The Role of Exercise Prehabilitation Prior to Oncological Resection

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Declaration

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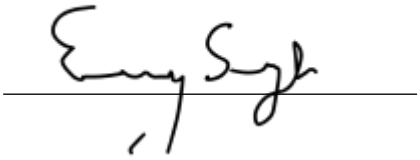
Emily Smyth 28/08/2023 

Summary

Cancer is characterised by uncontrolled cell growth within the body. Surgical resection is the primary curative treatment for solid tumours. However, surgery is invasive and associated with significant morbidity and mortality. Surgical factors and patient-related factors, such as preoperative cardiopulmonary fitness influence the risk of complications. Reduced preoperative cardiopulmonary fitness is associated with postoperative complications. Exercise prehabilitation is a preoperative intervention targeting fitness in order to reduce risk. However, the successful delivery of an effective intervention within the preoperative period poses challenges: limited timeframes, patients' physical and mental ability to participate; and the acceptability of the service. HIIT may represent an effective approach to optimising cardiopulmonary fitness within the short timeframes available. However, there is a need to clarify the role of exercise prehabilitation to identify the most meaningful and effective approaches for patients. The aim of this thesis was to examine the role of exercise prehabilitation prior to oncological resection. The specific objectives were to assess the acceptability of exercise prehabilitation prior to oncological resection, evaluate the effectiveness, feasibility and acceptability of high intensity interval training (HIIT) as a prehabilitation approach and explore the impact of HIIT on postoperative complications.

To address the aims and objectives of this thesis, one systematic review and meta-analysis and three studies were undertaken. A systematic review and meta-analysis examining the impact of preoperative HIIT on cardiopulmonary fitness and postoperative complications in patients scheduled for oncological resection was completed. Results demonstrate there is insufficient evidence to support HIIT as a method of improving preoperative fitness prior to oncological resection; however, it is a safe and feasible approach. Further work is needed to determine if specific HIIT parameters can be adapted to improve efficacy over short timeframes.

Study I examined the feasibility of the 'Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus' (PRE-HIIT) trial. PRE-HIIT is a randomised controlled trial (RCT) assessing the effect of a hybrid HIIT prehabilitation programme in patients scheduled for lung and oesophageal resection on cardiopulmonary fitness and postoperative complications. Despite the challenges in recruitment and completion of all assessments, preoperative HIIT completed face-to-face or via telehealth is feasible, safe, and acceptable for participants. However, interpretation of preliminary data analysis on the effect of HIIT on cardiopulmonary fitness was limited by small numbers, attrition, equipment malfunction and COVID-19.

Gaining an understanding of participants' experiences participating in preoperative HIIT is vital to identify barriers to participation and to facilitate integration into a clinical setting. Therefore, a qualitative analysis of semi-structured interviews from a sub-set of patients in the PRE-HIIT trial was completed. This study explored patients' motivations for participating in prehabilitation and examined their experiences preparing for surgery on the PRE-HIIT trial. Results suggest participants valued and enjoyed PRE-HIIT trial participation and its benefits. Key factors to facilitate participation identified were as follows: recommendations from the surgical team, support from the physiotherapy team and accessibility through multiple mediums.

Finally, a mixed-methods study, underpinned by the Theoretical Framework of Acceptability, examined the acceptability of exercise prehabilitation among patients, family members and healthcare providers. The participants recruited to Study III were different to those who participated in the PRE-HIIT trial presented in Study I and Study II. Results indicate that exercise prehabilitation is highly acceptable to key stakeholders. Although prehabilitation may be associated with some burden, it is perceived as a worthwhile, positive and effective intervention. Stakeholders understand its purpose, are confident in patients' ability to participate and regard it as an important intervention contributing to patients' psychological and physical wellbeing.

Collectively, these studies suggest that the effect of preoperative HIIT is unclear. However, it represents a feasible, acceptable and enjoyable approach to exercise prehabilitation. Furthermore, stakeholders value the role of prehabilitation and believe it to be an acceptable approach to enhancing fitness preoperatively. These findings contribute to a comprehensive understanding of the role and effectiveness of exercise prehabilitation in the context of oncological resection.

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I am extremely lucky to have been surrounded by a wonderful team, and friends and family throughout this process and there are many people who have been instrumental throughout. Firstly, I would like to say a special thank you to all the participants who took part in the various thesis studies. Thank you for giving your time so generously. Working with you was an absolute pleasure and a highlight of this experience.

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List of Abbreviations

ACSM	American College of Sports Medicine
ATS/ACCP	American Thoracic Society/American College of Chest Physicians
≥	Greater than or Equal to
1RM	One Repetition-maximum
6MWD	Six Minute Walk Test
95% CI	95% Confidence Interval
ADL	Activities of Daily Living
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
AT	Anaerobic Threshold
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BP	Blood Pressure
CDC	Clavien–Dindo Classification of Surgical Complications
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Test
CRF	Clinical Research Facility
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EG	Emer Guinan
EPR	Electronic Patient Record
ERAS	Enhanced Recovery After Surgery
ES	Emily Smyth

GORD	Gastro-Oesophageal Reflux Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GT	Grounded Theory
HCPs	Healthcare Providers
HIIT	High Intensity Interval Training
HR	Heart Rate
HR-QL	Health Related Quality of Life
Hrmax	Heart Rate Maximum
IQR	Interquartile Range
JH	Juliette Hussey
LCRS	Lung Cancer Rehabilitation Study
LLL	Left Lower Lobe
LOC	Louise O'Connor
LON	Linda O'Neill
LUL	Left Upper Lobe
MC	Mean Change
MD	Mean Difference
MET-HOUR	Metabolic Equivalents Per Hour
MS	Mandeep Sekhon
NCRI	National Cancer Registry Ireland
NK	Neil Kearney
NSCLC	Non-Small Cell Lung Carcinoma
OR	Odds Ratio
PET	Positron Emission Tomography

PICO	Population, Intervention, Comparison, Outcome
PIL	Participant Information Leaflet
PPCs	Postoperative Pulmonary Complications
PPO	Peak Power Output
PRE-HIIT	Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
Q-Q	Quartile-quartile Plot
Rs	Correlation Coefficient
RCT	Randomised Controlled Trial
RLL	Right Lower Lobe
RoB2	Cochrane Collaboration's 'Risk of Bias'
RR	Risk Ratio
RUL	Right Upper Lobe
SCC	Squamous Cell Carcinoma
SCLC	Small Cell Lung Carcinoma
SD	Standard Deviation
SJH	St James's Hospital
SPO_2	Oxygen Saturation
SPPB	Short Physical Performance Battery
T0	Baseline Assessment
T1	Post-intervention Assessment
T2	Postoperative Period
TA	Thematic Analysis
TFA	Theoretical Framework of Acceptability

THS	Transhiatal
TNM	Tumour Node Metastasis
TUQ	Telehealth Useability Questionnaire
VO2	Oxygen Consumption
VO_{2peak}	Peak Oxygen Consumption
VATs	Video-Assisted Thoracoscopic Surgery
VCO_2	Volume of Carbon Dioxide
VO_{2AT}	Oxygen Consumption at Anaerobic Threshold
VO_{2max}	Maximum Oxygen Consumption
VO_{2peak}	Peak Oxygen Consumption
WRp	Work Rate Peak

