied endpoints were heavily influenced by outliers such as LOS which although low (mean: 6 days, IQR 4-10 days), had a significant positive skew (range: 27 days).

6.4 Ongoing Work of Note

Though the *EPiC* study and the work presented here focussed on the addition of RET to HIIT in those with operable CRC, there are some ongoing of trials with similar aims.

6.4.1 ONCOFIT

The ONCOFIT study[440] is a Spanish-based, single-centre, RCT comparing usual care with combination, multimodal pre- and rehabilitation with exercise (HIIT and RET), nutritional

intervention (education) and psychological support in those with operable CRC. The primary measure is postoperative morbidity and mortality with secondary measures including functional capacity, body composition, physical activity, dietary habits, and cost effectiveness. Recruitment is ongoing with an aimed n=90. It differs from the EPiC study both in terms of multimodal therapy and the inclusion of rehabilitation[87].

6.4.2 PREPARE-ABC

The PREPARE-ABC[441] study is a multicentre, RCT designed to assess the effects of hospital-based versus home-based exercise (aerobic, interval and RET) prehabilitation and postoperative exercise on 30-day morbidity, and 12-month HR-QoL in those with operable CRC. Secondary outcome measures include CRF, HGS, LOS, readmission rate and psychological health status. The planned sample size is n=1,146[442]. It differs from the EPiC study in that it includes patients receiving long-course chemo-radiotherapy, includes a home-supported exercise arm, has no minimum requirement for exercise sessions attended and continues to encourage exercise (over and above standard care) in the postoperative period[441–443]. Initial reports showed no difference in any of the aforementioned endpoints, though patients randomised to an exercise group were more likely to engage with postoperative exercise[444], which has been shown to increase disease-free survival in individuals with CRC treated with adjuvant therapy[445].

6.4.3 WesFit

The WesFit[446] study is a multi-centre, RCT comparing i) standard care; ii) preoperative HIIT-based prehabilitation; iii) psychological support and; iv) combined preoperative HIIT-based prehabilitation and psychological support in patients with operable CRC. The primary outcome is LOS with secondary outcomes including survival, morbidity, CRF and HR-QoL. The

planned recruitment is n=1,560. The study differs from EPiC in that the exercise intervention is HIIT only, and there is no lower limit on the number of exercise sessions attended[446].

6.5 Future Work

As touched on elsewhere there are a number of directions in which *EPiC* can progress or be built upon. Firstly, recruitment is ongoing with an aim of n=56 which should give sufficient power to comment on the main composite outcome. Secondly the addition of control group/s should be considered depending on the initial results. Currently, the HIIT group has shown a promising response to exercise in terms of CRF, should this maintain, a control group of usual care might be able to identify the magnitude of this HIIT-induced change. Further, it would allow the comparison, at 6-week postoperative assessment, between prehabilitated and non-prehabilitated patients. Currently most patients achieve similar results on their baseline and 6-week postoperative assessments which is encouraging, but it is not clear that this is due to prehabilitation. A second consideration regarding control groups would be a healthy volunteer group who undergo the same training regime (HIIT or ReHIIT). This would help determine if any changes seen in either group are different to that of a healthy population, or if the regime works as expected in a healthy population.

Although the results here are preliminary, given the lack of improvement in many metrics of clinical and functional outcomes with ReHIIT when compared with HIIT, future studies may consider a multimodal approach. As argued in chapters 2 and 3, multimodal therapy often demonstrates preoperative gains in physical function, but the multitude of ways in which multimodal prehabilitation is undertaken, coupled with large variability in reported outcomes means deciphering which interventions work, and in what outcomes, is difficult. Efforts to improve this situation have been made with a 2024 study defining standards and core

outcomes for clinical trials in prehabilitation for colorectal surgery[447]. Future work should aim to satisfy these standards and multi-arm, multi-stage trials could be utilised to add in and subtract different elements of prehabilitation such as exercise, nutrition and psychological support to best optimise for the outcome of choice[448]. This would have the advantage of comparing multiple interventions at once, and responding to data as it is collected meaning that fewer participants would be required than if each arm was a separate trial as recruitment can be a limitation of a complex and intense study.

For EPiC, only around one in five (18%) of potentially eligible patients agreed to participant, should the exercise intervention alone be adopted more globally, a higher proportion of patients would likely participate. The time commitment and length of intervention for either HIIT or ReHIIT sessions alone, is considerably less than the intervention in addition to the assessment requirements (assessment days, activity tracking etc.). Should the results from the EPiC study be positive and give insight into a translational target, there would be no need to continue to study this phenomenon to such a degree.

Formal, structured interviews could be employed to better understand themes surrounding exercise intervention in the preoperative period, but also in those who did not participate, in that it could offer insight into what might make patients more likely to undertake preoperative exercise regimes. *NHS England* have suggested that, as part of the reform in elective care, patients should be 'optimised' prior to surgery, to reduce cancellations, LOS and reduce postoperative complications[449]. Again, these outcomes could be compared with a control group as, at least on an anecdotal level, participants in the EPiC study had issues which may have delayed their surgery which were resolved in part by being involved in the study. Though the implementation of prehabilitation into existing cancer care pathways is

recommended[85] there is still some way to go towards fulfilling this aim, with only recent shifts towards prehabilitation for individuals with cancer being the norm[85]. Given the complexity of, especially multimodal prehabilitation, implementing complex interventions in the current NHS climate would pose a challenge, but universal adoption of prehabilitation in cancer care could help those most in need, making patients '*fit for surgery*' not just '*fitter for surgery*' and opening-up the possibility of operating in those who are currently not being offered their only chance at a cure.

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Appendices

Appendix A- Full Search Strategies

Each search strategy was undertaken on 20/01/2023 and updated on 23/11/2023.

CINAHL

Initial Search:

MY

EBSCOhost

Friday, January 20, 2023 1:24:50 PM

#	Query	Limiters/Expanders	Last Run Via	Results
S47	(((S21 AND S32) OR S6) AND S46)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	237
S46	S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S45	TI strengthening OR AB strengthening OR MW strengthening	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S44	TI weight training OR AB weight training OR MW weight training	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S43	TI weightlifting OR AB weightlifting OR MW weightlifting	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S42	TI weight lifting OR AB weight lifting OR MW weight lifting	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S41	TI exercise training OR AB exercise training OR MW exercise training	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display

S40	TI resistance training OR AB resistance training OR MW resistance training	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S39	TI muscle training OR AB muscle training OR MW muscle training	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S38	TI strength training OR AB strength training OR MW strength training	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S37	TI resistance exercise OR AB resistance exercise OR MW resistance exercise	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S36	TI RET OR AB RET OR MW RET	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S35	(MH "Weight Lifting")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S34	(MH "Muscle Strengthening+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S33	(MH "Resistance Training")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S32	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display

S31	TI tumour OR AB tumour OR MW tumour	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S30	TI tumor OR AB tumor OR MW tumor	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S29	TI neoplas# OR AB neoplas# OR MW neoplas#	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S28	TI malignan# OR AB malignan# OR MW malignan#	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S27	TI adenocarcinoma OR AB adenocarcinoma OR MW adenocarcinoma	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S26	TI carcinoma OR AB carcinoma OR MW carcinoma	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S25	TI cancer OR AB cancer OR MW cancer	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S24	(MH "Neoplasms+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S23	(MH "Adenocarcinoma+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display

S22	(MH "Carcinoma+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S21	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S20	TI bowel OR AB bowel OR MW bowel	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S19	TI appendi* OR AB appendi* OR MW appendi*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S18	TI caecal OR AB caecal OR MW caecal	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S17	TI cecal OR AB cecal OR MW cecal	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S16	TI sigmoid OR AB sigmoid OR MW sigmoid	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S15	TI rect* OR AB rect* OR MW rect*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S14	TI colon* OR AB colon* OR MW colon*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	Display

			Database - CINAHL Complete	
S13	TI colorectal OR AB colorectal OR MW colorectal	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S12	(MH "Appendix")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S11	(MH "Cecum+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S10	(MH "Sigmoid")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S9	(MH "Colon, Ascending")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S8	(MH "Rectum+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S7	(MH "Colon+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S6	S1 OR S2 OR S3 OR S4 OR S5	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S5	(MH "Cecal Neoplasms")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	Display

			Database - CINAHL Complete	
S4	(MH "Sigmoid Neoplasms")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S3	(MH "Rectal Neoplasms+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S2	(MH "Colonic Neoplasms+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S1	(MH "Colorectal Neoplasms+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display

Updated Search (November 2023):

As above, in addition:

S48	(((S21 AND S32) OR S6) AND S46)	Limiters - Publication Date: 20230101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Ultimate	13

CENTRAL

Initial Search:

Search Name: CRC_RET_Cochrane
Date Run: 20/01/2023 16:37:49
Comment:

ID	Search	Hits
#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	9388
#2	MeSH descriptor: [Rectal Neoplasms] explode all trees	2063
#3	MeSH descriptor: [Sigmoid Neoplasms] explode all trees	75
#4	MeSH descriptor: [Cecal Neoplasms] explode all trees	21
#5	MeSH descriptor: [Appendiceal Neoplasms] explode all trees	13
#6	#1 OR #2 OR #3 OR #4 OR #5	9396
#7	MeSH descriptor: [Colon] explode all trees	1650
#8	MeSH descriptor: [Rectum] explode all trees	1468
#9	MeSH descriptor: [Colon, Sigmoid] explode all trees	125
#10	MeSH descriptor: [Colon, Descending] explode all trees	11
#11	MeSH descriptor: [Colon, Transverse] explode all trees	9
#12	MeSH descriptor: [Colon, Ascending] explode all trees	28
#13	MeSH descriptor: [Cecum] explode all trees	191
#14	MeSH descriptor: [Appendix] explode all trees	45
#15	colorectal	23320
#16	colon*	38717
#17	rect*	22932
#18	sigmoid	1314
#19	c?ecal	1108
#20	appendi*	13924
#21	bowel	23249
#22	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	94228
#23	MeSH descriptor: [Neoplasms] explode all trees	90677
#24	MeSH descriptor: [Carcinoma] explode all trees	15247
#25	MeSH descriptor: [Adenocarcinoma] explode all trees	8444
#26	MeSH descriptor: [Neoplasms] explode all trees	90677
#27	MeSH descriptor: [Neoplasms] explode all trees	90677
#28	MeSH descriptor: [Neoplasms] explode all trees	90677
#29	cancer	213366
#30	carcinoma	46735
#31	adenocarcinoma	12665
#32	malignan*	32804
#33	neoplas*	94856
#34	tumo?r	76731
#35	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	272099
#36	MeSH descriptor: [Resistance Training] explode all trees	4262
#37	MeSH descriptor: [Weight Lifting] explode all trees	972
#38	RET	1350
#39	resistance exercise	17090
#40	strength training	19883

#41 muscle training 25076
#42 resistance training 16306
#43 exercise training 42202
#44 weight lifting 1667
#45 weightlifting 185
#46 weight training 12508
#47 strengthening 7457
#48 #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 68015
#49 (((#22 AND #36) OR #6) AND #48) 300

Updated Search (November 2023):

Search Name: CRC_RET_Cochrane
Date Run: 23/11/2023 23:37:22
Comment:

ID Search Hits
#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees 11287
#2 MeSH descriptor: [Rectal Neoplasms] explode all trees 2494
#3 MeSH descriptor: [Sigmoid Neoplasms] explode all trees 82
#4 MeSH descriptor: [Cecal Neoplasms] explode all trees 28
#5 MeSH descriptor: [Appendiceal Neoplasms] explode all trees 20
#6 #1 OR #2 OR #3 OR #4 OR #5 11299
#7 MeSH descriptor: [Colon] explode all trees 1827
#8 MeSH descriptor: [Rectum] explode all trees 1820
#9 MeSH descriptor: [Colon, Sigmoid] explode all trees 140
#10 MeSH descriptor: [Colon, Descending] explode all trees 11
#11 MeSH descriptor: [Colon, Transverse] explode all trees 13
#12 MeSH descriptor: [Colon, Ascending] explode all trees 31
#13 MeSH descriptor: [Cecum] explode all trees 304
#14 MeSH descriptor: [Appendix] explode all trees 57
#15 colorectal 24620
#16 colon* 40720
#17 rect* 24263
#18 sigmoid 1380
#19 c?ecal 1174
#20 appendi* 14438
#21 bowel 24720
#22 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 99230
#23 MeSH descriptor: [Neoplasms] explode all trees 113268
#24 MeSH descriptor: [Carcinoma] explode all trees 18366
#25 MeSH descriptor: [Adenocarcinoma] explode all trees 10489
#26 MeSH descriptor: [Neoplasms] explode all trees 113268
#27 MeSH descriptor: [Neoplasms] explode all trees 113268
#28 MeSH descriptor: [Neoplasms] explode all trees 113268
#29 cancer 223821
#30 carcinoma 49805
#31 adenocarcinoma 13396
#32 malignan* 34854
#33 neoplas* 111700
#34 tumo?r 81361

#35 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 287420
#36 MeSH descriptor: [Resistance Training] explode all trees 5573
#37 MeSH descriptor: [Weight Lifting] explode all trees 1085
#38 RET 1414
#39 resistance exercise 18495
#40 strength training 21807
#41 muscle training 27470
#42 resistance training 17726
#43 exercise training 46154
#44 weight lifting 1763
#45 weightlifting 201
#46 weight training 13515
#47 strengthening 8345
#48 #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 74206
#49 (((#22 AND #36) OR #6) AND #48) 381

Embase

Initial Search:

20/01/2023, 13:31 Ovid: Saved Searches https://ovidsp.dc1.ovid.com/ovid-a/ovidweb.cgi 1/2

1.	exp colorectal cancer/ or exp colorectal adenoma/ or exp colorectal carcinoma/ or exp colorectal tumor/
2.	exp colon cancer/ or exp colon tumor/
3.	exp rectum tumor/ or rectum/
4.	exp sigmoid cancer/ or sigmoid/ or exp sigmoid carcinoma/
5.	exp cecum tumor/ or exp cecum carcinoma/ or exp cecum cancer/
6.	exp appendix carcinoma/ or exp appendix tumor/
7.	1 or 2 or 3 or 4 or 5 or 6
8.	exp descending colon/ or exp colon/ or exp ascending colon/ or exp transverse colon/
9.	exp rectum/
10.	exp sigmoid/
11.	exp cecum/
12.	exp appendix/
13.	colorectal.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, devicetrade name, keyword heading word, floating subheading word, candidate term word]
14.	colon*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device tradename, keyword heading word, floating subheading word, candidate term word]
15.	rect*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device tradename, keyword heading word, floating subheading word, candidate term word]
16.	sigmoid.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, devicetrade name, keyword heading word, floating subheading word, candidate term word]
17.	c?ecal.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device tradename, keyword heading word, floating subheading word, candidate term word]
18.	appendi*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, devicetrade name, keyword heading word, floating subheading word, candidate term word]
19.	bowel.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device tradename, keyword heading word, floating subheading word, candidate term word]
20.	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21.	exp malignant neoplasm/
22.	exp carcinoma/
23.	exp adenocarcinoma/
24.	exp neoplasm/
25.	cancer.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device tradename, keyword heading word, floating subheading word, candidate term word]
26.	carcinoma.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, devicetrade name, keyword heading word, floating subheading word, candidate term word]
27.	adenocarcinoma.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,device trade name, keyword heading word, floating subheading word, candidate term word]
28.	malignan*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, devicetrade name, keyword heading word, floating subheading word, candidate term word]
29.	neoplas*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, devicetrade name, keyword heading word, floating subheading word, candidate term word]
30.	tumo*r.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device tradename, keyword heading word, floating subheading word, candidate term word]
31.	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32.	exp resistance training/
33.	exp muscle training/
34.	exp weight lifting/
35.	exp weight training/
36.	RET.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device tradename, keyword heading word, floating subheading word, candidate term word]
37.	resistance exercise.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,device trade name, keyword heading word, floating subheading word, candidate term word]
38.	strength training.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,device trade name, keyword heading word, floating subheading word, candidate term word]
39.	muscle training.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,device trade name, keyword heading word, floating subheading word, candidate term word]