Appendices Table of Content

Dissemination of Research

First Author Published Papers:

- **SMYTH, E**., O'CONNOR, L., MOCKLER, D., REYNOLDS, J. V., et al. (2021). Preoperative high intensity interval training for oncological resections: A systematic review and meta-analysis. Surgical Oncology, 38, 101620.https://doi.org/10.1016/j.suronc.2021.101620

Relevant Published Papers:

- O'CONNOR, L., SMYTH, E., BENNETT, A. E., SMITH, V., et al. (2021). Identifying outcomes reported in exercise interventions in oesophagogastric cancer survivors: a systematic review. BMC Cancer, 21, doi:586.10.1186/s12885-021-08290-w.
- BRENNAN, L., SADEGHI, F., O'NEILL, L., GUINAN, E., SMYTH, E., et al. (2022a). Telehealth Delivery of a Multi-Disciplinary Rehabilitation Programme for Upper Gastro-Intestinal Cancer: ReStOre@Home Feasibility Study. Cancers (Basel), doi:14.10.3390/cancers14112707
- BRENNAN, L., SHEILL, G., O'NEILL, L., O'CONNOR, L., E., SMYTH et al. (2022b). Physical Therapists in Oncology Settings: Experiences in Delivering Cancer Rehabilitation Services, Barriers to Care, and Service Development Needs. Physical therapy, doi:pzab287.10.1093/ptj/pzab287.

Platform Presentations:

<u>World Physiotherapy Congress 2023, Dubai</u>

- SMYTH, E,. BRENNAN L., SEKHON, M., DICKSON, J., ENRIGHT, R., et al. The Acceptability of Exercise Prehabilitation Prior to Oncological Resection Among Key Stakeholders.

Oral On Demand Presentations:

<u>Irish Society of Chartered Physiotherapists Conference 2022, Online</u>

- SMYTH, E., O'CONNOR, L., MOCKLER, D., REYNOLDS, J. V., et al. Preoperative high intensity interval training for oncological resections: A systematic review and meta-analysis.

Poster Presentations:

Irish Association for Cancer Research Conference 2022, Cork

- SMYTH, E., SEKHON, M., HUSSEY, J., GUINAN, E. The Acceptability of Exercise Prehabilitation Before Cancer Surgery: Results from an Online Survey.

International Cancer Conference, Dublin 2022

- SMYTH, E., SEKHON, M., HUSSEY, J., GUINAN, E. The Acceptability of Exercise Prehabilitation Before Cancer Surgery.

Upcoming Poster Presentations:

International Conference on Physiotherapy in Oncology, Amsterdam September 2023

- SMYTH, E., O'NEILL, L,. REYNOLDS, J., HUSSEY, J., GUINAN, E., Experiences of patients participating in prehabilitation prior to complex surgery for cancer of the lung or oesophagus.
- SMYTH, E., O'NEILL, L,. REYNOLDS, J., HUSSEY, J. et al. The feasibility of preoperative high intensity interval training in patients scheduled for complex surgery for cancer of the lung or oesophagus.

Chapter 1 Introduction

Cancer is a term used to describe a diverse group of diseases which are characterised by uncontrolled cell growth within the body (Hanahan and Weinberg, 2000, Ruddon, 2007). This uncontrolled proliferation results from an insult to a cell causing alterations in gene expression and ultimately an imbalance between cell growth and death, resulting in growth of a tumour cell population (Ruddon, 2007, Hanahan and Weinberg, 2000). A distinctive characteristic of cancerous cells is their ability to invade surrounding tissues and metastasise to other organs (Hanahan and Weinberg, 2000, Ruddon, 2007). Globally, cancer is ranked as the leading cause of death in 112 countries and was responsible for 9.9 million deaths in 2020 (Sung et al., 2021). Treatment for cancer includes surgery, systemic anti-cancer therapies such as chemotherapy and immunotherapy, and radiotherapy (National Cancer Registry Ireland (NCRI), 2018).

1.1 Pathogenesis of Cancer

Cancer can arise from any cell in the body, these cells are known as cells-of-origin, and they begin the multi-step process from normal cell to cancer, this is known as tumourigenesis (Cooper, 2000, Bi et al., 2022, Rycaj and Tang, 2015). Tumour initiation is the first step of tumourigenesis and begins with mutations in a cell's gene expression in response to oncogenic factors (Bi et al., 2022). This is followed by tumour promotion, during which the cells selectively clone and become pre-malignant cells (Bi et al., 2022). Following this, malignant conversion occurs where the pre-malignant cells begin to transform into malignant cells and finally to tumour progression where cells have transformed into malignant cancer cells with specific biological characteristics (Bi et al., 2022). These biological characteristics include unregulated cell proliferation, the capacity for cell invasion and resistance to cell death (Cooper, 2000, Bi et al., 2022).

One of the primary biological characteristics which identifies cancerous cells is unregulated cell proliferation (Bi et al., 2022, Cooper, 2000). In many cancers this results from a reduction in the cells' dependency on serum growth hormone to stimulate cell growth (Cooper, 2000). Other mutations cause cells to produce their own growth hormone, known as autocrine growth stimulation, resulting in uncontrolled cell proliferation (Cooper, 2000). Some cancers are caused by substances which stimulate cell proliferation itself, rather than the cell mutation (Cooper, 2000). Uncontrolled cell proliferation results in the growth of malignant tumours which can spread locally, by invading surrounding tissue, or can spread to distant body sites (Bi et al., 2022, Cooper, 2000).

The capacity for tissue invasion is another primary biological characteristic of cancer cells and tumours (Bi et al., 2022, Cooper, 2000). Cancerous cells invade other surrounding tissue cells by secreting an enzyme which breaks down the extra-cellular wall of cells. As previously mentioned,

many cancerous cells secrete their own growth factor. This allows the growth of new blood vessels, which are easily penetrated by the malignant cells, to supply oxygen and blood and provide access to the circulatory system (Bravo-Cordero et al., 2012). Once the cancerous cells have invaded the circulatory or lymphatic system they can migrate to distant sites around the body, where they colonise. This process is known as metastasis (Bravo-Cordero et al., 2012).

Resistance to cell death is another characteristic of cancer cells (Cooper, 2000, Bi et al., 2022). Cancer cells tend not to progress to their intended mature form (known as differentiation) as effectively as non-cancerous cells (Cooper, 2000). A key step in cell differentiation is cell death or 'apoptosis' (Cooper, 2000). As cancer cells are poorly differentiated, they do not undergo cell apoptosis causing cells to have longer lifespans significantly driving tumour development (Cooper, 2000). Cancer is classified by the tissue it arises from and by the histological type (Cooper, 2000). Cancers which arise from epithelial cells are called carcinomas and make up approximately 90% of cancers (Cooper, 2000). Leukaemias and lymphomas arise from blood cells and are responsible for approximately 8% of cancers (Cooper, 2000). Cancers which arise from mesenchymal cells have the lowest incidence (1%) and are called sarcomas (Cooper, 2000, Bhatt et al., 2016).

1.2 Causes of Cancer

The process of gene mutation and cell invasion is complex, and these changes are seldom caused by a single event. Risk factors and carcinogens, substances which stimulate the alteration in gene expression, have been identified (Cooper, 1999, Ruddon, 2007). Well documented carcinogens include viruses such as human papilloma virus; chemicals, including the chemicals present in cigarettes; toxins produced by mould; and radiation, including ultra-violet radiation (Vineis and Wild, 2014). In 2016, the National Cancer Registry Ireland (NCRI) found that one in three invasive cancers in Ireland could be attributed to a modifiable risk factor (National Cancer Registry, 2020). These modifiable factors included tobacco smoking, high body mass index, infection, alcohol, sun-burn, radiation, processed meat consumption, use of oral contraceptives and hormone replacement therapy, lack of physical exercise and air pollution (National Cancer Registry, 2020).

The chemicals present in cigarettes are well documented carcinogens. Smoking is a significant risk factor for cancer, predominantly of the lung, causing greater than 76% of cases in Ireland. It is also connected with 67% of cancers of the larynx, 47% of cancers of the bladder, doubles the risk of oesophageal cancer and significantly increases risk for multiple other types (National Cancer Registry, 2020, Fan et al., 2008). There is dose-response relationship with smoking and incidence of cancer, the risk increases per cigarette smoked with a linear relationship between number of cigarettes smoked per day and age specific risk of lung cancer (Gandini et al., 2008). There is a direct

correlation between oesophageal cancer and the amount of time smoking and number of cigarettes smoked in a day (Zhang, 2013). Stopping smoking can mitigate the risk of cancer, with risk in ex-smokers reducing from nine times that of a non-smoker to four times (National Cancer Registry, 2020).

Infections from various microorganisms are well established carcinogens and have been recognised to cause 14 types of cancer (National Cancer Registry, 2020). The human papilloma virus is responsible for 91% of cancers of the cervix, 75% of cancers of the vagina and 91% cancers of the anus and also contributes to development of cancers in the penis, vulva and oropharynx (Muñoz et al., 2006, National Cancer Registry, 2020). *Helicobacter pylori* is a bacteria, which contributes to development of 39% of gastric cancers (National Cancer Registry, 2020).

Increased body weight was responsible for 5% of all invasive cancers in Ireland in 2016 (National Cancer Registry, 2020). Increased weight is a risk factor for 13 different types of cancer, including 23% of kidney cancers, 23% of liver cancers and 18% of gallbladder cancers in Ireland (National Cancer Registry, 2020, Bianchini et al., 2002). The increase in body weight is thought to increase risk by causing alterations in sex hormone metabolism, insulin levels and causes systemic inflammation (National Cancer Registry, 2020, Zhang, 2013, Bianchini et al., 2002). Alcohol was responsible for 2.6% of invasive cancers in Ireland in 2016. Consumption of alcohol has been reported to increase risk of seven different types of cancer, predominantly the pharynx (32%), oral cavity (29%) and larynx (21%) (NCRI, 2022). Physical inactivity is associated with an increased risk of multiple different types of cancer with strong evidence for bladder, breast, colon, endometrial and oesophageal cancer and moderate evidence for gastric and renal cancer (McTiernan et al., 2019).

1.3 Incidence of Cancer

In 2020, 19.2 million new cancer cases of cancer were reported globally (Sung et al., 2021). In Ireland, between 2018 and 2020 an estimated 43,470 people were diagnosed per year (NCRI, 2022). Of this 43,470, 18% (n=7645) were non-invasive carcinomas, 26% (n=11,498) were non-melanoma skin cancers and 56% (n=24,327) were invasive cancers which required treatment. This thesis will focus on those with invasive cancer requiring treatment.

Worldwide during 2020, the top 10 most diagnosed cancers made up over 60% of new diagnoses and were responsible for more than 70% of cancer-related deaths (Figure 1.1) (Sung et al., 2021). In men and women the most common new cases were female breast cancer (11.7%), lung cancer (11.4%), colorectal cancer (10%), prostate cancer (7.3%) and stomach cancer 5.6% (Figure 1.1) (Sung et al., 2021). In 112 countries, including Ireland, prostate cancer was the leading cancer

diagnosed for men, followed by lung and colorectal cancer in 35 countries and liver cancer in 11 countries (Sung et al., 2021, NCRI, 2022). For women, cancer was the most frequently diagnosed cancer type in 159 countries, including Ireland, followed by cervical cancer in 23 countries (Sung et al., 2021, NCRI, 2022). The incidence of all cancer types was 19% higher in men than women, with 222 new cases per 100,000 in men and 186 per 100,000 in women (Sung et al., 2021).

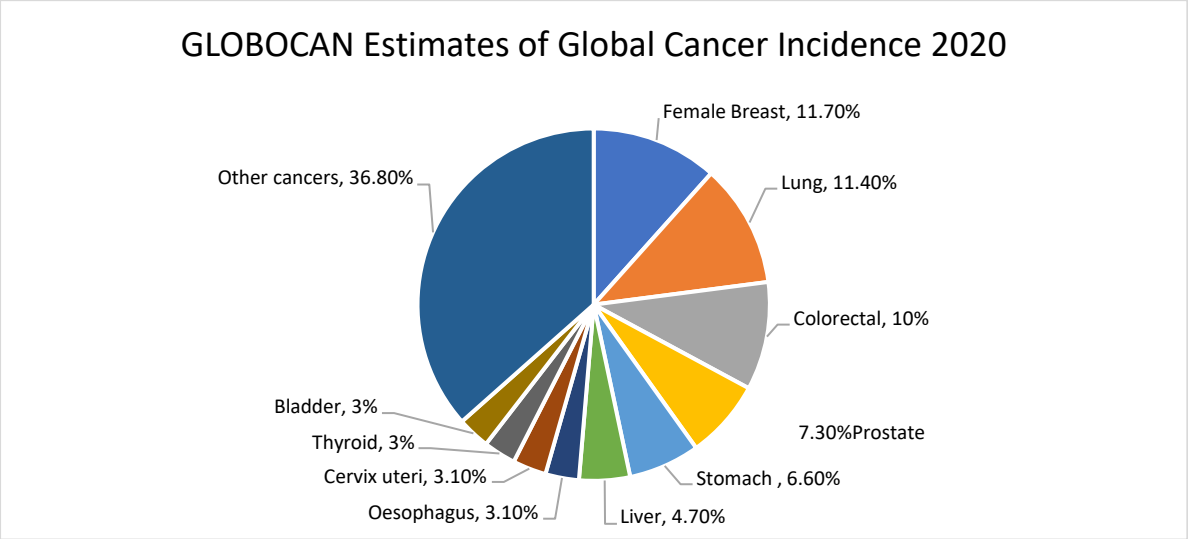

Figure 1.1 GLOBOCAN Estimates of Global Cancer Incidence 2020

Data from the NCRI indicates that between 2018 and 2020 prostate, breast, lung and colorectal were the most commonly diagnosed cancers in Ireland (Figure 1.2) (NCRI, 2022). In men the most frequent diagnoses were prostate (30%), lung (11%) and 11% colorectal cancers (NCRI, 2022). In women 30% of cancer diagnoses were breast, 11% lung cancer and 10% colorectal cancer (NCRI, 2022). The yearly incidence rate of all cancers for men was 716 cases per 100,000 and 456 per 100,000 in women (NCRI, 2022, Sung et al., 2021).