40.	resistance training.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,device trade name, keyword heading word, floating subheading word, candidate term word]
41.	exercise training.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,device trade name, keyword heading word, floating subheading word, candidate term word]
42.	weight lifting.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, devicetrade name, keyword heading word, floating subheading word, candidate term word]
43.	weightlifting.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, devicetrade name, keyword heading word, floating subheading word, candidate term word]
44.	weight training.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,device trade name, keyword heading word, floating subheading word, candidate term word]
45.	strengthening.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,device trade name, keyword heading word, floating subheading word, candidate term word]
46.	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47.	20 and 31
48.	7 or 47
49.	46 and 48

Updated Search (November 2023):

As above, with addition:

50.	limit 49 to yr="2023"

Medline

Initial Search:

Set	Search Statement	Annotations	Insert	Edit	Delete
1.	exp Colorectal Neoplasms/				
2.	exp Rectal Neoplasms/				
3.	exp Cecal Neoplasms/				
4.	exp Sigmoid Neoplasms/				
5.	exp Appendiceal Neoplasms/				
6.	exp Colonic Neoplasms/				
7.	1 or 2 or 3 or 4 or 5 or 6				
8.	exp Colorectal Surgery/				
9.	exp Colon, Ascending/ or exp Colon, Transverse/ or exp Colon/ or exp Colon, Sigmoid/ or exp Colon, Descending/				
10.	exp Rectum/				
11.	exp Cecum/				
12.	exp Appendix/				
13.	colorectal.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
14.	colon*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
15.	rect*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
16.	sigmoid.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
17.	c?ecal.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
18.	appendi*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
19.	bowel.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
20.	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19				
21.	exp Neoplasms/				
22.	exp Carcinoma/				
23.	exp Adenocarcinoma/				

24.	word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
25.	carcinoma.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
26.	adenocarcinoma.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	

27.	malignan*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
28.	neoplas*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
29.	tumo?r.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
30.	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29				
31.	exp Resistance Training/				
32.	exp Weight Lifting/				
33.	RET.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
34.	resistance exercise.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
35.	strength training.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
36.	muscle training.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
37.	resistance training.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
38.	exercise training.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
39.	weight lifting.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
40.	weightlifting.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
41.	weight training.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
42.	strengthening.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]				
43.	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42				
44.	20 and 30				
45.	7 or 44				
46.	43 and 45				

Updated Search (November 2023):

As above, in addition:

47. limit 46 to yr="2023"

PubMed

Initial Search:

Search: **(((#2 AND #3) OR #1) AND #6)**

((("colorectal surgery"[MeSH Terms] OR "colon, ascending"[MeSH Terms] OR "colon"[MeSH Terms] OR "colon, transverse"[MeSH Terms] OR "colon, sigmoid"[MeSH Terms] OR "colon, descending"[MeSH Terms] OR "rectum"[MeSH Terms] OR "cecum"[MeSH Terms] OR "appendix"[MeSH Terms] OR "colorectal"[All Fields] OR "colon*"[All Fields] OR "rect*"[All Fields] OR ("colon, sigmoid"[MeSH Terms] OR ("colon"[All Fields] AND "sigmoid"[All Fields]) OR "sigmoid colon"[All Fields] OR "sigmoid"[All Fields] OR "sigmoidal"[All Fields] OR "sigmoidally"[All Fields] OR "sigmoidicity"[All Fields] OR "sigmoiditis"[All Fields] OR "sigmoids"[All Fields]) OR ("cecum"[MeSH Terms] OR "cecum"[All Fields] OR "caecal"[All Fields] OR "cecal"[All Fields]) OR ("cecum"[MeSH Terms] OR "cecum"[All Fields] OR "caecal"[All Fields] OR "cecal"[All Fields]) OR "appendi*"[All Fields] OR ("bowel s"[All Fields] OR "bowell"[All Fields] OR "intestines"[MeSH Terms] OR "intestines"[All Fields] OR "bowel"[All Fields] OR "bowels"[All Fields])) AND ("neoplasms"[MeSH Terms] OR "carcinoma"[MeSH Terms] OR "adenocarcinoma"[MeSH Terms] OR ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields] OR "carcinoma s"[All Fields]) OR ("adenocarcinoma"[MeSH Terms] OR "adenocarcinoma"[All Fields] OR "adenocarcinomas"[All Fields] OR "adenocarcinoma s"[All Fields]) OR "malignan*"[All Fields] OR "neoplas*"[All Fields] OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]))) OR ("colorectal neoplasms"[MeSH Terms] OR "rectal neoplasms"[MeSH Terms] OR "cecal neoplasms"[MeSH Terms] OR "sigmoid neoplasms"[MeSH Terms] OR "appendiceal neoplasms"[MeSH Terms] OR "colonic neoplasms"[MeSH Terms])) AND ("resistance training"[MeSH Terms] OR "weight lifting"[MeSH Terms] OR "RET"[All Fields] OR "resistance exercise"[All Fields] OR "strength training"[All Fields] OR "muscle training"[All Fields] OR "resistance training"[All Fields] OR "exercise training"[All Fields] OR ("weight

lifting"[MeSH Terms] OR ("weight"[All Fields] AND "lifting"[All Fields]) OR "weight lifting"[All Fields]) OR ("weightlifter"[All Fields] OR "weightlifters"[All Fields] OR "weightlifting"[All Fields]) OR "weight training"[All Fields] OR ("strengthen"[All Fields] OR "strengthened"[All Fields] OR "strengthening"[All Fields] OR "strengthens"[All Fields]))

Translations

colon, ascending[MeSH Terms]: "colon, ascending"[MeSH Terms]

colon, transverse[MeSH Terms]: "colon, transverse"[MeSH Terms]

colon, sigmoid[MeSH Terms]: "colon, sigmoid"[MeSH Terms]

colon, descending[MeSH Terms]: "colon, descending"[MeSH Terms]

sigmoid: "colon, sigmoid"[MeSH Terms] OR ("colon"[All Fields] AND "sigmoid"[All Fields]) OR "sigmoid colon"[All Fields] OR "sigmoid"[All Fields] OR "sigmoidal"[All Fields] OR "sigmoidally"[All Fields] OR "sigmoidicity"[All Fields] OR "sigmoiditis"[All Fields] OR "sigmoids"[All Fields]

cecal: "cecum"[MeSH Terms] OR "cecum"[All Fields] OR "caecal"[All Fields] OR "cecal"[All Fields]

caecal: "cecum"[MeSH Terms] OR "cecum"[All Fields] OR "caecal"[All Fields] OR "cecal"[All Fields]

bowel: "bowel's"[All Fields] OR "bowell"[All Fields] OR "intestines"[MeSH Terms] OR "intestines"[All Fields] OR "bowel"[All Fields] OR "bowels"[All Fields]

cancer: "cancer's"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]

carcinoma: "carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields] OR "carcinoma's"[All Fields]

adenocarcinoma: "adenocarcinoma"[MeSH Terms] OR "adenocarcinoma"[All Fields] OR "adenocarcinomas"[All Fields] OR "adenocarcinoma's"[All Fields]

tumour: "cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor's"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]

tumor: "cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor's"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]

cecal neoplasms[MeSH Terms]: "cecal neoplasms"[MeSH Terms]

weight lifting: "weight lifting"[MeSH Terms] OR ("weight"[All Fields] AND "lifting"[All Fields]) OR "weight lifting"[All Fields]

weightlifting: "weightlifter"[All Fields] OR "weightlifters"[All Fields] OR "weightlifting"[All Fields]

strengthening: "strengthen"[All Fields] OR "strengthened"[All Fields] OR "strengthening"[All Fields] OR "strengthens"[All Fields]

Updated Search (November 2023):

Search: **((((((((((((((((((("colorectal surgery"[MeSH Terms]) OR (colon, ascending[MeSH Terms])) OR ("colon"[MeSH Terms])) OR (colon, transverse[MeSH Terms])) OR (colon, sigmoid[MeSH Terms])) OR (colon, descending[MeSH Terms])) OR ("rectum"[MeSH Terms])) OR ("cecum"[MeSH Terms])) OR ("appendix"[MeSH Terms])) OR (colorectal)) OR (colon*)) OR (rect*)) OR (sigmoid)) OR (cecal)) OR (caecal)) OR (appendi*)) OR (bowel)) AND ((((((((("neoplasms"[MeSH Terms]) OR ("carcinoma"[MeSH Terms])) OR ("adenocarcinoma"[MeSH Terms])) OR (cancer)) OR (carcinoma)) OR (adenocarcinoma)) OR (malignan*)) OR (neoplas*)) OR (tumour)) OR (tumor))) OR ((((((("colorectal neoplasms"[MeSH Terms]) OR ("rectal neoplasms"[MeSH Terms])) OR (cecal neoplasms[MeSH Terms])) OR ("sigmoid neoplasms"[MeSH Terms])) OR ("appendiceal neoplasms"[MeSH Terms])) OR ("colonic neoplasms"[MeSH Terms]))) AND ((((((((((("resistance training"[MeSH Terms]) OR ("weight lifting"[MeSH Terms])) OR ("RET")) OR ("resistance exercise")) OR ("strength training")) OR ("muscle training")) OR ("resistance training")) OR ("exercise training")) OR (weight lifting)) OR (weightlifting)) OR ("weight training")) OR (strengthening))) - From 2023-01-23 08:05:52 to 2023-11-23 07:46:00 - Saved search** Sort by: **Most Recent**

((("colorectal surgery"[MeSH Terms] OR "colon, ascending"[MeSH Terms] OR "colon"[MeSH Terms] OR "colon, transverse"[MeSH Terms] OR "colon, sigmoid"[MeSH Terms] OR "colon, descending"[MeSH Terms] OR "rectum"[MeSH Terms] OR "cecum"[MeSH Terms] OR "appendix"[MeSH Terms] OR "colorectal"[All Fields] OR "colon*"[All Fields] OR "rect*"[All Fields] OR ("colon, sigmoid"[MeSH Terms] OR ("colon"[All Fields] AND "sigmoid"[All Fields]) OR "sigmoid colon"[All Fields] OR "sigmoid"[All Fields] OR "sigmoidal"[All Fields] OR "sigmoidally"[All Fields] OR "sigmoidicity"[All Fields] OR "sigmoiditis"[All Fields] OR "sigmoids"[All Fields]) OR ("cecum"[MeSH Terms] OR "cecum"[All Fields] OR "caecal"[All Fields] OR "cecal"[All Fields]) OR ("cecum"[MeSH Terms] OR "cecum"[All Fields] OR "caecal"[All Fields] OR "cecal"[All Fields]) OR "appendi*"[All Fields] OR ("bowel s"[All Fields] OR "bowell"[All Fields] OR "intestines"[MeSH Terms] OR "intestines"[All Fields] OR "bowel"[All Fields] OR "bowels"[All Fields])) AND ("neoplasms"[MeSH Terms] OR "carcinoma"[MeSH Terms] OR "adenocarcinoma"[MeSH Terms] OR ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR

"neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields] OR "carcinoma s"[All Fields]) OR ("adenocarcinoma"[MeSH Terms] OR "adenocarcinoma"[All Fields] OR "adenocarcinomas"[All Fields] OR "adenocarcinoma s"[All Fields]) OR "malignan*"[All Fields] OR "neoplas*"[All Fields] OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]))) OR ("colorectal neoplasms"[MeSH Terms] OR "rectal neoplasms"[MeSH Terms] OR "cecal neoplasms"[MeSH Terms] OR "sigmoid neoplasms"[MeSH Terms] OR "appendiceal neoplasms"[MeSH Terms] OR "colonic neoplasms"[MeSH Terms])) AND ("resistance training"[MeSH Terms] OR "weight lifting"[MeSH Terms] OR "RET"[All Fields] OR "resistance exercise"[All Fields] OR "strength training"[All Fields] OR "muscle training"[All Fields] OR "resistance training"[All Fields] OR "exercise training"[All Fields] OR ("weight lifting"[MeSH Terms] OR ("weight"[All Fields] AND "lifting"[All Fields]) OR "weight lifting"[All Fields]) OR ("weightlifter"[All Fields] OR "weightlifters"[All Fields] OR "weightlifting"[All Fields]) OR "weight training"[All Fields] OR ("strengthen"[All Fields] OR "strengthened"[All Fields] OR "strengthening"[All Fields] OR "strengthens"[All Fields])) AND "2023/01/23 08:05":"2023/11/23 07:46"[Date - MeSH]

Translations

colon, ascending[MeSH Terms]: "colon, ascending"[MeSH Terms]

colon, transverse[MeSH Terms]: "colon, transverse"[MeSH Terms]

colon, sigmoid[MeSH Terms]: "colon, sigmoid"[MeSH Terms]

colon, descending[MeSH Terms]: "colon, descending"[MeSH Terms]

sigmoid: "colon, sigmoid"[MeSH Terms] OR ("colon"[All Fields] AND "sigmoid"[All Fields]) OR "sigmoid colon"[All Fields] OR "sigmoid"[All Fields] OR "sigmoidal"[All Fields] OR "sigmoidally"[All Fields] OR "sigmoidicity"[All Fields] OR "sigmoiditis"[All Fields] OR "sigmoids"[All Fields]

cecal: "cecum"[MeSH Terms] OR "cecum"[All Fields] OR "caecal"[All Fields] OR "cecal"[All Fields]

caecal: "cecum"[MeSH Terms] OR "cecum"[All Fields] OR "caecal"[All Fields] OR "cecal"[All Fields]

bowel: "bowel's"[All Fields] OR "bowell"[All Fields] OR "intestines"[MeSH Terms] OR "intestines"[All Fields] OR "bowel"[All Fields] OR "bowels"[All Fields]

cancer: "cancer's"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]
carcinoma: "carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields] OR "carcinoma's"[All Fields]
adenocarcinoma: "adenocarcinoma"[MeSH Terms] OR "adenocarcinoma"[All Fields] OR "adenocarcinomas"[All Fields] OR "adenocarcinoma's"[All Fields]
tumour: "cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor's"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]
tumor: "cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor's"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]
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weightlifting: "weightlifter"[All Fields] OR "weightlifters"[All Fields] OR "weightlifting"[All Fields]
strengthening: "strengthen"[All Fields] OR "strengthened"[All Fields] OR "strengthening"[All Fields] OR "strengthens"[All Fields]

Appendix B- TIDieR Checklist

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
1.	**BRIEF NAME** Provide the name or a phrase that describes the intervention.	4.3.1.7	
2.	**WHY** Describe any rationale, theory, or goal of the elements essential to the intervention.	4.3.1 & 2	
3.	**WHAT** 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).	4.3.1.7.1 & 2	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	4.3.1.7.1 & 2	
5.	**WHO PROVIDED** For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	4.3.1.7.1	
6.	**HOW** 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.	4.3.1.7.1 & 2	
7.	**WHERE** Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	4.3.1.7	

8.	**WHEN and HOW MUCH** 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.	4.3.1.7	
9.	**TAILORING** If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	4.3.1.7.1 & 2	
10.‡	**MODIFICATIONS** If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	
11.	**HOW WELL** 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.	4.3.1.7.1 & 2	
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Tables 4.1 & 4.2	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

Appendix C- Initial REC Letter of Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Bethan Phillips
Room 3011 Medical School
Royal Derby Hospital
Uttoxeter Road, Derby
DE22 3DT

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

19 April 2023

Dear Professor Phillips

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

Study title:	**A Randomised Controlled Trial of Pre-Operative High-Intensity Interval Training versus High-Intensity Interval Training plus Resistance Exercise Training in Patients with Colorectal Cancer Scheduled for Surgery with Curative Intent: A Study to Establish Mechanisms of Adaption to Advance Optimisation and Stratification**
IRAS project ID:	**321484**
Protocol number:	**23005**
REC reference:	**23/SC/0115**
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 **321484**. Please quote this on all correspondence.