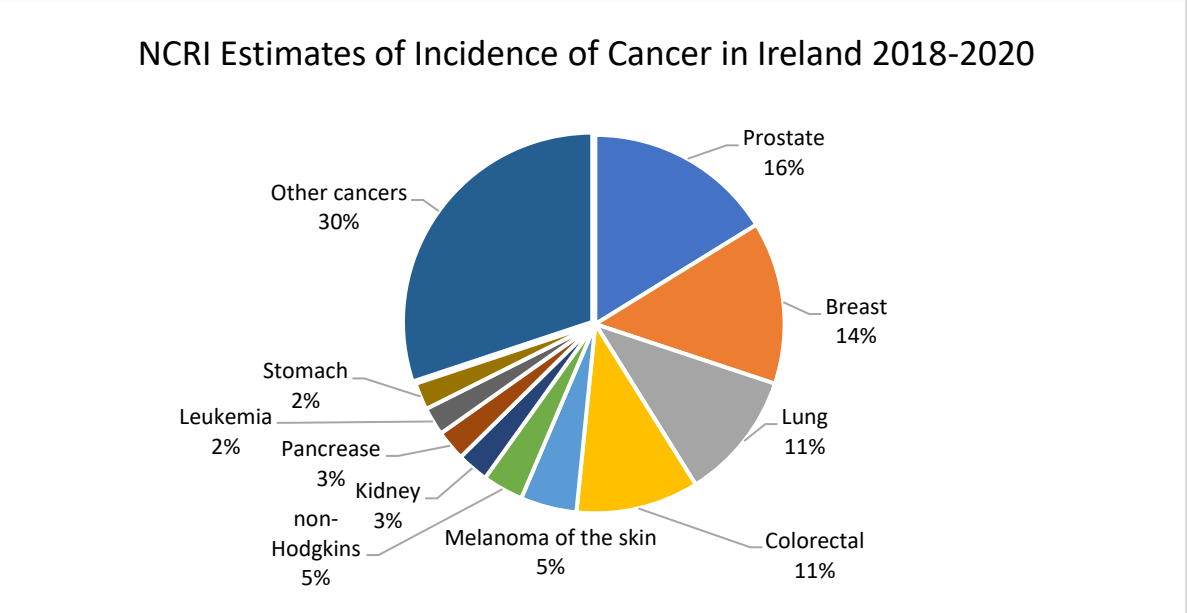

Figure 1.2 National Cancer Registry Ireland Estimates of Incidence of Cancer in Ireland 2018-2020

1.4 Clinical Staging

After tissue diagnosis, the extent of tumour spread is categorised and staged based on anatomical progression of the disease using the tumour node metastasis (TNM) system (Detterbeck et al., 2017, Amin et al., 2017). This can be assessed using computed tomography (CT) scan or positron-emission tomography (PET) scans to identify metastasis. The designation 'T' describes the extend of the primary tumour invasion to surrounding tissue and size (Detterbeck et al., 2017, Amin et al., 2017). These scores range from T0 to T4, with T0 expressing carcinoma in situ, the grade then increases from T1-4 depending on tumour size. 'N' describes lymph node involvement, with N1-3 progressively indicating extent of nodal spread. 'M' describes distant metastases (Detterbeck et al., 2017, Amin et al., 2017). The TMN classification can then be used to identify the stage of cancer diagnosis (Table 1.1). TNM classification and staging are crucial factors in optimisation of treatment and assists in providing focussed care to each patient.

Table 1.1 Tumour Node Metastasis Classification and Stage

Stage	TNM Classification
Stage 0	Indicates carcinoma in situ. Tis, N0, M0.
Stage I	Localised cancer. T1-T2, N0, M0.
Stage II	Locally advanced cancer, early stages. T2-T4, N0, M0
Stage III	Locally advanced cancer, late stages. T1-T4, N1-N3, M0
Stage IV	Metastatic cancer. T1-T4, N1-N3, M1.

1.5 Cancer Treatment

Cancer can be treated using chemotherapy, radiotherapy, immunotherapy, hormone therapy and surgery. The focus of this thesis is on the surgical treatment of cancer. Surgical resection is the primary curative treatment for solid tumours and involves the removal of the cancerous tissue or organ (Deo et al., 2022, Global Health Research Unit on Global Surgery, 2019, Sullivan et al., 2015). Worldwide, over 80% of cancers require surgical intervention for either curative resection or palliative treatment (Deo et al., 2022). In Ireland, between 2013-2015, approximately 47% of all patients diagnosed with cancer and over 20% of patients diagnosed with lung and oesophageal cancer patients underwent surgery within the first year (NCRI., 2018a, NCRI., 2018b, NCRI., 2018). While an essential feature of curative treatment, surgery is invasive and places significant stress on the body. Improvements in surgical techniques, centralisation of services, multidisciplinary involvement and intraoperative management strategies have led to a reduction in mortality (Wyld et al., 2015, Moran et al., 2016a). Nevertheless, surgery is associated with postoperative morbidity, impacting health-related quality of life, readmission rates, early cancer recurrence, length of hospital stay and mortality (Wyld et al., 2015, Pinto et al., 2016, Low et al., 2015).

1.6 Cancer Mortality

Improvements in screening, detection and treatment have resulted in a downwards trend in cancer-related mortality (Sung et al., 2021, NCRI, 2022). However, one in eight men and one in eleven women will die from cancer. It is the leading cause of death in 112 countries, with lung cancer responsible for 18% of cancer deaths worldwide followed by colorectal (9.4%), liver (8.3%) stomach (7.7%), female breast (6.9%) and oesophagus (5.5%) (Sung et al., 2021, NCRI, 2022). Between 2018-2020, there was an average of 9,493 cancer-related deaths per year in Ireland, of which lung cancer was the leading cause (NCRI, 2022). Cancers of the pancreas, oesophagus and liver despite having a low incidence rate rank as the fourth, fifth and sixth most frequent causes of

death from cancer (NCRI, 2022). There is a significant gender gap in mortality rates with death rates 43% higher in men than women (Sung et al., 2021). The median age for death was 74 years (NCRI, 2022).

The five-year survival rate describes the percentage of people alive five years following a cancer diagnosis. This has increased significantly for all cancer types from 44% in 1994-1998 to 65% 10 years later (NCRI, 2022). Five-year survival rates vary greatly by cancer site (NCRI, 2022, Wyld et al., 2015). Cancer of the testis has the highest survival rate with a 96% five-year survival rate compared to pancreas, which is 14% (NCRI, 2022). Of all cancer types pancreas, liver, oesophagus, lung and brain currently have the lowest survival rates (Figure 1.3) (NCRI, 2022).

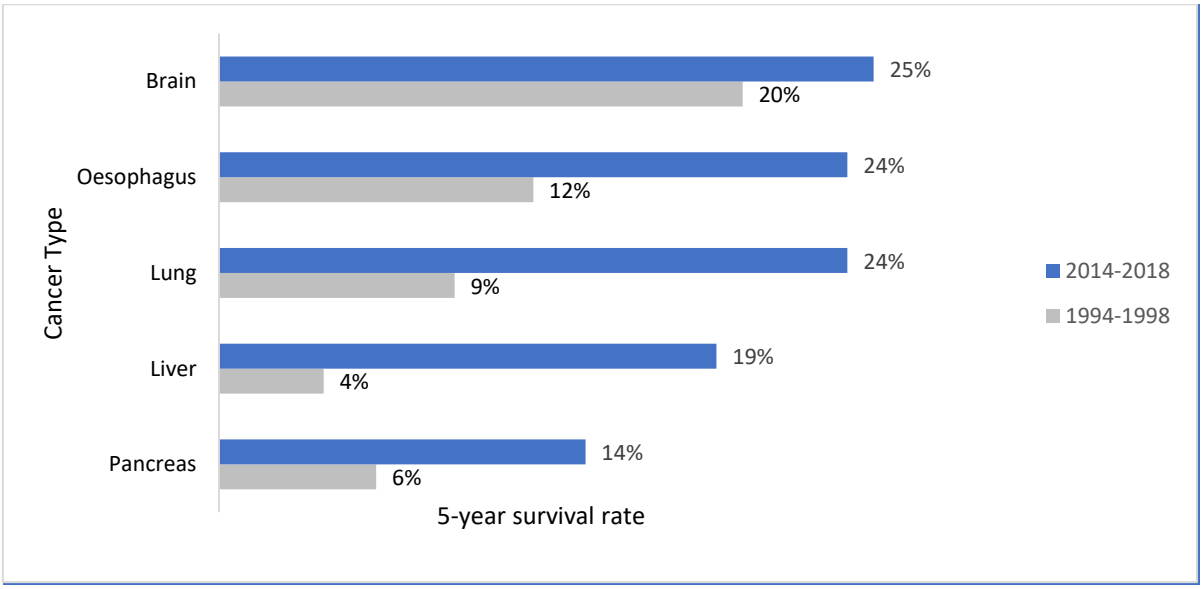

Figure 1.3 National Cancer Registry Ireland Five-year Survival Rate by Cancer Type

Lung and oesophageal cancer are cancers of particular interest in this thesis and therefore will be discussed separately in the following sections.

1.7 Lung Cancer

Lung cancer is the second most commonly diagnosed cancer globally and the primary cause of cancer-related death (Sung et al., 2021). The lungs are the major organ of the respiratory system, the primary function of the lungs is to obtain oxygen for use in the body's cells. Anatomically the lungs have three surfaces converging at the apex of the lungs, above the first rib. The lungs are made up of five lobes. The right lung is made up of three lobes: right upper lobe (RUL), right middle lobe (RML) and right lower lobe (RLL). The left lung is made up of two lobes: left upper lobe (LUL) and left lower lobe (LLL) (Figure 1.4). Each lobe further divides into bronchopulmonary segments,

each supplied by a specific segmental bronchus, which contain bronchioles ultimately leading to alveoli where gas exchange takes place.

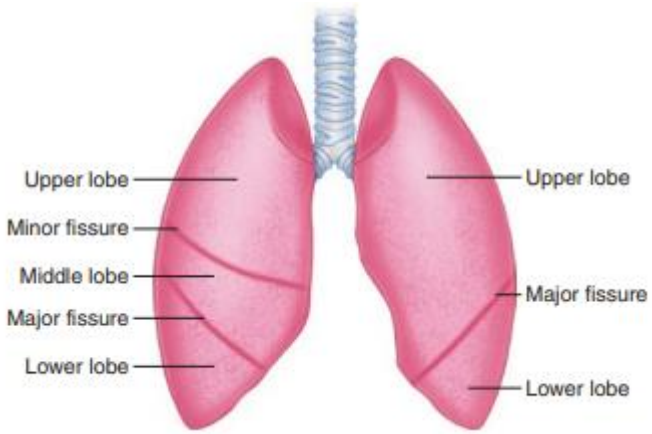

Figure 1.4 Anatomy of the Lungs (Liszewski et al., 2020)

Lung cancers can be divided into two histological categories: non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC) (Schabath and Cote, 2019). NSCLC is the dominant diagnosis with over 85% of lung cancers falling within this group (Schabath and Cote, 2019, Herbst et al., 2018). The most commonly identified sub-types of NSCLC are adenocarcinoma and squamous cell carcinoma (SCC) (Schabath and Cote, 2019, Herbst et al., 2018). Adenocarcinoma arises from the glandular cells that are responsible for mucous production in the lining of the lungs and generally occurs in the periphery of the lung (Collins et al., 2007). Adenocarcinomas are associated with early metastasis and have a lower survival rate than other sub-types (Collins et al., 2007). Adenocarcinomas are now the most prevalent subtype of lung cancer, surpassing SCC, and accounting for approximately 40-50% of diagnoses globally (Succony et al., 2021, NCRI, 2015). In Ireland, between 2011-2013, adenocarcinoma accounted for 35% of lung cancer diagnoses. SCC accounts for 20-30% of lung cancers and originates from the squamous cells lining the airways and are generally centrally located tumours (Succony et al., 2021, NCRI, 2015, Collins et al., 2007). Between 2011-2013, SCC accounted for 25% of diagnosis, a drop from approximately 30% between 1994-1998 (NCRI, 2015).

Smoking is the leading risk factor for lung cancer and is associated with greater than 80% of lung cancer mortality (Huang et al., 2022, Malhotra et al., 2016, Collins et al., 2007). Other risk factors include family history of early-onset lung cancer, chronic inflammation from medical conditions, ionising radiation, air pollution and occupational exposures such as carcinogenic chemicals and asbestos (Malhotra et al., 2016). In Ireland, between 2011-2013 the median age for diagnosis was

70.8 years in women and 70.9 years in men, with a higher incidence in men than women (NCRI, 2015).

Approximately 10% of patients with lung cancer are diagnosed due to an incidental finding and are therefore asymptomatic (Collins et al., 2007). Patients who present with symptoms, commonly present with chest discomfort, cough, dyspnoea, and haemoptysis. Approximately 75% of patients will present with cough, 60% with dyspnoea and 35% with haemoptysis (Collins et al., 2007). As the disease spreads, symptoms progress. Intrathoracic spread is associated with oesophageal symptoms, Horner syndrome, phrenic nerve paralysis and pleural effusion (Collins et al., 2007). Extra-thoracic spread is associated with seizures, weakness, weight loss, bone pain and fractures, headaches, nausea and vomiting. Nearly half of patients present with symptoms of intrathoracic spread and one third present with symptoms of extra-thoracic spread (Collins et al., 2007).