Yours sincerely,
Hayleigh Keating
Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Ms Angela Shone*

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 [UoN NCA Interventional Studies_data sharing_ finance_v4.6]		27 March 2023
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Certificate of Insurance]	1.0	17 February 2023
GP/consultant information sheets or letters [GPLetter_EPiC]	1.1	13 April 2023
GP/consultant information sheets or letters [GPLetter_EPiC]	1.1 (Tracked)	13 April 2023
IRAS Application Form [IRAS_Form_16032023]		16 March 2023
Letter from sponsor [Sponsor Letter]	1.0	17 February 2023
Organisation Information Document [OID]	1.0	17 February 2023
Organisation Information Document [OID]	1.6	30 March 2023
Other [Delegation Log]	1.0	17 February 2023
Other [Grant Award Letter EPiC]	1.0	12 April 2023
Other [DXA Leaflet]	1.2 (Tracked)	13 April 2023
Other [REC/HRA Responses]		18 April 2023
Participant consent form [Consent Form]	1.2	13 April 2023
Participant consent form [Consent Form (Tracked)]	1.2 (Tracked)	13 April 2023
Participant information sheet (PIS) [PIS (Tracked)]	1.3 (Tracked)	17 April 2023
Participant information sheet (PIS) [PIS]	1.3	17 April 2023
Research protocol or project proposal [Protocol]	1.2	17 April 2023
Sample diary card/patient card [Diet Diary]	1.0	17 February 2023
Schedule of Events or SoECAT [SoECAT_EPiC_FINAL_v1.0_date_17.02.2023]	1.0	17 February 2023
Schedule of Events or SoECAT [SoECAT]	1.0	17 February 2023
Summary CV for Chief Investigator (CI) [Prof B Phillips CV]	1.0	17 February 2023
Summary CV for student [Joshua Wall CV]	1.0	12 April 2023
Summary CV for supervisor (student research) [Jon Lund CV]	1.0	17 March 2023
Validated questionnaire [Questionnaire DASI]	1.0	17 February 2023
Validated questionnaire [Questionnaire EORTC QLQ C30]	1.0	17 February 2023

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 NHS organisation participating as a research site in this study. 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 intending to use a separate agreement with participating NHS organisations. The sponsor has supplied a modified model agreement and intends to use this with participating NHS organisations. The agreement has been modified as	Please provide a letter from the funder detailed in A65 of the IRAS form confirming funding is in place for this study. Study funding arrangements are detailed in the Organisation Information Document	A Principal Investigator should be appointed at participating NHS organisations.	Where an external individual who does not already hold an NHS employment contract will be conducting any of the research activities that will be undertaken at this site type then they would be expected to hold an Honorary Research Contract. External staff holding pre-existing NHS employment contracts should obtain a Letter of Access. These should confirm Occupational Health Clearance. These should confirm enhanced DBS checks and appropriate barred list checks.
		follows; The front page has been amended to include additional identifiers and logo. Formatting changes have been made to reduce the number of pages. Study drug has been redefined in the definitions as Investigational Medicinal Product so that this is not misinterpreted when a drug is used in a non-CTIMP. Clauses 3.9 – 3.12 have been removed as they can never be applicable when the University is the sponsor. Clauses 3.13 and 3.14 have been therefore been renumbered			

		3.9 and 3.10 accordingly. Clause 6.1 has been amended to include that the CI can provide permission on behalf of the sponsor These changes are provided by the sponsor and the HRA and HCRW take no position on their acceptability. Participating NHS organisations should now determine the acceptability of the proposed agreement and liaise with the sponsor to confirm its content			

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 intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix D- EPiC Study Protocol

University of Nottingham
UK | CHINA | MALAYSIA

A Randomised Controlled Trial of Pre-Operative High-Intensity Interval Training versus High-Intensity Interval Training plus Resistance Exercise Training in Patients with Colorectal Cancer Scheduled for Surgery with Curative Intent: A Study to Establish Mechanisms of Adaption to Advance Optimisation and Stratification

Final Version 1.4
22nd November 2023

Short title:	Exercise Prehabilitation in Colorectal Cancer
Acronym:	EPiC
Trial Registration:	
ISRCTN:	18133394
IRAS Project ID:	321484
Trial Sponsor:	University of Nottingham
Sponsor reference:	23005
Funding Source:	Medical Research Council

TRIAL / STUDY PERSONNEL AND CONTACT DETAILS

Sponsor:
Contact name

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Medical Expert & Co-investigator:
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Trial / Study Coordinating Centre:
University of Nottingham Medical School at Derby, Royal Derby Hospital, Uttoxeter New Road, Derby DE22 3DT

SYNOPSIS

Title	A Randomised Controlled Trial of Pre-Operative High-Intensity Interval Training versus High-Intensity Interval Training plus Resistance Exercise Training in Patients with Colorectal Cancer Scheduled for Surgery with Curative Intent: A Study to Establish Mechanisms of Adaption to Advance Optimisation and Stratification

Acronym	EPiC
Short title	Exercise Prehabilitation in Colorectal Cancer
Chief Investigator	Professor Bethan Phillips
Objectives	Primary: To compare composite change in anaerobic threshold *and* whole-body muscle mass. Secondary: 1) To determine the effects of high-intensity interval training (HIIT) versus HIIT plus resistance exercise training (RET) (ReHIIT) prehabilitation on cardiorespiratory and skeletal muscle function. 2) To determine the effects of HIIT vs. ReHIIT prehabilitation on biological markers of post-operative recovery. 3) To determine the relationship between biological features of colorectal cancer and exercise adaptation, and probable prognostic markers of responses to prehabilitation. 4) To determine the effects of HIIT vs. ReHIIT on clinical outcomes post-operatively.
Trial Configuration	Single centre randomised controlled trial
Setting	Centre of Metabolism, Ageing & Physiology (COMAP), University of Nottingham Medical School at Derby, Royal Derby Hospital, Uttoxeter Road, Derby, DE22 3DT. Recruitment will take place at: - Royal Derby Hospital (NHS), Uttoxeter Road, Derby, DE22 3NE - Queen's Hospital Burton, Belvedere Road, Burton-on-Trent, DE13 0RB
Sample size estimate	Based on power calculations, the n of each arm (HIIT or ReHIIT) was determined to be 18 for a power of 90%. Computed simulations determined n to be 20 so a target of 22 per group was chosen to ensure a power of >90%. Based on an assumed drop-out rate of 20% (based on experience with similar trials) and a post-surgery clinical complication rate of c.7%, we will aim to recruit 28 patients to each arm.
Number of participants	56 HIIT, n=28 ReHIIT, n=28
Eligibility criteria	• Age ≥18 year at the time of discussion at the multidisciplinary team meeting (MDT) • MDT outcome of a tissue-proven, or radiologically and clinically suspected colorectal neoplasia or dysplasia with the intention to treat with curative surgery

	• Due to undergo elective operative resection (by any route) with curative intent • Ability to and willingness to participate in exercise regimes and assessments • Able to travel to the Royal Derby Hospital for the duration of the study to facilitate exercise sessions • Availability for the study period to attend a minimum of 8 exercise sessions and 3 assessment sessions
Description of interventions	Selection & Assessment: After selection against eligibility criteria and participants offering informed consent, participants will undergo a screening assessment. They will then be randomised to 8-12 sessions of supervised HIIT or ReHIIT prior to surgery. Reassessment will take place after all exercise sessions have been undertaken, but prior to surgery. A third assessment session will then take place approximately six weeks after surgery. Assessments will be multimodal and will include: • A muscle biopsy of vastus lateralis (VL) to determine changes to muscle protein synthesis, muscle protein breakdown and mitochondrial respiration (eligible participants only) • Blood tests to support the measures outlined above and to determine systemic metabolomic and inflammatory profiles • Saliva collection to facilitate determination of muscle protein synthesis (eligible participants only) • Urine collection to assess whole-body contractile mass • Consumption of Deuterium Oxide (D_2O) in eligible participants only, D^3-Creatine (D3-Cr) & D^3-Methylhistidine (D3-MH) stable isotope tracers which, in conjunction with bio-samples, will assess muscle protein synthesis, muscle protein breakdown and whole-body contractile mass • Cardiopulmonary exercise testing (CPET) on a cycle ergometer • Assessment of upper a lower body muscle strength • Electromyography (EMG) to determine neuromuscular function • Physical function testing, including balance and power • Quality-of-life and physical activity questionnaires • Assessment of dietary intake via a 4-day food diary • A 4-day assessment of habitual physical activity using an activPAL accelerometer • Respirometry • Leg muscle ultrasound to assess muscle structure (thickness, pennation angle and fascicle length) • A Dual-Energy X-Ray Absorptiometry (DXA) scan

	Assessment sessions will take place at baseline; post-exercise regime but prior to surgery, and approximately six weeks post-surgery (range: five to seven weeks). Interventions: Participants randomly allocated to the HIIT arm of the study will aim to undertake 12 sessions of HIIT in the weeks leading up to their surgery. Sessions will last approximately 16.5 minutes and consist of: • A 2-minute unloaded warm-up period • 5 periods of cycling against for resistance one minute followed by 1.5 minutes of unloaded cycling • 3.5 minutes of unloaded recovery Participants randomly allocated to the ReHIIT arm of the study will, **in addition to** the HIIT regime, undertake RET at each exercise session, lasting approximately 30 minutes and consisting of: • 2 sets of 10-12 repetitions at 70% 1-RM for 3 upper body exercises, and • 2 sets of 10-12 repetitions at 70% 1-RM for 3 lower body exercises.
Duration of study	3 years 6 months Participants will be involved in the study for approximately 10-12 weeks from identification of eligibility to final assessment, but we expect some variation around this owing to a variable amount of time between MDT outcome and surgery.
Randomisation and blinding	Participants will be randomised using www.sealedenvelope.com. The randomisation codes will be generated via stratified randomisation by a member of the research team not involved with recruitment of participants. Participants will be stratified by sex and age-group (five-year divisions). Allocations will be sealed using opaque envelopes. Group allocation will be selected on the first assessment visit. Patients will not be blinded to the intervention given the nature of the study.
Outcome measures	Primary: Composite change in anaerobic threshold (AT) *and* whole-body muscle mass. Secondary: Muscle protein synthesis, muscle protein breakdown, peak O_2 consumption (VO_2 peak), leg muscle architecture, neuromuscular function, mitochondrial respiration, anabolic cell signalling, measured physical activity, and subjective questionnaire data with regards to quality-of-life, diet and habitual activity.
Statistical methods	Study data will be analysed by members of the research team using GraphPad Prism (GraphPad Prism version 7 (or later) for Windows, GraphPad Software, San Diego, California USA) SPSS (version 25, IBM, USA) or RStudio (RStudio Team (2022 or later), RStudio: Integrated Development Environment for R. RStudio,

	PBC, Boston, MA, USA). Computers within the University of Nottingham (UoN) and their corresponding servers will be used to analyse and store data. To determine differences between and within groups for all primary and secondary endpoints, a linear mixed-effect model approach will be used and implemented through the LIMMA or lme4 packages. This is preferred over standard statistical approaches as it deals better with designs where the repeated measure is continuous, where the design may become unbalanced and where non-independence of data due to clustering within individuals exists. Following determination of the effects of cancer burden and responses to prehabilitation, Linear Discriminant Analyses (LDA) will be used to determine which metabolic/ molecular/ physiological variables best predict responsiveness to prehabilitation. Using the results from the LDA analyses we will assign a probability of response by using Bayesian analyses and the rstanarm R package.

ABBREVIATIONS

1-RM	1 Repetition Maximum
6MWT	6-minute Walk Test
AE	Adverse Event
ALS	Advanced Life Support
AT	Anaerobic Threshold
BLS	Basic Life Support
CI	Chief Investigator Overall
COAG	Coagulation (Blood Test)
COMAP	Centre of Metabolism, Ageing & Physiology
CPET	Cardiopulmonary Exercise Testing
CRF	Case Report Form
CRP	C-Reactive Protein
D_2O	Deuterium Oxide
D3-Cr	D^3-Creatine
D3-MH	D^3-Methylhistidine
DXA	Dual-Energy X-Ray Absorptiometry
DMEC	Data Monitoring and Ethics Committee
DTT	Decision-to-Treat
ECG	Electrocardiogram
EMG	Electromyography
EPiC	Exercise Prehabilitation in Colorectal Cancer
FBC	Full Blood Count
GCP	Good Clinical Practice
HBA1c	Glycated haemoglobin
HIIT	High Intensity Interval Training
ICF	Informed Consent Form
ID	Identity Code
ILS	Immediate Life Support
LDA	Linear Discriminant Analyses
LFT	Liver Function Test
MDT	Multidisciplinary Team
NHS	National Health Service
PI	Principal Investigator at Local Centre
QHB	Queen's Hospital Burton
PIS	Participant Information Sheet
QoL	Quality-of-Life
R&D	Research and Development Department
RDH	Royal Derby Hospital
REC	Research Ethics Committee
ReHIIT	Resistance Exercise Training AND High Intensity Interval Training
RET	Resistance Exercise Training
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPPBT	Short Physical Performance Battery Tests
TFT	Thyroid Function Tests
U&E	Urea and Electrolytes
UK	United Kingdom
UoN	University of Nottingham
US	Ultrasound
VL	Vastus Lateralis
VO_2 Peak	Peak O_2 Consumption

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Colorectal cancer is the fourth most common cancer in the United Kingdom (UK), with over 40,000 cases diagnosed each year. Of these individuals, 66% have surgery as part of their primary cancer treatment. In addition, approximately 6 in 10 individuals diagnosed with colorectal cancer are aged 75 or over, and as such, the burden of pre-existing comorbidities and age-related physiological declines is significant [1].

Despite good overall-survival rates, individuals who undergo surgical resection for colorectal cancer are more limited in their physical function than age-match individuals who have not had colorectal cancer and surgery [2]. One theorised approach to combat this loss in function is via 'prehabilitation', defined as "the process of enhancing the functional capacity of an individual to enable him or her to withstand a stressful event" [3], with cardiorespiratory and skeletal muscle 'fitness' widely accepted as the primary targets for surgical prehabilitation.

High-intensity interval training (HIIT) is an exercise concept that combines high-intensity physical exertion with periods of rest, and is used widely to improve aerobic/cardiorespiratory fitness [4], especially when available time is limited (such as before surgery). Research undertaken by our group has shown that HIIT-alone can improve the anaerobic threshold (AT) of patients scheduled for surgery for urological malignancy [5], but these effects were not replicated in individuals with colorectal cancer [6]; suggesting a causative mechanism specific to colorectal cancer as opposed to cancer in general [7].

Conversely to HIIT which primarily improves processes relating to oxygen utilisation, resistance exercise training (RET) is usually employed to improve muscle mass and function and as such can offset many negative characteristics of advancing age (i.e., muscle mass and strength losses). Importantly, RET has also been shown to increase both AT and VO_2 peak (oxygen utilisation) and functional measures (such as the six-minute walk test (6MWT)) in older adults [8][9].

Although the mechanisms as to why HIIT-alone is not effective in prehabilitating patients prior to surgical resection for colorectal cancer are not well understood, we hypothesise that adding RET to a regime of HIIT will summate the positive effects of both modalities. Although it may be that a longer HIIT-alone regime is needed to elicit benefit, the UK government mandates a 31-day window between decision-to-treat (DTT) and first definitive treatment for all cancers; in practical terms this mandate stipulates that any prehabilitation exercise regime must be able to fit a window of one month or less [10].

This study will allow a comparison of HIIT versus ReHIIT in a timeframe that is in-keeping with the window allowed in patients with colorectal cancer prior to surgical resection. Beyond an assessment of changes in cardiorespiratory and muscle 'fitness' with each of these regimes, this study also aims to uncover the mechanisms of adaptive resistance to exercise in colorectal cancer patients and determine a biological signature of those patients who best respond to exercise prehabilitation.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE
To determine and delineate the underlying biological features of colorectal cancer burden in relation to cardiorespiratory and skeletal muscle adaptation to both HIIT and ReHIIT.

PRIMARY OBJECTIVE
In relation to individuals with colorectal cancer scheduled for treatment with curative intent allocated to either HIIT or ReHIIT study arms:

1) To compare composite change in anaerobic threshold *and* whole-body muscle mass.

SECONDARY OBJECTIVES
1) To compare changes in each of cardiorespiratory and skeletal muscle function with HIIT vs. ReHIIT.
2) To determine the effects of HIIT vs. ReHIIT on biological markers of post-operative recovery.
3) To determine the relationship between biological features of colorectal cancer and exercise adaptation, and probable prognostic markers of responses to prehabilitation.
4) To determine the effects of HIIT vs. ReHIIT on clinical outcomes post-operatively.

DETAILS OF PRODUCT(S)

No investigative product will be administered as part of this trial. However, stable-isotope tracers will be given to facilitate measures of physiological changes to skeletal muscle. Details of these tracers are provided below.

Description
D_2O: Deuterium oxide
D3-Cr: D3-labelled Creatine
D3-MH: D3-labelled Methylhistidine

Manufacture
D_2O: Merck Life Science UK Limited, The Old Brickyard, New Road, Gillingham, Dorset, SP8 4XT
D3-Cr: Cambridge Isotope Laboratories, Inc. 50 Frontage Road, Andover, MA 01810, USA
D3-MH: Cambridge Isotope Laboratories, Inc. 50 Frontage Road, Andover, MA 01810, USA

Packaging and labelling
D_2O- provided in labelled <50ml aliquots based on body weight.
D3-Cr: provided in labelled single doses in 50mls water
D3-MH: provided in labelled single doses in 50mls water

Storage, dispensing and return
D_2O, D3-Cr and D3-MH will all be stored as a liquid at room temperature in a locked storage cabinet in the Clinical Suite at the UoN Royal Derby Hospital Centre. We anticipate no surplus or unused stock as these substances will be issued to participants from a communal stock. Should disposal be required, this will be in line with local protocol.

Placebo
There is no placebo.

Known side effects

D_2O is exceptionally well tolerated, with the vast majority of consumers suffering no ill consequence. Self-limiting dizziness occasionally occurs and this resolves spontaneously; however, we have previously minimised the incidence of this by splitting the initial priming dose into two smaller doses which are taken at spaced intervals. This method will be applied in this study. The side effect profile is thought to be dose-dependent (total body pool enrichment) and we will aim for an enrichment level of 0.4% which is well within safe limits as shown previously. D2O has been used by our research group previously in pre-operative patients with no known interactions between D_2O and other medications known meaning it will not influence routine clinical care.

There are no known side effects of taking either D3-Cr nor D3-MH.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

Single centre, randomised-controlled trial with stratified computer-generated (for age-group and gender) randomisation.

Primary endpoint

A composite primary endpoint of change in anaerobic threshold determined via CPET (Hedges g effect size: 1.32) and whole-body muscle mass measured by DXA (Hedges g effect size: 1.1) with HIIT vs. ReHIIT.

Secondary endpoints

Changes in muscle protein synthesis, muscle protein breakdown, whole-body contractile mass, $\dot{V}O_2$ peak, VL muscle architecture, neuromuscular function, mitochondrial respiration, and anabolic cell signalling with HIIT vs ReHIIT. Differences in clinical outcomes, dietary intake, measures of functionality (including physical activity) and self-reported QoL with HIIT vs ReHIIT.

Safety endpoints

As part of the screening process, a fully qualified medical doctor with current NHS practice experience will perform a general examination with a specific focus on the cardiovascular and respiratory systems including an electrocardiogram (ECG). Blood testing will be undertaken and interpreted by a fully qualified medical doctor with current NHS practice experience. Any adverse events throughout the study will be reported to the study doctor with specific exclusion criteria related to safety detailed below. Adverse events will be recorded and reported as a safety endpoint.

Stopping rules and discontinuation

Should a patient be no longer willing to participate at any time during the study, they will be able to withdraw their consent at any time and without reason. It will be explained to them that this will not impact their normal care. Participants who lose the ability to give informed consent will be immediately withdrawn from the study, however in both of these situation's data and tissue collected would be retained and used where appropriate. In addition, should screening reveal anything concerning, this will be discussed with the study doctor and their participation re-evaluated based on individual factors. Specifically, regarding exercise testing and training, should any of the following occur, the programme will be terminated immediately, and the participant withdrawn:

- Ischaemic ECG changes
- Complex ectopy
- Second- or third-degree heart block
- Fall in systolic pressure >20mmHg from the highest value during the test
- Hypertension (>250mmHg systolic; > 120mmHg diastolic)
- Severe desaturation (SP_{O2} ≤80 when accompanied by symptoms and signs of severe hypoxia)
- Sudden pallor
- Loss of co-ordination
- Mental confusion
- Dizziness or faintness
- Signs of respiratory failure

RANDOMIZATION AND BLINDING

Participants will be randomised using www.sealedenvelope.com. The randomisation codes will be generated via stratified randomisation, by a member of the research team not involved with recruitment of participants. Participants will be stratified by sex and age-group (five-year divisions). Allocations will be sealed using opaque envelopes. Group allocation will be selected on the first assessment visit. Participants will not be blinded to the intervention given the nature of the study. Where possible, analysis will be undertaken in a single-blinded manner, i.e., analysis of data without prior knowledge of participant study arm allocation.

Maintenance of randomisation codes and procedures for breaking code

Code breaking will not be required. Owing to the nature of the intervention, blinding of participants and, to some extent, the research team will not be possible.

TRIAL/STUDY MANAGEMENT

The clinical team in charge of patient's care will initially approach potential participants to inform them about the trial and to offer them a PIS. This will take place in the outpatient clinic of the Royal Derby Hospital (RDH) and Queen's Hospital Burton (QHB). A clinical research fellow (Mr J Wall) will then organise initial screening and all assessment sessions and will be the lead for participant data collection.

The CI has overall responsibility for the study and shall oversee all study management.

The data custodian will be the CI.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Study Duration:

The study will last approximately 42 months and will begin at enrolment of the first participant. This will take place once ethical approval has been granted. Enrolment will cease after enrolment of 56 patients, or completion of 18 participants in each arm.

Participant Duration:

Under normal circumstances, each participant can be expected to be in the trial for a maximum of 87 days as detailed below. This period may be extended however, owing to external factors such as changes in the date of surgery:

- 31-day from the MDT decision-to-treat to first definitive therapy for cancer (surgery). This is when the exercise intervention will take place.
- 49 days from the day of surgery to the 'six-week' assessment. There is no intervention during this time.
- Five to 7 days from final assessment to removal of sutures from the biopsy site.

End of the trial

Participants will be no longer actively involved in the trial once they have their sutures removed after their final (3rd) assessment session. The trial will conclude once 56 patients have been enrolled into the study or 18 in each arm have undergone full participation including final assessment.

The end of the study will be the last suture removal of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

The trial will be undertaken at the UoN COMAP based at the RDH site. Potential participants will be recruited from the colorectal outpatient clinic at the RDH or QHB after they have been given a clear treatment plan from the team responsible for their clinical care. Participants eligible for the study will have a diagnosis of colorectal cancer which is amenable to surgical resection with curative intent. The decision to offer this treatment option will be via the MDT meeting. RDH and QHB are high-volume centres with expert teams of surgeons and nurse specialists who are experienced in managing patients with colorectal cancer and have a good track record of research participation.

Usual management involves a face-to-face meeting between the clinical team and patients to inform them of their diagnosis and formulate a plan. Patients who are potentially eligible will be approached by a member of the clinical team to ask if they would be interested in participation in the trial. If a patient is interested in participation, and consents to their data being passed to the research team, this will be undertaken by the clinical team member.

Once the clinical team has identified a patient who is interested in study participation and has consented for data sharing, the clinical team member will issue the potential participant with a PIS detailing the aims of the study and what the study will involve. The patient will then be contacted by a member of the research team after a minimum period of 24 hours. During this contact, the potential participant will be able to ask any questions regarding the PIS or the study. If a potential participant is willing to proceed, they will be invited to a screening session at the research unit where consent will be formalised. After consent, participant's NHS records will be accessed to ascertain past medical history to ensure they meet inclusion criteria.

During this initial contact, the study team will answer any questions pertaining to the trial and the PIS. Those who are interested in participation will be invited to a screening session. Patients who do not reach eligibility criteria (e.g., those who are scheduled neoadjuvant chemotherapy) will not be contacted. Inclusion and exclusion criteria are detailed below.

It will be explained to potential participants 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 and without giving reason. In the event of withdrawal, it will be explained to them that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

For full disclosure, some members of the clinical team are also members of the research team but will act in the designated manner when dealing with patients/participants.

Eligibility criteria

Inclusion criteria

- Age ≥18 year at the time of discussion at the multidisciplinary MDT

- No maximum age range so long as the participant is deemed fit for surgery by the clinical team
- MDT outcome of a tissue-proven, or radiologically and clinically suspected colorectal neoplasia or dysplasia with the intention to treat with curative surgery
- Due to undergo elective operative resection (by any route) with curative intent
- Ability to and willingness to participate in exercise regimes and assessments
- Able to travel to the RDH for the duration of the study to facilitate exercise sessions
- Availability for the study period to attend a minimum of 8 exercise sessions and 3 assessment sessions

Participants who do not take anticoagulant medication (with the exception of low-dose ((≤75mg/day) aspirin), will be eligible for inclusion in all trial assessments. Those who take alternative, combined or higher-dose anticoagulation than specified will be eligible for participation in the trial with the exception of muscle biopsy and related D_2O consumption/ saliva sampling. This is to reduce the likelihood of bleeding post biopsy.

Exclusion criteria

- Unable to offer informed consent
- Undergoing emergency surgery for colorectal cancer
- Past medical history including:
    - Myocardial infarction within the last 6 months or unstable angina
    - Heart failure (New York Heart Association Class III/IV)
    - Uncontrolled hypertension (Blood pressure systolic >160 and/or diastolic >100mmHg)
    - Previous stroke/TIA
    - Aneurysm of a named blood vessel
    - Exercise-induced, or brittle asthma
- Abnormal blood and/or ECG results (at the discrepancy of the study doctor)
- Patients who are unable to undergo CPET based on ATS/ACSS guidelines [11]
- Pre-existing clotting disorders known to the patient
- Family history of severe bleeding requiring medical intervention
- Not enough time between enrolment into the study and scheduled operation date in order to facilitate assessments and exercise sessions
- Concomitant enrolment in another study which will affect the results of either study
- Pregnant or breastfeeding

Expected duration of participant participation

Study participants will be participating in the study for approximately 87 days.

Removal of participants from therapy or assessments/Participant Withdrawal

Participants may withdraw from the trial at any time and without reason. This will not affect their clinical care and efforts will be made to ensure they understand this. Aside from this, participants may be removed from the trial at the discretion of the research team. Reasons for this include, but are not limited to, new clinical developments resulting in ineligibility as per the criteria set out above. Should clinical need arise, participants, and potentially their general practitioners will be made aware of these developments so standard care and advice can be sought. It is outside of the remit of the study team to provide healthcare advice and this will be made clear to participants. Failure of participants to attend a minimum of eight exercise sessions and three assessment sessions will lead to incomplete data collection. Participants will be excluded from the trial if they cannot complete eight exercise sessions, e.g., if their scheduled surgery date is brought forward.

Informed consent
Potential participants will be directly approached to offer informed consent. This will involve a full explanation of the trial and a discussion about the PIS and any other questions a potential participant has. Consent will be formalised by a member of the research team trained in the consent process. Continuing consent will be checked at every encounter, and it will be made clear to participants they can withdraw consent at any time, and that this will not affect their clinical care.

All participants will provide written informed consent. The ICF will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a PIS, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and medical history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

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 ICF which will be signed by the participant.

TRIAL / STUDY REGIMEN

Potential participants identified from the outpatient colorectal clinic at the RDH or QHB will be invited to attend the UoN COMAP research unit at the RDH site. After volunteering informed consent, they will undergo an initial screening session to review their past medical history and have an ECG and blood pressure assessment, all of which will be cross-referenced with the inclusion and exclusion criteria set out above. If deemed eligible to participate, participants will then be randomised into HIIT or ReHIIT study arms. Should they not reach inclusion/ exclusion criteria, they will be withdrawn from the study with immediate effect. Only participants who are eligible for the study will count towards the aimed sample size of 56 and as such, should a participant be excluded at this point, the aim would be to find another suitable candidate.

Assessment sessions:
After successful consent, screening and randomisation, participants will attend a baseline assessment session. Two other sessions, one after completion of the exercise regime but before surgery; and one approximately six weeks after surgery will also take place, all identical to the initial assessment session. All equipment used is property of and maintained by UoN. The assessment sessions will consist of:

- Establishment of 1-RM for 6 exercises:
    - Upper Limb:
        - Chest Press
        - Latissimus Dorsi (Lat) Pulldown
        - Seated row
    - Lower Limb:
        - Leg Press
        - Leg Curl
        - Chest Press
- A single VL biopsy (See eligibility criteria for details)
- Blood sampling
- CPET

- DXA
- EMG
- Physical function testing (including gait, balance and jump power)
- Questionnaires (on QoL)
- Respirometry
- US assessment of VL

Establishment of 1-RM for 6 exercises:
Participants will be asked to lift the maximum weight possible for each of the exercises. After technique training by a member of the research team for each exercise, verbal encouragement will be used to encourage participants to exert maximal strength according to a departmental SOP which includes warm-up repetitions, pre-defined rest periods and a maximum number of attempts (5). Should it not be possible to determine 1-RM due to, for example, joint limitations and/or participant preference, 5-RM will be determined and 1-RM calculated using validated tables [12]. In total, these assessments will take approximately 45 minutes.

VL biopsy:
Using a departmental SOP, a VL biopsy will be taken by a qualified medical doctor. The muscle tissue will be processed immediately and/or stored in aliquots at -80°C for later analysis, potentially including for use in research not within the direct scope of this project. Including time for set-up, explanation and the local anaesthetic to take effect, the biopsy will take approximately 20 minutes. This will only be undertaken in eligible participants.

Blood sampling:
The blood sample at screening will be analysed for clinical markers such as full blood count (FBC), urea & electrolytes (U&E), liver function (LFT), clotting function (COAG), and thyroid function (TFT), with other tests including, but not limited to, glycated haemoglobin (HBA1c), lipid profile, and C-reactive protein (CRP) performed based on potential participant previous medical history if needed. Blood samples from assessment sessions will be used to determine changes in systemic inflammation across the study, and for the determination of muscle protein breakdown. For ease of multiple venous blood sampling during a single assessment session, a cannula will be inserted allowing multiple samples to be taken with minimal participant discomfort. Approximately 70mls of blood will be required from each participant at each study session (total 210mls). In addition, routine testing including blood clotting profile will be undertaken on every potential participant prior to entry into the study. It is anticipated that this will be no more than 20mls meaning a theoretical maximum of 230mls of blood taken throughout the study.

CPET:
Participants will complete a CPET assessment to determine anaerobic threshold (AT) and VO_2Peak as measures of CRF. CPET will also allow for the measurement of maximum wattage attained by any given participant as a measure of exercise tolerance. Individualised HIIT protocols will be based on the initial CPET. 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, USA) and will last for 8-12 minutes [13]. A modified Bruce-Ramp CPET protocol will be used as is common practice, with ramp starting point and incremental level based on participants age, gender, 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 appropriately trained staff. In an emergency, first aid will be provided and transfer to a medical setting will be sought via standard NHS routes such as via 999. Including set-up and explanation, the CPET will take approximately 30 minutes.