1.7.1 Treatment for Lung Cancer

Treatment options for lung cancer include surgical resection, chemotherapy and radiotherapy. Surgical resection is the primary treatment for curative intent. Patients who present with a localised tumour with no nodal involvement or metastases (T1N0M0) will often undergo surgical resection followed by chemotherapy (Amin et al., 2017). Patients with locally advanced early-stage lung cancer (T1N2M0, T2N2M0) are treated with surgical resection and chemotherapy with or without radiotherapy. Patients with locally advanced disease are assessed and may be treated with surgery, if the tumour is resectable, or with chemotherapy if not (Amin et al., 2017). Stage of diagnosis in Ireland between 2013-2018 is presented in Figure 1.5 (NCRI, 2018a)

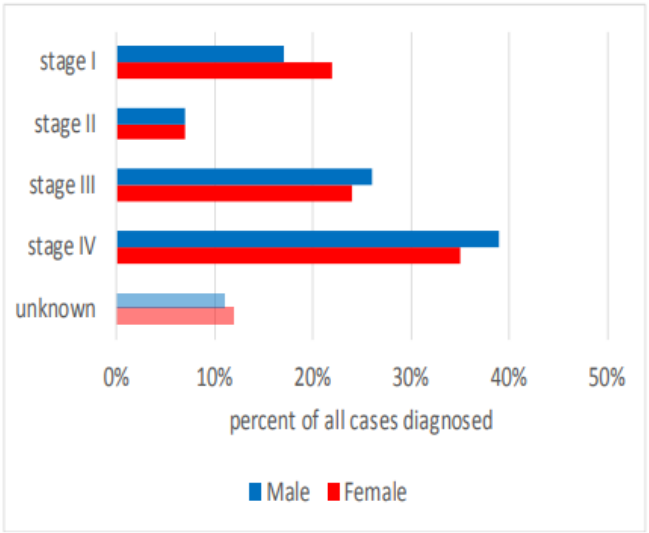

Figure 1.5 Stage of Lung Cancer at Diagnosis in Ireland 2013-2018

1.7.1.1 Lung Cancer Surgery: Procedure and Postoperative Risk

Lung resection is the primary option for curative treatment of lung cancer. Stage I and II cancers are primarily treated with surgical resection (Lackey and Donington, 2013). Surgical resection involves the removal of the affected part of the lung, this can be a sub-lobar resection, lobectomy or pneumonectomy.

A sub-lobar resection (wedge resection or segmentectomies) is used to remove the small area of a lung where the cancer is. Wedge resections remove a wedge-shaped area around the tumour and segmentectomies remove a larger segment, but less than the full lobe. This minimally invasive approach may be used for peripheral tumours which are smaller than 2cm in patients with a low functional reserve (Wolf et al., 2011). As the surgical approach is minimally invasive, less stress is placed on the patient therefore reducing the impact of surgery and preserving pulmonary function (Lackey and Donington, 2013). However, there is controversy over the effectiveness of this approach in ensuring clear margins (Lackey and Donington, 2013).

The most common surgical resection approach is lobectomy, which involves the removal of the whole lobe affected by the cancer. This surgery can be completed using minimally invasive video assisted techniques (video-assisted thoracoscopic surgery (VATs)) or open thoracotomy. Thoracotomy is an open surgical approach used in lung resection and oesophagectomy. Incisions are often made in the thoracic wall between the fifth and sixth rib and abdomen to enable access to the thoracic cavity. The lungs are spread using retractors or parts of the rib may be removed if required and the lung is collapsed to allow access. Patients are supported by one lung ventilation throughout the surgery. The extent of the surgical incision and one lung ventilation (leading to atelectasis) causes significant surgical trauma and postoperative physical inactivity (Motono et al., 2021, Taguchi et al., 2003, Carli and Scheede-Bergdahl, 2015). In recent years, there has been a move towards the VATs approach, as it is associated with less postoperative pain and shorter length of stay (Lackey and Donington, 2013). While VATs are associated with reduced morbidity, lobectomies are still associated with significant risk of postoperative complications which are reported in approximately 37% of patients (Lackey and Donington, 2013). Postoperative mortality ranges between 1-4% and the primary causes of fatalities are pneumonia and respiratory failure (Lackey and Donington, 2013).

Pneumonectomy is the most invasive surgical approach for lung resection and involves the removal of the entire lung in which the tumour is located. This is not a commonly used approach and is reserved for advanced disease, where the tumour is in the main stem bronchus or extends across

a major fissure. This approach is associated with surgical (14.9%), cardiovascular (14.1%), pulmonary (11.5%) and infection (2.7%) complications. Pneumonectomy has a postoperative mortality rate of 7.8%, the most common cause of which can be attributed to pulmonary complications (34%) (Thomas et al., 2015).

1.7.2 Lung Cancer Mortality

Within lung cancer, the five year survival depends on the stage at diagnosis (Collins et al., 2007). Patients diagnosed at stage I have a five year survival of approximately 60-70% (Collins et al., 2007). This rate decreases as the disease progresses. Patients diagnosed at stage II have a 40-50% five year survival rate and those diagnosed at stage III 10-20% (Collins et al., 2007). As discussed in Section 1.7, a significant number of patients are diagnosed with disease which has progressed past stage I or II (Collins et al., 2007). In Ireland between 2013-2018, 63% of patients were diagnosed at stage III or higher (Figure 1.5) (NCRI, 2015).

1.8 Oesophageal Cancer

Oesophageal cancer is the seventh most commonly diagnosed cancer (Figure 1.6) and has the fourth lowest survival rates of all cancer types (Sung et al., 2021). The oesophagus is a muscular elongated organ of the digestive system, which connects the pharynx with the stomach. It lies behind the trachea and heart and in front of the spinal column and passes through the diaphragm before entering the stomach. The main function of the oesophagus is to allow for food to travel downwards to the stomach to facilitate digestion and nutrient absorption. The oesophagus also allows for the upward passage of food during vomiting or reflux. Anatomically, the oesophagus divided into three sections the cervical, thoracic and abdominal oesophagus (Figure 1.6).

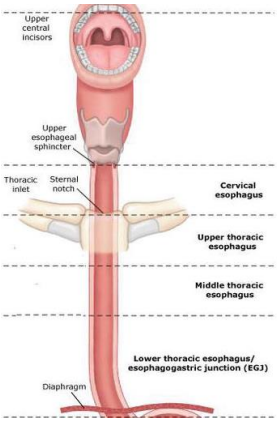

Figure 1.6 Anatomy of the Oesophagus (Ferhatoglu and Kıvılcım, 2017)

Most oesophageal cancers can be classified into two main histopathological types, adenocarcinoma and SCC (Arnold et al., 2015). Adenocarcinoma arises from the glandular cells in the lining of the oesophagus and generally occur in the lower third of the oesophagus (Arnold et al., 2015). Globally the incidence of adenocarcinoma varies by geographical location with an overall the incidence of 0.7 per 100 000 (1.1 in men and 0.3 in women) (Arnold et al., 2015). This increases significantly in northern and Western European countries (3.4 per 100,000), Oceania (3.1 per 100,000) and North America (3.5 per 100,000) and drops to as low as 0.2 per 100,000 in East and Central Asia, sub-Saharan Africa and Eastern Europe (Arnold et al., 2015). Ireland was reported to have the third highest incidence of oesophageal adenocarcinoma globally in 2012, with an incidence of 5.4 per 100,000 in men and 2.9 in women and adenocarcinoma made up 42.7% of oesophageal diagnosis in Ireland between 1994 and 2009 (Arnold et al., 2015, NCRI, 2011). Smoking and second-hand smoking, Barrett's oesophagus, gastroesophageal reflux and increased weight are risk factors for adenocarcinoma (Zhang, 2013). Barrett's oesophagus occurs when the normal epithelia cells which cover the lining of the oesophagus are replaced by columnar cells (Shaheen and Ransohoff, 2002). These chronic changes over time result in an a risk of progressing to adenocarcinoma that is eleven times higher than in a person without Barrett's oesophagus (Shaheen and Ransohoff, 2002). However, while the relative risk for patients who have Barrett's oesophagus is greater, the absolute risk remains low (Shaheen and Ransohoff, 2002).