DXA:
DXA will be used to determine body composition (fat vs. fat-free mass) and bone-health parameters (bone mineral density (BMD) and content (BMC)). Participants will be informed about the risks associated with DXA scanning such as the radiation dose and potential effects via the PIS and a separate DXA information sheet. The DXA scan will last <10 minutes, but the procedure including set-up and explanation will take approximately 30 minutes.

EMG:
EMG will allow us to determine if our interventions are impacting central and/or peripheral components of neuromuscular function. Performed at the same time as a motor control (force steadiness) assessment, participants will be seated in a leg extension dynamometer for their EMG assessment. Measurement of EMG will include the use of transcutaneous electrodes being placed on the skin directly superficial to the vastus lateralis muscle (VL) to measure motor unit potential. Participants will be asked to apply force through their leg which will be secured to the dynamometer via an ankle strap. Measurements will then be taken as the participant performs several exercises utilising their VL. EMG measurement will take approximately 20 minutes.

Physical function testing:
Participants will undergo testing of physical function via several methods:

1) 6MWT: distance walked in 6-minutes on a 30-metre track to determine functional mobility,
2) Handgrip strength to measure upper-body function,
3) SPPBT: measuring balance, chair-rise ability and natural gait speed to measure physical functionality,
4) Vertical jump test on a Gait'n'Motion platform to measure lower limb power,
5) Leg-extension dynamometery to assess motor control.

Questionnaires:
Participants will complete questionnaires to quantify their physical activity and quality-of-life (QoL) throughout the study. Physical activity will be quantified using the Duke Activity Status Index (DASI)[14] and QoL using the EORTC QLQ-C30[15].

Respirometry:
Simple measurements of lung function will be undertaken via respirometry. This will require patients to blow into a tube on three occasions, with the best reading of the three being recorded and analysed.

US assessment of VL:
US will be used to determine muscle thickness, pennation angle, fascicle length and cross-sectional area (CSA) of VL muscles.

Suture removal:
The VL biopsy site will be closed under sterile conditions by a qualified medical doctor trained in the VL biopsy technique. If non-absorbable sutures are used, participants will require suture removal between five and seven days after insertion and this will be facilitated by a member of the research team.

Differences between assessment sessions:
All three assessment sessions will be identical except for at assessment session 2 the biopsy will not be taken until the day of surgery. We anticipate that assessment session 2 will be within the 72h prior surgery and as such, after liaising with clinical colleagues, we will take the VL biopsy whilst the patient is under a general anaesthetic for their cancer operation. This is to lessen the burden associated with a VL biopsy. Should participants want to have the biopsy at

their assessment session (as they will with assessment session 1 and 3) this will be facilitated. Participants who do not undergo VL biopsy will note no difference in their assessment sessions.

Assessment of nutritional intake & habitual physical activity:
Participants will undergo monitoring of their habitual activity and nutritional intake for four days at four points during the study:

1) Prior to assessment 1
2) Between assessment 1 and 2
3) Immediately after surgery
4) Three weeks after surgery

Habitual physical activity will be measured using an tri-axial accelerometer (ActivPAL) which will be placed on the upper leg and covered with a waterproof dressing such that it can remain in place during all normal activity such as showering. In addition, participants will also complete a short form international physical activity questionnaire (IPAQ).[16]

Nutritional data will be captured via a paper-based diet diary. This will then be analysed via Nutritics software after data is inputted by the study team. The diet diary that participants will be asked to complete contains simple instructions on how to do this, and food-grade scales will be provided to participants for the duration of their study involvement if requested.

D_2O, D3-Cr & 3-MH consumption and associate bio-sample collection:
To help quantify changes in whole-body contractile mass, muscle protein synthesis, and muscle protein breakdown, participants will take varying amounts of D_2O, D3-Cr, D3-MH across the study and give timed, urine, blood and saliva samples:

D_2O
Eligible participants will be required to take a 'loading dose' of D_2O 72 hours prior to their first assessment session. This initial dose will be 3ml/kg of body weight. They will then take a smaller amount of D_2O after three days, and then once every seven days throughout the study.

D3-Cr
Participants will also consume 30mg of D3-Cr (dissolved in water) 72 hours prior to each assessment session, totalling 3 episodes throughout the study.

3-MH
Participants will consume 10mg of 3-MH (dissolved in water) 18 hours prior to each assessment session, totalling 3 episodes throughout the study.

Urine collection
Participants will collect total urine production over 24 hours at 3 periods over the study to determine whole-body contractile mass. This will be the period immediately after D3-Cr consumption (72 to 48 hours prior to each assessment session). In addition, they will take 3 further spot collections: 1) prior to consuming D3-Cr, 2) 48h after consuming D3-Cr, and 3) at the start of the assessment session (72h after consuming D3-Cr). This will total one 24h urine collection and three spot collections per assessment session per participant.

Saliva collection
Eligible participants will provide a saliva sample prior to and 2 hours after ingestion of D_2O, both at the first assessment session and with the weekly top-ups, which in combination with the VL biopsies will facilitate determination of rates of muscle protein synthesis.

Blood collection

As part of the assessment sessions, 5 blood samples each 45 minutes apart from 18 hours after 3-MH consumption will be collected via an in-situ cannula to determine rates of muscle protein breakdown.

These 3 tracers have been used collectively by our research group before to measure the muscle metabolism of cancer patients and octogenarians. Full, clear written instructions on all tracer consumptions and sample requests will be provided to participants.

Medical Notes:
Towards the end of a participants participation in the trial, their medical records will be accessed to collect clinical data on surgical outcomes such as length-of-stay. If all information needed cannot be accessed locally, participant's health status may be confirmed via centrally held records.

Interventions:
HIIT
All participants, after screening and assessment session 1 will undergo a minimum of eight and a maximum of 12 supervised HIIT sessions. Session numbers will be determined by availability of the participant and of the study team/ equipment. For example, participants would not be able to undergo sessions supervised sessions at weekend or over Bank Holidays. The ability to participate in a minimum of eight exercise sessions would be determined at the screening assessment. Should a participant not be able to make a minimum of eight exercise sessions, they would be withdrawn from the study. The HIIT will last approximately 16.5 minutes as following:

- 2 minutes warm-up
- 5 periods of 1-minute cycling against the pre-determined resistance at a cadence above 60rpm, interspersed by 1.5 minutes unloaded cycling
- 3.5 minutes recovery

ReHIIT
In addition to the HIIT regime above, participants randomised into the ReHIIT arm will undergo a further approximately 30 minutes of supervised RET consisting of:

- 2 sets of 10-12 repetitions at 70% 1-RM for 3 upper body exercises, and
- 2 sets of 10-12 repetitions at 70% 1-RM for 3 lower body exercises.

Participants will be supervised during the exercise programmes by a suitably qualified research team member as per departmental policy.

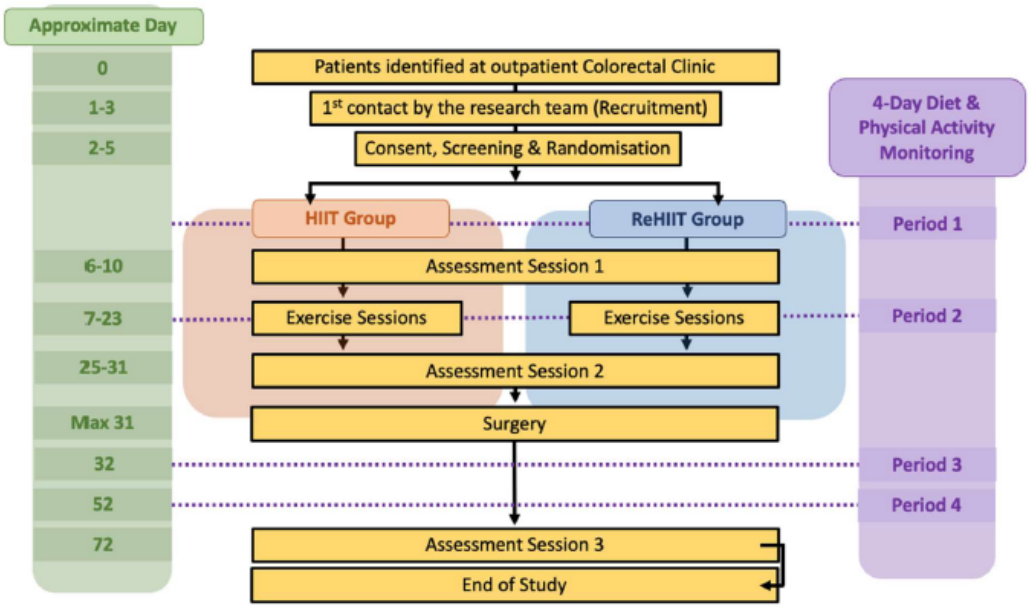

Figure 1- Schematic of the EPiC Study

Compliance

Participants will be assessed for compliance by participation in the proposed exercise regime. As the sessions are supervised, it will be clear if a participant is present and to what extent they can complete the exercise regime. Participants will need to complete a minimum of eight exercise sessions to be eligible for inclusion in the trial and those who are unable to complete this will be excluded from data analysis and will not undergo further assessment sessions (i.e., sessions 2 and 3). Participants who attempt any part of the exercise regime will be recorded as having undertaken an exercise session and should participants exercise further on their own volition, this will not render them ineligible for study participation. This will allow an intention-to-treat analysis and will help collect valuable 'real-world' data. The extent of participation in the exercise regime will be recorded.

Participants will need to attend three assessment sessions to be fully compliant with the study. Those who cannot attend session 3 will still have data analysed from the first and second visits. Those who cannot attend session 2 will have data analysed from the first visit only.

Criteria for terminating the trial

Rates of adverse outcomes will be monitored by the study doctor (Mr Joshua Wall) and reported to the study clinical lead (Mr Jon Lund) who may terminate the trial if concerns arise. The trial may also be terminated if recruitment is deemed too challenging to reach the required sample size. Any data or samples collected at the point of trial termination may be stored and analysed.

RADIATION EXPOSURE

Details of diagnostic or therapeutic ionising radiation

DXA:

All participants will be required to undergo a Total Body Dual-Energy X-ray Absorptiometry (DXA) scan at all three assessment sessions. Thus, they will undergo three scans, all of which will be performed within our department in the RDH site of the UoN. A total of three interpretable scans will be required, one from each timepoint. If a scan is rendered difficult to interpret (for example, due to movement of the participant) one repeat scan will be attempted (with agreement from the participant). Thus, the maximum number of scans a participant will have in this study is six.

Purpose and Justification:

Although D3-Cr accurately measures muscle mass, DXA scans provide a measure of total lean body and lean leg mass, which is required for analysis of muscle protein synthesis (expressed per 100g lean leg/body). Furthermore, it provides other measures of body composition (such as fat-mass), which helps provide physiological explanations for any results identified. Alternative methods of assessing body composition without the use of x-rays (such as bioimpedance, air-displacement plethysmography and skin-fold thickness) cannot provide accurate regional lean mass measures, and as such, are inappropriate for this study.

As we are assessing the effect of our interventions on body composition prior to and (six weeks) after surgery, DXA scans are required at week 0 (before intervention as baseline), at the end of the intervention period (~21-28 days later and before surgery) and six-weeks after surgery. The intervention phase is short, based on the National Cancer Action Team guideline on decision-to-treat to treatment being <31-days, and as such any intervention to improve physiological resilience (including body composition parameters) of these patients before surgery needs to be efficacious in this timeframe. We have published work (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8350218/) using the exact same HIIT as proposed herein and observed significant increases in total fat-free mass (FFM), FFM index and reductions in total fat mass and total fat percentage. Further, as this study will compare this HIIT regime with HIIT plus resistance exercise training (RET), we have also shown RET to elicit increases in FFM over an even shorter timeframe (~3 weeks; https://pubmed.ncbi.nlm.nih.gov/26169934/). As such, we fully expect to be able to determine the impact of these interventions on our chosen aspects of body composition over the outlined timeframes, in the setting of surgical prehabilitation.

Scan Details:

All DXA scans will follow the protocol for total body measurement and analysis specified in the DXA Manual (Encore-based X-ray Bone Densitometer User Manual, GE Healthcare Lunar,2013). The height and weight of the participant are inputted into the encore software by the DXA operator at the start of the scan. The Bone Densitometer sets the scan protocol to either thin, standard or thick scan based on height and weight. The scan type determines the exposure dose which is set by the DXA machine to 0.8 µSV and is not adjusted by the DXA operator.

Each scan will take ~5-10-minutes to complete depending on body habitus, although the complete process, including changing into suitable attire (i.e., a gown), explanation and positioning will take ~20-25-minutes.

The performance of the DXA equipment (Lunar Prodigy; GE Medical) will be monitored using daily quality assurance checks and weekly assessment of a spine phantom to ensure that the X-ray tube and all the machine's safety features are functional. The DXA machine is also checked by the UoN Safety Office and serviced annually by the manufacturer.

The weight limit for the DXA scan is 159kg and individuals above this weight will not be scanned. This DXA scan protocol has been executed for multiple studies in our laboratories and we have many years of experience in this procedure. DXA scans will only be performed by trained DXA operators who are experienced in total body composition measurement.

The MPE (Andrea Williamson- Imaging physicist and Clinical Scientist, Nottingham University Hospital NHS Trust) has prepared the following:

Trial radiation procedures:
A participant in this trial would undergo three visits for bone density and body composition measurements, using DEXA (week 0 (d6-10), after training (d25-30) and 6 weeks after surgery (d72)). This is x-ray exposure the participants would not have otherwise received.

The DXA whole body bone scan is likely to provide 0.8 µSv effective dose [2, 3, 4].

Estimated effective dose:
Typical dose for each planned scan visit is very low, less than 1µSv. If a re-take is required due to movement, this means, as a worst-case scenario each scan may be carried out twice at each visit. This gives a potential maximum dose of around 2µSv per visit, with most participants receiving much less.

The estimated total research protocol dose is therefore set at 6µSv for the three planned visits including a margin of variability due to individual build and equipment performance. All of this is additional exposure through participation in the trial.

Estimated Risk:
Ionising radiation can cause cancer which manifests itself after many years or decades. The risk of developing cancer as a consequence of taking part in this study is 0.00003%, which is very low. For comparison, the natural lifetime cancer incidence in the general population is about 50% - participating in this study would increase this to 50.00003%.

This is categorised as trivial in ICRP report 62 [6]. This is the equivalent of less than a day of UK background radiation and is within the variability of background radiation across the country.

For comparison, the lifetime risk of fatal cancer from all causes is 1 in 4.

References
2. PCXMC v2.0 PCXMC - A Monte Carlo program for calculating patient doses in medical x-ray examinations □ used for iDXA parameters
3. Technical white paper: bone densitometry. Conference of Radiation Control Program Directors Task Force on Bone Densitometry (H-30). Hawkinson J, Timins J, Angelo D, Shaw M, Takata R, Harshaw F. May 2007. https://www.jacr.org/article/S1546-1440(07)00051-8/fulltext
4. GE Encore Safety & Specification Product information sheet (standard patient scan)
5. HPA CRCE 028 Radiation risks from medical x-ray examinations as a function of the age and sex of the patient. Health Protection Agency, 2011.
6. Radiobiological protection in biomedical research. ICRP report 62. International Commission on Radiological Protection, 1993.

The CRE (Dr Richard O'Connor- Consultant Radiologist, Nottingham University Hospitals NHS Trust) has commented the following: '*These exposures are most unlikely to have any significant effect on the patient's health. They are necessary to evaluate the effectiveness of*

the exercise program. The study will provide useful information on whether specific exercise programs can improve a patient's post-operative outcome. Pregnant patients are excluded from the study.

TRANSPORT AND STORAGE OF THE TISSUES

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

Screening blood samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

Muscle samples will be taken and stored in aliquots, at -80°C in a COMAP freezer. Blood samples will be stored at -80°C in a COMAP freezer. Saliva and urine samples will be stored at <-20°C in a COMAP freezer.

The master database will be held by Mr Joshua Wall in a password encrypted file on a UoN secure server to which the CI will have access.

Sample analysis will take place with the UoN COMAP laboratories.

Volunteers will be asked to consent for their samples to be stored for future research. If they agree, samples will be stored at the UoN 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.

LABORATORY ANALYSES

Mass spectrometry will be used to determine muscle protein synthesis (saliva and muscle samples), muscle protein breakdown (blood samples) and whole-body contractile mass (urine samples). Mass spectrometry will also be used to determine metabolomic and proteomic profiles of both blood and muscle. Western blotting will be used to assess anabolic, catabolic and mitochondrial cell signalling pathways in skeletal muscle, with RT-PCR to look at associated changes in gene expression. Enzyme-linked immunosorbent assays (ELISA's) will be used to look at systemic markers of inflammation in blood. High-resolution tissue respirometry (Oroboros) will be used to measure muscle oxygen consumption. The research team have significant experience in each of these techniques as evidenced by publication.

STATISTICS

Methods

Participants will have data collected at three timepoints: i) baseline; ii) after completion of their exercise regime but before surgery; and iii) approximately 6 weeks post-surgery. The two study arms will be compared at these three timepoints, with comparison of the aforementioned outcomes measures analysed using statistical analysis.

Study data will be analysed by members of the research team. GraphPad Prism (GraphPad Software, San Diego, California USA), SPSS (version 25, IBM, USA) and RStudio (RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA, USA) will be used for data analysis. Computers within the UoN and their corresponding servers will be used to analyse and store data.

To determine differences between and within groups for all primary and secondary endpoints, a linear mixed-effect model approach will be used and implemented through the LIMMA or lme4 packages. This is preferred over standard statistical approaches as it deals better with designs where the repeated measure is continuous, where the design may become unbalanced and where non-independence of data due to clustering within individuals exists. Following determination of the effects of cancer burden and responses to prehabilitation, linear discriminant analyses will be used to determine which metabolic/ molecular/ physiological variables best predict responsiveness to prehabilitation. Using the results from the linear description analyses we will assign a probability of response using Bayesian analyses and the rstanarm R package.

Sample size and justification

56 participants will be recruited, with 28 being randomised into each study arm. Based on power calculations, the n of each arm (HIIT or ReHIIT) was determined to be 18 for a power of 90%. Computed simulations determined n to be 20 so a target of 22 per group was chosen to ensure a power of >90%. Based on an assumed drop-out rate of 20% (based on experience with similar trials) and a post-surgery clinical complication rate of ~7% we will aim to recruit 28 patients to each group.

Assessment of efficacy

Primary Efficacy Endpoint

The two endpoints of change in whole-body lean mass via DXA and change in cardiorespiratory fitness determined as anaerobic threshold will be linked together following the conversion of each associated outcomes to a binary form (categorised as being above or below a pre-defined measurement error and clinical threshold, respectively) to allow analysis of mean difference in change for 'physiological resilience' with HIIT versus ReHIIT.

This new composite binary factor can then also be used to build our bioinformatic models and assess which combination of variables/secondary outcomes (metabolic, molecular and/or physiological) best predict each individual primary endpoint outcome and importantly, our composite binary factor.

Secondary Efficiency Endpoints

The effect of HIIT vs. ReHIIT on:

1) neuromuscular structure (contractile mass and architecture) and function,
2) muscle protein metabolism (synthesis and breakdown) and oxygen consumption,
3) cellular signalling related to 1) and 2),
4) clinical and QoL-related outcomes post-surgery,
5) physical activity and dietary intake in the peri-operative period;

all of which will be analysed at baseline, after the intervention, and ~6-weeks after surgery, with the exception of physical activity and dietary intake which will be analysed for 4-days at 4 timepoints: before intervention, during intervention, immediately after surgery and ~3-weeks after surgery.

To determine differences between and within groups for all secondary endpoints, a linear mixed-effects model approach will be used and implemented through the LIMMA or lme4 R packages. Linear mixed-effect modelling is preferred over standard statistical approaches (i.e., repeated measures ANOVA) as it deals better with designs where the repeated measure is continuous (i.e. in this case, time), where the design may become unbalanced (i.e. due to attrition) and where non-independence of data due to clustering within individuals exists, as is likely the case here.

Assessment of safety

All assessment and intervention parameters will be performed and supervised by adequately trained members of the research team. Details are specified in the appropriate sections above.

Our department has previously shown that HIIT can safely be delivered in patients with cancer [5], and more specifically that exercise can be administered to pre-operative patients with colorectal cancer [17].

Patients will be asked about and monitored for adverse events at every visit and their responses documented. Participants General Practitioners (GPs) will be informed, via letter, of their patients' inclusion in the study. Should adverse events arise, they will be dealt with in accordance with standard NHS practice.

Procedures for missing, unused and spurious data

Should significant amounts of data be missing for a participant, they will be removed from the trial at the discretion of the research team. For participants who drop out mid-way through the trial, previously captured data will still be used for analysis, again at the discretion of the research team.

Definition of populations analysed

Safety set: All randomised participants who complete the first assessment.

Full analysis set: All randomised participants, who participated in at least eight exercise, and three assessment sessions, and for whom at least one post-baseline assessment of the primary endpoint is available.

Per protocol set: All participants in the full analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study.

ADVERSE EVENTS

Definitions

An adverse event (AE) 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 led 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 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.

Examples specific to this study may include post-biopsy wound break down or infection requiring antibiotics or surgical intervention.

CPET safety & adverse events

Should any of the following occur during exercise training or CPET, the programme will be terminated immediately, and the participant withdrawn:

- Ischaemic ECG changes
- Complex ectopy
- Second- or third-degree heart block
- Fall in systolic pressure >20mmHg from the highest value during the test
- Hypertension (>250mmHg systolic; > 120mmHg diastolic)
- Severe desaturation (SPO_2 ≤80 when accompanied by symptoms and signs of severe hypoxia)
- Sudden pallor
- Loss of co-ordination
- Mental confusion
- Dizziness or faintness
- Signs of respiratory failure

The reason(s) for stopping the test will be documented by the research team member responsible for monitoring said test. The list above is not exhaustive and careful monitoring should identify any other potential issues.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial 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 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 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 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 each 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 intervention is not the cause. The CI shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant they will be immediately excluded from any further involvement with the trial as per the exclusion criteria.

All intervention 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 CI shall be responsible for all adverse event reporting.

Trial 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 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 CI.

The CI will:

- Assess the event for seriousness, expectedness and relatedness to the trial 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 or intervention shall inform the REC using the reporting form found on the NRES 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 investigators.

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

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code (ID), allocated at randomisation if appropriate, for use on paper Case Report Forms (CRFs) other trial documents and the electronic database. The documents and database will also use the prefix 'EPiC', participant's initials and a unique number assigned at randomisation. An example would be: EPiC-JW-00.

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 Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled, and dated. The Chief or Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Sample Labelling

Each participant will be assigned a trial identity code number for use on the samples, consent forms and other study documents and the electronic database. The documents and database will also be labelled with their trial ID. Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

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., Human Tissue Authority).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method). Information about

the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format. Each participant will be pseudorandomised at randomisation using a unique ID code as detailed above. With the exception of the aforementioned exceptions, this ID code will be used to link data ascertaining to a single participant such as an exercise training log, or results from an assessment session. Using this ID, the participant can be traced in the electronic database and, should the need arise, back to original documents such as the ICF for deanonymisation.

Access to electronic data will be restricted by user identifiers and passwords and held on UoN computers. All consent and hard copies of any participant data will be kept in a lockable filing cabinet in a locked office based at COMAP, UoN.

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 UoN as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in 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

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. 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.

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.

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 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. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

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 collected from this study will be used, in part to form part of a PhD students (Mr Joshua Wall)'s doctoral thesis. In addition, data will be analysed and presented at conferences and published in peer-reviewed journals. The findings will be disseminated in lay terms to participants interested in the results of the study should they express this wish at screening.

USER AND PUBLIC INVOLVEMENT

COMAP has a dedicated PPI-E group who have been consulted at all stages of research development (i.e., project planning, grant application, participant-facing materials

development) leading to this submission and who will continue to be involved for the duration of this trial.

STUDY FINANCES

Funding source

This study is funded by an Experimental Medicine research grant from the Medical Research Council (MRC) covering 100% of the total cost of the study. Mr Joshua Wall is self-funding his PhD and is employed by University Hospitals of Derby and Burton NHS Trust as a Surgical Research Fellow.

Participant stipends and payments

Participants will be offered a one-off payment of up to £150 for participation in the study. This is to help with the cost of study participation such as travel. Travel to and from the research centre will be funded for assessment sessions.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

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Appendix E- Participant Information Sheet

PARTICIPANT INFORMATION SHEET
(Final version 1.4: 22/11/2023)

IRAS Project ID: 321484

Title of Study: A Randomised Controlled Trial of Pre-Operative High-Intensity Interval Training versus High-Intensity Interval Training plus Resistance Exercise Training in Patients with Colorectal Cancer Scheduled for Surgery with Curative Intent: A Study to Establish Mechanisms of Adaption to Advance Optimisation and Stratification.

Short Title: **Exercise Prehabilitation in Colorectal Cancer (EPiC)**

Name of Chief Investigator:
Professor Bethan Phillips
Local Researcher(s):
Mr Jon Lund, Consultant General Surgeon
Mr Joshua Wall, Clinical Research Fellow
Mrs Amanda Gates, Specialist Clinical Measurement Technician
Miss Eleanor Jones, Postdoctoral Research Fellow

We would like to invite you to take part in our research study. Before you decide if you would like to take part, we would like you to understand why the research is being done and what it would involve for you. If you do decide to take part, one of our team will go through this information sheet with you and answer any questions that you may have. Talk to others about the study if you wish and please ask us if there is anything that is unclear.

What is the purpose of the study?
We would like to know if combining two different types of exercise helps build muscle strength and function in addition to cardiorespiratory (heart and lung) health in patients with colorectal cancer- also known as bowel cancer. We know that high-intensity rhythmic exercise (e.g., cycling) can help with cardiorespiratory health and that resistance exercise (e.g., lifting weights) can build muscle, but we do not know if combining the two leads to larger improvements in both of these areas. We also know that patients with colorectal cancer do not have the same response to exercise as people without cancer and would like to investigate why this is. Based on previous research we want to investigate if high intensity exercise, without and without resistance exercise, can be effective in the short period between diagnosis and surgery in changing the structure and make up of muscle, as well as in changing levels of cardiorespiratory fitness.

Why have I been invited?
You are being invited to take part because you have been diagnosed with colorectal cancer that may be treated with surgery alone. We are inviting 56 participants like you to take part.

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.

What will happen to me if I take part?

If you agree to take part, you will first be invited to attend a screening session at the University of Nottingham Medical School at the Royal Derby Hospital. At this session, consent will be sought to taking part in the study and a researcher will look at and ask you about your past medical history and will take a small blood sample. You will also have an ECG (a trace of your heart) and a blood pressure check to check you are eligible to participate in the study. You will be informed verbally if there is any reason you won't be able to participate either in person, or over the phone. This will be verified via an email.

After screening, if you are eligible to participate, you will be assigned to one of two exercise training groups. This will be done at random, and neither you or the study team will be able to choose which group you are in. One group will do high-intensity interval training (also known as HIIT) only, while the other group will do HIIT plus resistance exercise training (also known as RET). The combined training is known as ReHIIT. HIIT involves cycling on a static bicycle as quickly as possible for 5 short bursts (1-minute each), with 90 seconds rest in between each burst. RET involves using machines to move weights, using both the upper and lower body. You will be closely supervised during all exercise sessions and the level of exercise will be tailored to your individual ability.

Before the first exercise session, you will undergo an assessment session. The details of this are provided in the section below. This assessment session will be repeated twice more over the course of the study. First after finishing the exercise programme but before surgery, and again approximately six weeks after surgery.

Members of the research team will be with you every step of the way and you can ask any questions at any time.

We expect you to be involved in the study for about 10 weeks in total, including 3-4 weeks of exercise sessions 2-4 times each week before your surgery. Overall, you would need to attend:

- 1 screening session- approx. 2 hours
- 3 assessment sessions- approx. 4 hours each
- 8-12 exercise sessions- approx. 1-2 hours each depending on which group you are in.

With the exception of the final assessment session, all of these visits will be before your surgery.

Being involved in this study will not affect your normal NHS care in any way.

A diagram of the study is on the last page of this document.

Study Overview:

We appreciate there is a lot of information to take in. Below is a simple version of what will be expected of you, and where that will take place:

Activity	Details	Location	Approximate Time to Complete
Screening	This is the first time we meet face-to-face. We will talk about the study and you can ask any questions. We will also take some blood samples and simple observations such as blood pressure and a heart trace. This is to make sure it is safe for you to take part.	The Medical School	2 hours
Food diary	We will ask you to record what you eat over 4 days in a simple booklet. This will happen at 4 times: before any exercise, during the exercise period, soon after your operation and a few weeks after your operation. You do not need to change what you eat.	Home	15 minutes a day, for 4 days. This happens 4 times over the study.
Activity Monitor	At the same time as the food diary, we will ask you to wear a small monitor to see how much you move about. You do not need to change how much you move and can continue to shower etc. as normal.	Home	Wear at all times for 4 days. This happens 4 times over the study.
Assessment Sessions	We will undertake 3 assessment sessions: before any exercise, after exercise but before surgery and 6 weeks after surgery. During the assessment, we will take blood and muscle samples (unless you are on blood thinning medication; 'anticoagulation'), test your fitness on a bike, test your lung and muscle function, undertake some scans and ask you to do some simple tests like walking a short distance and complete some questionnaires.	The Medical School	4 hours per session. 3 Sessions in total.
Drink 'heavy water'	We will ask you to drink a small amount (less than a normal glass) of heavy water at the start of the study, after 3 days and once a week thereafter. If you take blood thinning medication, we will ask you to skip this step.	Home	1 minute per drink. 11 drinks over the study.
Saliva Collection	We will ask you to collect samples of your saliva on the same day as you drink the heavy water. If you take blood thinning medication, we will ask you to skip this step.	Home	1 minute per sample. 22 samples over the study.
Drink 'tracers'	Prior to each assessment session, we will ask you to drink small amounts of safe, colourless, tasteless substances. We will measure this all out for you.	Home	1 minute per drink. 3 drinks over the study.
Urine Collection	We will ask you to collect samples of your urine for 2 days before, and on the day of the assessment sessions. This will be all the urine produced over the course of a day, followed by a 2 single samples over the next 2 days.	Home	1 minute per sample. Varies depending on how much you pass urine.

Exercise	We would need you to exercise about 2-4 days a week in the weeks leading up to your surgery. We would be with you for all these sessions, and it would be a good opportunity for you to ask any questions you may have.	The Medical School	20 **or** 50 minutes per session. Repeated 8-12 times over the study.

More in-depth details about the assessment sessions can be found below.

Assessment Sessions:

The assessment sessions are where we can see if the exercises you've been doing have been working. To understand this best, we need to do an assessment before you have done any exercise so we can compare this to the assessments after you have done exercise. The assessment sessions will be made up of several tests, some of which you will need to do prior to coming into the medical school:

Firstly, after the screening visit, you will be given a small device (an activity monitor) that can be worn on your thigh for four days. This measures movement and from that we can estimate how active you are normally. The device is very light and should not stop your normal day-to-day activity such as showering. In addition, we will also need you to record what you are eating in a food diary. You will need to do this on 4 separate occasions over the course of the study.

We will also need you to drink small amounts of substances that can help us determine how your muscles are working as well as giving us some samples of urine and saliva:

- Saliva- 2 samples 3 days apart, then a sample every week thereafter.
- Urine- all urine produced in 24 hours, followed by a single sample 24 hours later and a third 24 hours later again. This will be repeated three times through the study.

Everything you need for this will be given to you and we will make it clear what has to be done and when as we appreciate this can be a lot to remember. In addition, you can contact the study team via email or phone throughout the study if you have any questions.