SCC arises from the epithelial cells in the upper two-thirds of the oesophagus (Arnold et al., 2015). As with adenocarcinoma, the incidence varies greatly from country to country. Globally SCC has an incidence of 5.2 per 100,000 (7.7 in men and 2.8 in women) (Arnold et al., 2015). Approximately 80% of SCC cases occur in eastern and South-East Asia (Arnold et al., 2015). In Ireland between 1994-2012 41.3% of oesophageal cases were SCC (NCRI, 2011). The incidence of SCC has been found to significantly increase in the presence of certain factors including poor diet, alcohol consumption, increased body weight, smoking, gastroesophageal reflux which cause chronic inflammation and lower socio-economic status (Zhang, 2013). The most common symptoms of oesophageal cancer include progressive dysphagia and unintentional weight loss (ACS, 2020). Other symptoms include cough and vomiting, and patients with advanced disease may present with chest pain or bone pain (ACS, 2020). Diagnosis is made using endoscopy and confirmatory biopsy (Berry, 2014).

1.8.1 Oesophageal Cancer Mortality

Thirty two percent of patients with oesophageal cancer present with regional disease. This is associated with a five-year survival of 10-30%, depending on stage, location and histology of the tumour (Berry, 2014). In Ireland between 2013-2015, over 50% of men and over 35% of women presented with stage III or greater (Figure 1.7) (NCRI, 2018b). Approximately 50% of patients present with metastatic disease and are treated palliatively (Berry, 2014).

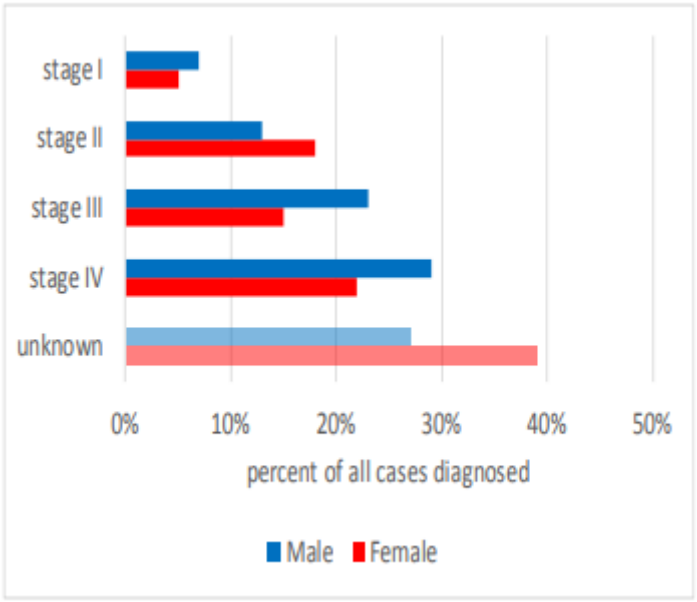

Figure 1.7 Stage of Oesophageal Cancer at Diagnosis

1.8.2 Treatment for Oesophageal Cancer

Treatment options for oesophageal cancer vary significantly depending on stage and include local mucosal resection or ablation therapies, oesophagectomy, chemotherapy and radiation therapy (Berry, 2014). Patients with T1aN0 stage are often treated with local mucosal resection or ablation therapies and surveillance (Berry, 2014). Patients with T1b-2N0 are often treated with oesophagectomy alone. Stages greater than T1b-2N0 are treated with various options such as neoadjuvant chemotherapy or chemoradiotherapy or adjuvant chemotherapy depending on disease progression and patient factors (Berry, 2014).

1.8.3 Neoadjuvant Therapy

Neoadjuvant therapy is used as a primary step in treatment to shrink tumour size before surgery. The two main approaches for treatment of oesophageal cancer are preoperative chemotherapy (FLOT protocol) or preoperative chemoradiotherapy (CROSS protocol) (Donlon et al., 2022). The CROSS protocol has become a standard of care for neoadjuvant chemoradiotherapy (Eyck et al.,

2021). This approach consists of five weekly cycles of chemotherapy with concurrent radiotherapy, five days a week. The CROSS protocol has increased two-year overall survival, compared with surgery alone, from 50% to 67%, and ten-year survival from 25% to 38%. The FLOT protocol, consists of four two-week cycles chemotherapy and has become the standard of care for preoperative chemotherapy (Al-Batran et al., 2019, Stüben et al., 2022). When compared with alternative chemotherapy regimen, FLOT has an increased median overall survival of 50 months, compared to 35 months and an estimated increase in two-year survival from 59% to 68% (Al-Batran et al., 2019). While neoadjuvant treatment does increase overall survival, the treatment has a physiological impact on patients. Neoadjuvant therapy is associated with toxicities, reduction in pulmonary function, sarcopenia and decreased cardiopulmonary fitness (Donlon et al., 2022, Bor et al., 2021). These side effects have a significant impact on the physiological reserve of patients impacting, postoperative complication rates.

1.8.4 Oesophageal Cancer Surgery: Procedure and Postoperative Risk

As in lung cancer, surgical resection is the primary curative treatment option. Oesophagectomy is a surgery which removes part or all of the oesophagus, often using the stomach a conduit (ACS, 2020). There are three main approaches transhiatal (THS), transthoracic and minimally invasive (ACS, 2020). The surgical approach used depends on the stage, location, extent and type of tumour (Obermannová et al., 2022). The overall incidence of complications for oesophagectomy is 59%, with 56.6% experiencing multiple complications, and mortality rates varying from 1.5% to 9% (Low et al., 2015, Biere et al., 2012, Van der Werf et al., 2020, Low et al., 2019).

1.8.4.1 Oesophagectomy

Transthoracic oesophagectomies, which include two and three stage resections, are the most commonly used approach. Transthoracic surgeries are significantly more invasive than THS, however they may be associated with reduced local and regional disease recurrence (Hulscher et al., 2002). The two stage oesophagectomy is often called the Ivor-Lewis oesophagectomy. This approach is usually used for distal tumours and involves an abdominal incision and a right sided thoracotomy. Thoracotomies are discussed in Section 1.7.1. A three stage involves three incisions: abdominal, thoracotomy and cervical, this surgery is often used in mid and upper oesophageal tumours (McKeown, 1976). The surgery is completed in three main stages (McKeown, 1976). Stage one is an abdominal incision stage which is used to mobilise the stomach, stage two, a right thoracotomy to excise the oesophagus and stage three, a right cervical incision to perform an oesophagogastric anastomosis (McKeown, 1976). Transthoracic oesophagectomy is associated with significantly more postoperative complications compared to THS (27% versus 57% p=0.001)

(Hulscher et al., 2002). Transthoracic oesophagectomies are associated with higher postoperative complication rates and longer length of stay than THS (Motono et al., 2021, Taguchi et al., 2003).