On the day of the assessment, we will need you to have not eaten for at least six hours, this means you will likely need to skip breakfast. Once at the medical school, we will insert a cannula and take some blood samples and send them off to the laboratory for assessment. We will also collect the urine and saliva samples, as well as the food diary you have produced in the days leading up to the assessment. If you prefer, you can return the activity monitor in person, alternatively we can arrange a pre-paid envelope so you can send it back in the post. We will download the data from the activity monitor after each use. After taking blood samples, we will take a muscle biopsy from your thigh, unless you take blood thinning medication. We will do this using local anaesthetic to numb the area so this should not hurt. Once this is completed, we will give you some refreshments. We will then need to take some more blood samples, but we can do this through the cannula. At each session, we will need approximately 70mls of blood, and a further 20mls at the screening session totalling 230mls of blood overall- less than half a pint.

Next, we will assess your fitness levels. For this we will ask you to cycle on a machine whilst we monitor your heart and lungs. We will also ask you to lift some weights so we can assess your muscle function.

We will perform an ultrasound scan of the muscles in your thigh, this is painless and takes a few minutes and then we will assess how well the nerves communicate with the muscles in your body. This is called electromyography (EMG) and involves putting a sticker on your thigh whilst you sit on a chair and try to move your leg which will be secured to the chair.

We will assess how well your lungs are working by asking you to blow into a tube. This is called respirometry.

We will also take a series of X-Rays which will help us to determine how much of your body is made up of different things such as fat, muscle etc.

Finally, we will ask you to do some simple tasks such as gripping an instrument as tightly as possible, standing up from a chair and walking at your normal speed. We will then ask you to complete some short questionnaires.

Throughout the assessment sessions, a member of the research team will be with you to ensure your safety, and to answer any questions you may have. The second and third assessment sessions are exactly the same, with one exception. For those participants who have muscle biopsies, if you prefer, we can take the second biopsy whilst you are asleep for your planned cancer surgery. This will mean you do not remember this happening. If, however, you prefer, the biopsy can be taken at the same time as your assessment session, as is the case with the first and third assessment sessions.

Expenses and payments

Travel to and from the Medical School for the assessment sessions will be arranged usually via taxi, and free parking can be arranged for the exercise training sessions. In addition, at the end of the study a one-off payment of £150 will be made to you to help fund travel costs. Should you leave the study early, this payment will be proportionally less.

What are the possible disadvantages and risks of taking part?

We understand that this is a very challenging time for you and that by taking part in this study, you are giving up your time. We also understand that you will likely have more appointments at the Royal Derby Hospital or Queen's Hospital Burton over the coming days and weeks. We have undertaken similar studies with participants in a similar position and most participants manage this well. We will liaise closely with you and can work around hospital appointments etc. Of course, should study participation be too burdensome, you can withdraw from the study at any time. In addition to the time commitment, there are some potential disadvantages of taking part in the study and these are outlined below. However, most of our previous study participants have enjoyed the process and many have taken part in multiple studies.

Travel: Travel to and from the research centre can be a burden and, where possible we will seek to minimise this by working around your hospital appointments which will be on the same site. We will also provide transport for those who want it for the assessment sessions. Unfortunately, we do not have the ability to refund travel expenses, but we can ensure free parking in our car park for your exercise training sessions.

Completion of Food Diaries: We do not expect or require you to change your diet in any way during the study period. However, we do need to get a realistic impression of what you eat. As such, we will ask you to write down your food and drink intake for a period of four days, at four different points in the study. This usually takes a few seconds per meal but can be tailored to fit your day.

Physical Activity Monitoring: At the same time as the food diary, we will ask you to wear a small device on your thigh so that we can measure your physical activity. The device is very light and will be covered by a waterproof dressing, meaning you can shower or bathe as normal. This causes no issues for the vast majority of participants, but it may be a little annoying to some.

Muscle Biopsies: Over the course of the study, you will be asked to have three muscle biopsies taken from the front of your thigh. These will be taken by a qualified medical doctor. Before the biopsy, the area is thoroughly cleaned, and local anaesthetic is used to numb the area. Next, once the local anaesthetic is working, a small (less than 1cm) cut will be made in the thigh and a small sample of muscle removed using a specialist set of forceps. The cut will then be stitched, and the site will be dressed with a waterproof dressing. The process takes about ten minutes and is generally tolerated very well. Once the local anaesthetic wears off there may be some slight discomfort at the site, but this will fade and can usually be helped with some paracetamol. With the biopsy, there is a slight risk of an infection, bleeding and/or bruising. We will do everything we can do to reduce the chances of this, but should it occur, the study doctor will be informed, and you will be offered first aid if needed. As with any cut it will make a small scar that should fade with time. The stitches will need to be removed five to seven days after the biopsy, and we will arrange that for you. If you take blood thinning medications, we will not take any biopsies from your muscle.

Blood Samples: Many of the things we are looking at in this study can be monitored by taking blood samples. Some samples will just require a simple needle, the same type as has been used in the hospital for your previous blood samples. We do also require a few blood tests close to each other near the time we take your muscle biopsies. To make this as comfortable as possible for you, we will insert a cannula (a very small flexible tube) in your arm vein for these samples. This means that you do not need to have repeated needles. Blood sampling is a relatively simple, quick and safe procedure and we take such small amounts that it is very unlikely to be noticed by you or cause you any ill-effects. There is a small risk of infection, bleeding and bruising, but we will reduce the likelihood of this by cleaning the skin thoroughly before taking samples and applying pressure to the site afterwards.

Exercise Testing & Training: The aim of this study is to see if different types of exercise can affect the muscle and cardiorespiratory fitness of people with colorectal cancer. As such, you will undergo exercise testing and training as part of this study. During some of these tests you may feel 'pushed' towards your limits, however all exercise will be adapted to best suit each individual participant. Much like after going to the gym, especially if you are not used to it, you may feel some muscle weakness and tenderness in the hours and days following exercise, but this is well tolerated by most participants and lessens as you get used to exercise. We accept that, although very small, there is a risk of participants becoming unwell during exercise. To help prevent this, researchers are trained in recognising and dealing with any issues that may arise, and we can also directly contact the medical teams at the Royal Derby Hospital who are on the same site.

DXA: If you are participating in this trial, you will have three instances of x-ray imaging of your body, called DXA scanning, to estimate body composition and bone density.

DXA stands for Dual-energy X-ray Absorptiometry and is a test commonly used to measure the density of the bones and other structures that make up your body. A DXA scan is a simple procedure that requires you to lie on your back whilst an X-ray machine passes over you, you are not enclosed in a machine. This scan only takes less than 10 minutes. Prior to the scan, you will need to remove any metal such as zips and jewellery, complete a safety questionnaire and empty your bladder.

Exposure to x-rays brings a small risk of causing cancer years in the future. In this trial you will receive x-ray (radiation) exposure that you wouldn't have otherwise had, but this still amounts to the equivalent of less than a day of UK background radiation. This means that the risk is small enough to be considered trivial.

EMG: EMG stands for electromyography and is a way of measuring how your nerves are communicating with your muscles. To do this, we will put a small electrode on your thigh, and ask you to do various movements with your leg, whilst seated in a special chair. Most participants enjoy this assessment.

Other: Other things we want to test include basic tests of physical function, such as walking, jumping, and standing from a chair. The aim of these tests is to see how well you perform everyday tasks, and as such should be relatively simple to undertake. We will also take an ultrasound measurement of your thigh which requires us to put some jelly on the upper part of your leg to measure the muscle size and shape using an ultrasound machine. This measurement is painless and takes only a few minutes. We will also ask you to blow into a tube which can tell us about how well your lungs are working. Finally, we will also need to collect some urine and saliva samples, but this can be done at home. All containers for this will be provided and you will be given clear, written instructions of how and when to do this. These saliva and urine samples work with some special drinks that we will give you, so that we can measure how quickly your muscle is building and breaking down. The drinks are small in volume (less than half a pint) and tasteless. Occasionally one of the drinks causes some people to be a little dizzy but this goes away by itself and is not common in the small doses that we are giving.

What are the possible benefits of taking part?

We cannot promise that the study will help you but the information we get from this study may help us develop an exercise programme for patients undergoing surgery for colorectal cancer in the future. Participants in previous studies have enjoyed taking part and many express feelings of reward knowing they may help future patients.

What happens when the research study stops?

Once all participants have finished their final assessment, we will analyse the data and look if the exercise has caused any changes in the structure or function of muscles or heart and lungs. We will also look at why this might have been. We will then write our results up into scientific papers and publish these in the scientific literature meaning that other researchers, scientists, and clinicians around the world can use what we have done to try and improve the lives of patients or to help with their own research. We also aim to inform others about our research at conferences.

Your data will be stored in secure filing cabinets or on secure computers at the University of Nottingham. Any data we use from you in our study, including comments, will not be identifiable, that is no one will be know who has made the comments or who the data is from. We will take some personal details about you such as your phone number and email address so we can contact you regarding the study.

What if there is a problem?
If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this document. If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) at the Royal Derby Hospital, or Queen's Hospital Burton using the following details:

Call: 01332 785 156
Text Message: 07799337500
Email: uhdb.contactpalsderby@nhs.net
Address: Royal Derby Hospital, Uttoxeter Road, Derby, DE22 8NE

Call: 01332 785 156
Text Message: 07799337500
Email: uhdb.contactpalsderby@nhs.net
Address: Queen's Hospital Burton, Belvedere Road, Burton-on-Trent, DE13 0RB

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 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 (Prof Phillips) 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 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. It 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. We will also need this information if we need to follow up your medical records as part of the research, where we may need to ask the Government services that hold medical information about you (such as NHS Digital, the Office for National Statistics, among others) to provide this information to us. By signing the consent form you agree to the above.

Your contact information will be kept by the University of Nottingham for twelve months 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 any research data and only those who need to will have access to it. All other data (research data) will be kept securely for 7 years after the end of the study. 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 do need to share identifiable information, we will seek your consent for this and ensure it is secure.

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 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 will write to your GP informing them that you are involved in this study and they will also receive a copy of this leaflet detailing the study. Although the assessments undertaken are for research purposes (not medical) only, should any incidental findings be made, or should any adverse events happen whilst undertaking this study, we will discuss these with you and advise you to see your GP/ healthcare team regarding this. Where appropriate, we will provide you with written information to help with this.

What will happen to any samples I give?

Samples of tissue and body fluids such as muscle, urine, saliva and blood will be analysed on site at the University of Nottingham Medical School at the Royal Derby Hospital. Before analysis, these samples will be stored frozen at the Medical School. Biopsy samples and whole-blood fall under Human Tissue Authority (HTA) regulations and will be handled in accordance with this under the University HTA licence (no. 12265).

We would also like to seek your consent so that any remaining samples may be stored and used in possible future research – this is optional (please indicate you agree to this on the consent form). Some of these future studies may be carried out by researchers other than current team who are running this study, including researchers working for commercial companies. Any samples or data used will be anonymised, and you will not be identified in anyway. If you do not agree to this any remaining samples will be disposed of in accordance with the HTA code of practice.

Will any genetic tests be done?
If you agree to have your samples used in future research, then genetic testing may be undertaken on these. For this study however, we will not undertake any genetic testing.

What will happen to the results of the research study?
Once we have analysed the data, we plan to write the study up and publish it in scientific journals. We also aim to present the work at conferences both nationally and internationally. In addition, the study will make up part of a student PhD thesis. Should you wish, you will be able to obtain a report detailing the results of the study after the study has ended.

Who is organising and funding the research?
This research is being organised by the University of Nottingham and is being funded by the Medical Research Council (MRC).

Who has reviewed the study?
All research in healthcare is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Oxford Research Ethics Committee.

Research team contact details:
Mr Joshua Wall, Clinical Research Fellow
University of Nottingham, School of Medicine
Phone: 01332 724640
Email: joshua.wall@nottingham.ac.uk

Miss Eleanor Jones, Postdoctoral Research Fellow
University of Nottingham, School of Medicine
Phone: 01332 724676
Email: Eleanor.jones@nottingham.ac.uk

Mrs Amanda Gates, Specialist Clinical Measurement Technician
University of Nottingham, School of Medicine
Phone: 01332 724687
Email: amanda.gates@nottingham.ac.uk

Prof Bethan Phillips, Principal Investigator
University of Nottingham, School of Medicine
Phone: 01332 724676
Email: beth.phillips@nottingham.ac.uk

Mr Jon Lund, Study Clinical Lead
University of Nottingham, School of Medicine
Phone: 01332 724703
Email: jon.lund@nottingham.ac.uk

Study Diagram:

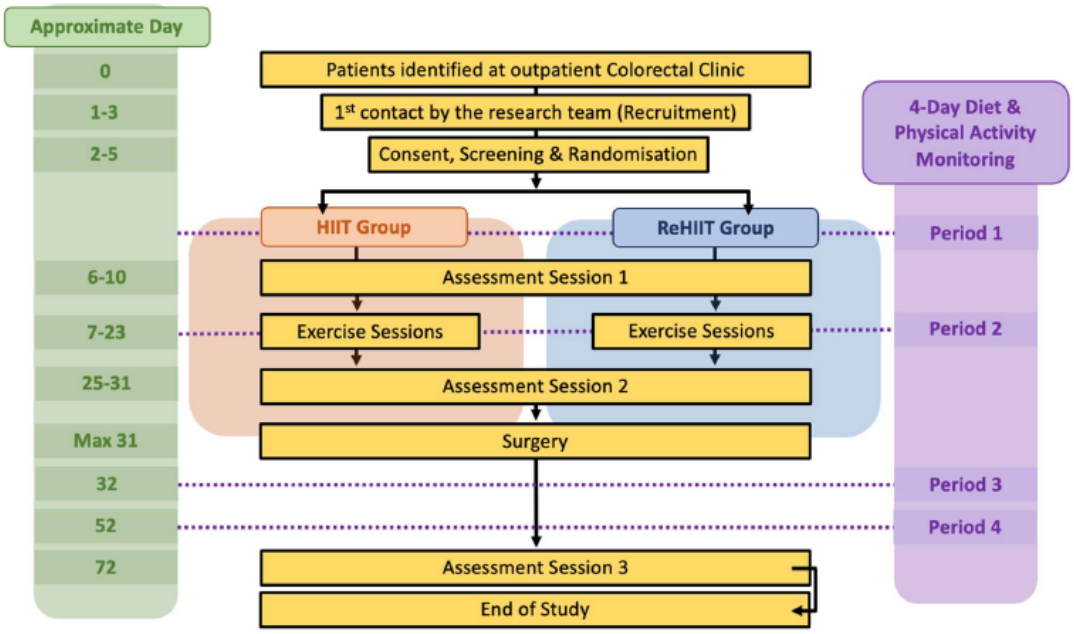

Figure above shows participant involvement in the study.

Appendix E- Screening Sheet

Exercise Prehabilitation in Colorectal Cancer

EPIC

Screening

Participant ID:

_____

Participant ID: _____

Date:

_____

Clinical Examination/ Demographics:

Age			
Sex			
Height			
Weight			
Blood Pressure			
Heart Rate			
Respiration Rate			

Tests:

- If blood samples >3 months old, new samples required

	Date Taken	Checked/Comment	Ok?
Bloods (FBC U&Es LFTs Clotting CRP HBA1c TFTs Lipid Profile)			
ECG			
Observations			
Notes:			

Medical History:

Diagnoses	

Medication	

Allergies (and details of reaction)

Smoking History

Alcohol History

GP Name & Address

Participant Address

Participant ID: _____

Inclusion/Exclusion Criteria	
Abnormal blood/ ECG results (consult study Dr)	
Abnormal scarring	
Aneurysm	
Anticoagulation (except low-dose aspirin) Biopsies only comment in notes	
Can give informed consent	
Clotting disorder/ family history	
Exercise-induced/ brittle asthma	
Fainting/ light-headedness/ dizziness	
Hypertension: Systolic > 160 or diastolic > 100	
Injuries that would preclude testing/ exercise	
MI in last 6 months or Unstable Angina?	
Participation in other project	
Stroke/TIA	

Notes/Comments

Additional Comments (preferred dates etc.)

Participant ID: _____

Checked by Study Physician

Comments/ Notes

Decision (Circle)

Include **Exclude**

Comment

Randomisation Group	

Checklist

Item	Date/Comment	Ok?
Participant Information Sheet		
Consent Form x3		
Booklet Given		
Consumables Given		
Food Diary Given		
ActivPAL Given	Letter:	
Urine Containers Given		
IPAQ		
Notes:		

Name:

_____

Signature:

_____

Date:

_____

Page 5 of 5

Appendix F- Consent Form

University of Nottingham
UK | CHINA | MALAYSIA

Exercise Prehabilitation in Colorectal Cancer

PARTICIPANT CONSENT FORM
(Final version 1.4: 22/11/2023)

IRAS Project ID: 321484

Title of Study: A Randomised Controlled Trial of Pre-Operative High-Intensity Interval Training versus High-Intensity Interval Training plus Resistance Exercise Training in Patients with Colorectal Cancer Scheduled for Surgery with Curative Intent: A Study to Establish Mechanisms of Adaption to Advance Optimisation and Stratification.

Short Study Title: **Exercise Prehabilitation in Colorectal Cancer (EPiC)**

Name of Researcher:

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the participant information sheet version number 1.4, dated 22/11/2023 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, as well as centrally held records 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.a. I understand and agree that three thigh muscle biopsies will be taken for analysis of muscle protein synthesis. ☐
Not to sign if taking anticoagulation medication (except 75mg Aspirin/ Day)

4.b. I understand and agree that multiple blood samples will be taken for analysis of organ function, markers of health and muscle protein breakdown. ☐

4.c. I understand and agree that multiple urine samples will be provided for analysis of whole-body contractile mass. ☐

4.d. I understand and agree that multiple saliva samples will be provided for analysis of muscle protein synthesis. ☐
Not to sign if taking anticoagulation medication (except 75mg Aspirin/ Day)

5. I understand that the information held and maintained by NHS England, the Office for National Statistics or other central UK NHS and government bodies may be used to help contact me or provide information about my health status. ☐

5. I agree to my GP being informed of my participation in this study, and understand that if any incidental findings are discovered ascertaining to me, I will be advised to contact my GP/ healthcare team and will be provided with written information to support this where appropriate. ☐

6. I agree to take part in the above study. ☐

7. I agree to being contacted via post, email, telephone and/or text message [delete as appropriate] in relation to the study. ☐

8. 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 Medical School in Derby, 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. Any samples or data used will be anonymised, and I will not be identified in anyway.

	Yes	No
	☐	☐

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

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

Appendix G- DXA Information Sheet

Having a DXA Scan

Information Leaflet- EPiC

Exercise Prehabilitation in Colorectal Cancer

University of Nottingham Medical School at Derby
Centre of Metabolism, Ageing & Physiology (COMAP)

What is a DXA scan and what does it measure?

DXA stands for 'Dual Energy X-ray Absorptiometry' and it is a test commonly used in hospitals to measure the density of bone. Density means how much of something there is in a certain amount of space and this test is usually used to help diagnose those who have brittle bones (osteoporosis). In physiology research, we use DXA to measure the amount of fat and lean (e.g., muscle) tissue you have in your body, as well as the density of your bones.

Figure A- *A DXA Couch*

How does a DXA scan work?

A DXA scan sends x-rays of two different strengths through the body. Bone blocks a certain amount of the x-rays, whereas muscle and fat block the x-rays to a lesser extent. The denser the tissue is, the fewer x-rays get through to the detector.

What does the scan involve?

DXA is a simple and painless procedure that requires very little preparation. However, metal objects, such as zips, buckles, bra clips/under wires and body piercings can affect the results of a DXA scan.

As such, it is advisable to wear loose clothing which has no zips or metal buttons etc. If you attend wearing clothing that is not suitable, you will be asked to change into a surgical gown prior to the scan. If you wear any kind of metal jewellery, you will need to remove it before the test. If you are unable to remove any items, please inform the DXA operator.

You will also:

1. Have your height and weight measured.
2. Complete a safety questionnaire. This questionnaire will ask you about any procedures or treatments that you may have had in the past year which involved X-rays, and any metal that you might have in your body.
3. Go to the toilet to empty your bladder before the scan.

The scan itself involves you lying on your back on a table whilst an X-ray arm passes over you. The X-ray arm does not touch you and you will not be in a "tunnel" (see Figure A).

You will need to remain completely still and not talk while the scan is being carried out.

If you have a hip, back or neck injury, please tell the DXA operator before the scan.

The actual scanning time is about 10 minutes, but you should allow 30 minutes for the entire procedure.

What are the risks?
During your DXA scan you will be exposed to a very small amount of x-ray radiation. X-rays can induce harmful effects such as the development of cancer. However, the amount you will be exposed to during a DXA scan is tiny and you experience a similar risk from 2.5 hours of natural background radiation in the UK (to which we are all constantly exposed), 15 minutes on a transatlantic flight, or the amount of radiation contained in 10 Brazil nuts. A similar risk of harm would also be experienced by smoking less than one cigarette.

Is there anyone who should not have this test?
It is not advisable for you to have this scan if you are pregnant, and pregnancy tests are available if you wish to use one. If you have had another X-ray, or if you have had a nuclear medicine (isotope) scan (such as a bone or thyroid scan) in the last 14 days, you should inform the DXA operator as it might affect the DXA results and therefore be inappropriate to continue.

If for any reason, you do not wish to proceed with the scan, please let the DXA operator know, you will not need to disclose the reason why.

What are the benefits?
A DXA scan is the most accurate way of measuring your total body composition and it is a quick and simple measurement to make.

For more information please contact:

Any member of the research team

OR

Debbie Rankin- *Radiation Protection Supervisor*
Tel: 01332 724631
Email: Debbie.rankin@nottingham.ac.uk

Appendix H- GP Letter

Exercise Prehabilitation in Colorectal Cancer
(Letter to GP Version 1.1- 13/04/2023)

University of Nottingham
UK | CHINA | MALAYSIA

Faculty of Medicine and Health Sciences
School of Medicine
Academic Unit of Injury, Recovery & Inflammation Sciences
University of Nottingham
Royal Derby Hospital Centre
Uttoxeter Road
Derby
DE22 3DT

t: +44 (0)1332 724618

www.nottingham.ac.uk/gem

Head of Unit:
Professor Ben Ollivere, FRCS (Tr & Orth)

Date: _____

Dear Dr,

Re: Research Study - "A Randomised Controlled Trial of Pre-Operative High-Intensity Interval Training versus High-Intensity Interval Training plus Resistance Exercise Training in Patients with Colorectal Cancer Scheduled for Surgery with Curative Intent: A Study to Establish Mechanisms of Adaption to Advance Optimisation and Stratification."

I am writing to inform you that your patient,

Name: _____ **Date of Birth:** _____

has provided informed consent to participate in the above research study that we are conducting within the Centre of Metabolism, Ageing & Physiology (COMAP) at the University of Nottingham Medical School at Derby. This research study will assess the effects of prehabilitation using either high-intensity interval training (HIIT) alone or HIIT in combination with resistance exercise training (ReHIIT) on skeletal muscle physiology and post-operative outcomes in patients with colorectal cancer. **Their usual NHS care will not be affected in any way due to participation in this study**.

This study has been approved by Oxford research ethics committee and IS NOT a drugs trial.

In addition to their usual care, by participating in our trial, your patient will undergo a thorough health assessment which is likely to be far in excess of their usual screening for surgery. This will involve venous blood samples, cardiopulmonary exercise testing (CPET), physical activity monitoring and a DXA scan to determine body composition. They will also undergo 3 muscle biopsies over the course of the study. Participants in both exercise groups (HIIT and ReHIIT) will attend for between 8 and 12 exercise sessions, in addition to 3 assessment sessions over the course of the study.

Furthermore, should we find clinical abnormalities we have reason to believe you are not aware of, we will advise the patient to share this information with you and will provide written information regarding this where appropriate.

If you have any questions about the participation of your patient in this 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 Joshua Wall

Mr Joshua Wall MBChB, MRCS (Study Co-Investigator),
Surgical Research Fellow
University of Nottingham, School of Medicine and Royal Derby Hospital.
Email: Joshua.wallottingham.ac.uk

Mr Jon Lund DM, FRCS (Study Clinical Lead)
Clinical Associate Professor and Consultant Colorectal Surgeon
University of Nottingham, School of Medicine and Royal Derby Hospital.
Email: jon.lund@nottingham.ac.uk

Prof Bethan Phillips (Study Chief Investigator)
Professor of Translational Physiology
University of Nottingham, School of Medicine.
Email: beth.phillips@nottingham.ac.uk

Miss Eleanor Jones
Postdoctoral Research Fellow
University of Nottingham, School of Medicine.
Email: eleanor.jones2@nottingham.ac.uk

Appendix I- HIIT Log

High Intensity Interval Training Logbook

Participant ID:

_____

Exercise Prehabilitation in Colorectal Cancer

Participant ID: _____

Wattage Calculations

Max Watt from CPET _____

Initial Assessment:

% Watt Max	Watt	Interval Achieved? ✓/X	Notes
90	CPET * 0.9	If ✓ Move to Next	
95	CPET * 0.95	If ✓ Move to Next	
100	CPET * 1	If ✓ Move to Next	
105	CPET * 1.05	If ✓ Move to Next	
110	CPET * 1.10	MAX	

	Pre	Max	Post
Heart Rate			
Bloods Pressure			

Participant ID: _____

HIIT Training Log

- Regime:
  - 2 minutes warm-up- unloaded.
  - 1 minute sets.
  - 90 seconds rest in between.
  - 3.5 minute rest after set 5 before dismounting bike.
- If participant cannot maintain wattage for 1 minute, reduce as per table above.
- If Borg <9 increase wattage by 5%, if unable to complete, reduce by 5%.

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
2	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
3	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
4	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
5	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
6	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Participant ID: _____

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
7	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
8	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
9	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
10	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
11	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Session	Watts	Pre		Max		Post		Notes
		HR	BP	HR	BP	HR	BP	
12	Set 1							
	Set 2							
	Set 3							
	Set 4							
	Set 5							Borg Achieved

Appendix J- RET Log

Resistance Exercise Training Logbook

Participant ID:

_____

Exercise Prehabilitation in Colorectal Cancer

Participant ID: _____

Notes

- If achieves 6 or more reps in all 3 sets- recalculate 1-RM using the calculator and increase weight for the next session.
- If unable to achieve 1 rep- record as '0' reps and reduce weight by 1 level (i.e. 1 weight on the machine) for the next session.
- Where able. all sessions are undertaken with dual limbs.
- For 70% 1-RM calculation- calculate the exact figure and round to closest weight plate.
- If 12 sessions, just add in notes box.

Participant ID: _____

Latissimus Dorsi (Lat) Pulldown

Achieved 1-RM (From Assessment)	Calculated 70% 1-RM

Training Log

Session	Set	Number of reps	Notes
1	1		
	2 min rest		
	2		
Weight	2 min rest		
70% 1-RM	3		
	2 min rest		

Session	Set	Number of reps	Notes
2	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
3	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
4	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
5	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
6	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
7	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
8	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
9	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
10	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
11	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Participant ID: _____

Seated Row

Achieved 1-RM (From Assessment)	Calculated 70% 1-RM

Training Log

Session	Set	Number of reps	Notes
1	1		
	2 min rest		
	2		
Weight	2 min rest		
70% 1-RM	3		
	2 min rest		

Session	Set	Number of reps	Notes
2	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
3	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
4	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
5	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes

6	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
7	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
8	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
9	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
10	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
11	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Participant ID: _____

Chest Press

Achieved 1-RM (From Assessment)	Calculated 70% 1-RM

Training Log

Session	Set	Number of reps	Notes
1	1		
	2 min rest		
	2		
Weight	2 min rest		
70% 1-RM	3		
	2 min rest		

Session	Set	Number of reps	Notes
2	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
3	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
4	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
5	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
6	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
7	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
8	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
9	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
10	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
11	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Participant ID: _____

Leg Press

Achieved 1-RM (From Assessment)	Calculated 70% 1-RM

Training Log

Session	Set	Number of reps	Notes
1	1		
	2 min rest		
	2		
Weight	2 min rest		
70% 1-RM	3		
	2 min rest		

Session	Set	Number of reps	Notes
2	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
3	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
4	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
5	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
6	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
7	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
8	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
9	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
10	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
11	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Participant ID: _____

Leg Extension

Achieved 1-RM (From Assessment)	Calculated 70% 1-RM

Training Log

Session	Set	Number of reps	Notes
1	1		
	2 min rest		
	2		
Weight	2 min rest		
70% 1-RM	3		
	2 min rest		

Session	Set	Number of reps	Notes
2	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
3	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
4	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
5	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
6	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
7	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
8	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
9	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
10	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
11	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Participant ID: _____

Leg Curl

Achieved 1-RM (From Assessment)	Calculated 70% 1-RM

Training Log

Session	Set	Number of reps	Notes
1	1		
	2 min rest		
	2		
Weight	2 min rest		
70% 1-RM	3		
	2 min rest		

Session	Set	Number of reps	Notes
2	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
3	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
4	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
5	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Participant ID: _____

Session	Set	Number of reps	Notes
6	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
7	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
8	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
9	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
10	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Session	Set	Number of reps	Notes
11	1		
	2 min rest		
	2		
Weight	2 min rest		
	3		
	2 min rest		

Appendix K- EPiC Collection Log

Participant ID _____

Date: _____

Assessment Session Number: ____

Demographics:

Age	Weight	Height

Day Planner:

Task	Est Time	Actual Time	✓
Cannula & Bloods 1 (10mls-1x Lit Hep, 1x EDTA, 1x SST)	08:00		
Returns			
Diet Diary			
ActivPALS			
Urine (Baseline (24h), 48h, 72h (/collect now)			
Saliva			
Questionnaires			
Respirometry			
Bloods 2 (5mls-1x Lit Hep)	08:45		
DXA			
Turn on CPET			
Bloods 3 (5mls-1x Lit Hep)	09:30		
ANS			
G Walk Tasks			
SPPBT			
Bloods 4 (5mls-1x Lit Hep)	10:15		
Ultrasound			
Biopsy			
(+Saliva on Assessment 2+3)			
Bloods 5 (5mls-1x Lit Hep) + Remove Cannula	11:00		

Lunch/ Snack	11:15		
CPET (Ramp: /)	12:00		

EMG	12:45		
Grip Strength	13:15		
Balance Board	13:20		
1-RMs	13:30		

Participant ID _____

Collection Log

24h Urine Catch Amount:

24h Mls	

Ultrasound:

Leg	

SPPBT:

	Time	Points
10s Side-by-Side		
10s Semi-Tandem		
10s Tandem		
Total		

4m Walk		

Chair Stand		

G-Walk:

Jump #	Height	Power	Take-Off Speed
1			
2			
3			

	✓
TUG	
6MWT	

Biopsy (+/- Saliva):

Leg	Time	Weight

RNA	Omics	Tracer	Oroboros

Participant ID _____

EMG:

Leg	

#	Spike MVC	HD MVC	Full	Ramps	MCon	Long	70% Ramps
1							
2							
3							

Notes:	

Grip Strength:

Attempt #	Right Hand	Left Hand
1		
2		
3		

Balance Board:

	Distance Travelled	Ellipse Area
30s Both Feet		
30s Right Leg Only		
30s Left Leg Only		

Participant ID _____

1-RM:

1-RM	Weight	#Reps	1-RM
Lat Pulldown			
Leg Press			
Seated Row			
Leg Extension			
Chest Press			
Leg Curl			

Bank Details (Assessment 3):