A THS oesophagectomy is a less invasive approach compared to transthoracic. This approach avoids the use of a thoracotomy, accessing the oesophagus to allow for mobilisation of the stomach into a conduit through an incision in the abdomen and neck. Additionally, this method also allows for a cervical anastomosis which reduces the associated risk if there was an anastomotic leak. Furthermore, the lack of thoracic incision used in other approaches aims to reduce pulmonary complications, and it is associated with shorter surgery duration and loss of blood. However, a THS approach is still associated with postoperative complications, with a rate of approximately 27%, of which 16% can be attributed to pulmonary complications (Hulscher et al., 2002).

Minimally invasive oesophagectomy is an approach which uses video-assisted thoracoscopic surgery combined with laparotomy to allow for mobilisation of the oesophagus. Minimally invasive oesophagectomy limits the surgical incisions required and has been found to be an effective, safe and feasible approach (Van der Sluis et al., 2019). Despite a longer time in surgery the minimally invasive approach is associated with lower incidence of postoperative complications, reduced blood loss during surgery, and shorter length of stay (Smithers et al., 2007, Van der Sluis et al., 2019).

1.8.5 Postoperative Complications

Postoperative complications are complications which occur following surgery. They can vary from mild not requiring intervention, to severe causing significant morbidity or mortality (Dindo et al., 2004). Postoperative complications include pain, delayed wound healing, infection, cardiac complications and postoperative pulmonary complications (PPCs). PPCs are among the most common and serious of postoperative complications (Miskovic and Lumb, 2017). PPCs commonly include respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, and aspiration pneumonitis (Miskovic and Lumb, 2017, Smetana, 2009). PPCs are associated with increased morbidity, mortality, length of inpatient stay, cost to the health system and rate of readmission (Agostini et al., 2010, Odor et al., 2020). Mortality in patients who develop PPCs varies from 14-30% in the first 30 days postoperatively (Odor et al., 2020). Over 50% (range 17-74%) of patients who undergo open oesophagectomy and 6–29% who undergo lung resection will develop PPCs (Low et al., 2015, Biere et al., 2012, Motono et al., 2021).

1.8.6 Surgical Risk Factors for Postoperative Complications

Different surgeries are associated with different incidence of PPCs. The reported incidence of PPCs varies from 1% to 40% depending on patient related and surgical factors (Smetana, 2009, Agostini

et al., 2010, Abbott et al., 2018, Odor et al., 2020). Surgical factors include anaesthetic used, length of surgery, complexity and surgical site (García-Miguel et al., 2003, Odor et al., 2020). General anaesthesia has an acute negative intraoperative impact on the respiratory system, depressing function (García-Miguel et al., 2003). Larger incisions and resulting postoperative pain can limit postoperative respiratory function (García-Miguel et al., 2003). Complex surgeries, lasting longer than three to four hours, are associated with an increased risk of PPCs (García-Miguel et al., 2003). Thoracic and abdominal surgeries have a higher rate of PPCs than other types of surgeries, as there is an inverse relationship between the distance of incision from the diaphragm and occurrence of PPCs (García-Miguel et al., 2003).

1.8.6.1 Management of Surgical Risk Factors

Improvement in outcomes postoperatively has continuously been linked with the volume of relevant surgeries completed in the institution (Low et al., 2015). Therefore high-risk surgeries, such as oesophagectomies, are typically performed in high volume specialised centres to minimise risk (Low et al., 2015). Minimally invasive approaches, such as VATs for lung resection, anaesthetic optimisation and the use of Enhanced Recovery After Surgery (ERAS) pathways aim to reduce the incidence of complications (Brindle et al., 2020). ERAS is a multidisciplinary approach to improve the quality of surgical care. ERAS guidelines make multiple recommendations with the overall goal to optimise care, support early mobilisation, early reintroduction of nutrition and allow for rapid discharge (Fearon et al., 2005). Recommendations include use of minimally invasive approaches where appropriate, preoperative education on the postoperative course to manage expectations for patients, reducing preoperative fasting from 12 hours to six to lessen the impact of preoperative hunger and thirst and early reintroduction of nutrition, optimisation of medications i.e. anti-thrombotic and antibiotic prophylaxis and pain relief, management of peri-operative fluid, temperature regulation, use of urinary catheter and early removal as appropriate and early mobilisation (two hours postoperatively) (Fearon et al., 2005). This multi-modal approach works holistically to enhance patients physiologically in the peri-operative phase and reduce the risk of postoperative complications (Fearon et al., 2005).

1.8.7 Patient-related Factors for Postoperative Complications

Prior to surgery, patients undergo anaesthetics assessments to identify any patient-related risk factors which may impact surgery and recovery. Identifying these risk factors allows planning and provides opportunity to address any modifiable factors in an effort to reduce postoperative complications (García-Miguel et al., 2003). Modifiable risk factors including smoking status, cardiopulmonary fitness and nutritional status.

1.8.7.1 Smoking

Smoking is a significant independent risk factor for postoperative complications and is associated with increase in risk of PPCs, impaired wound healing, higher risk of infection, neurological complications, cardiopulmonary complications and admission to intensive care units (Grønkjær et al., 2014, Yoshikawa and Katada, 2019). Individuals who are current smokers at the time of surgery have a 2.5 times greater risk of PPCs compared to non-smokers (Grønkjær et al., 2014). One study reported that current smokers at the time of lung resection had a significantly greater frequency of PPCs (22%) compared to non-smokers (2%) (p=0.004), and in patients undergoing oesophagectomy is associated with increased pulmonary morbidity (odds ratio (OR) 1.47 (95% CI 1.08-2.01)) and postoperative pneumonia (OR 2.29 (95% CI 1.34-9.93) (Yoshikawa and Katada, 2019, Lugg et al., 2017). Smoking is a modifiable risk, with cessation of smoking having an impact on wound healing in as little as three weeks preoperatively. Smoking cessation interventions reduce the risk of postoperative pulmonary complications significantly (risk ratio (RR) 0·56 (95% confidence interval (95%CI) 0·41 to 0·78), p< 0·001) (Thomsen et al., 2009). Longer duration of preoperative smoking cessation is associated with less severe postoperative complications following lung resection and oesophagectomy (Yoshida et al., 2016, Yoshida et al., 2018, Lugg et al., 2017).

1.8.7.2 Nutritional status

Nutritional status of patients preoperatively has a significant impact on postoperative recovery. Sarcopenia is the loss of skeletal muscle mass and strength and is related to nutritional status (Muscaritoli et al., 2010). Preoperative incidence of sarcopenia was associated with an increased risk of major morbidity (RR 1.40, 95% CI, 1.20–1.64, p < 0.001) (Simonsen et al., 2018).

1.8.7.3 Cardiopulmonary fitness

Cardiopulmonary fitness can be described as the efficiency of oxygen delivery and consumption in the muscle cells (Jones et al., 2009). Preoperative cardiopulmonary fitness is a valid prognostic measure of postoperative outcomes (Moran et al., 2016b, Sheill et al., 2020b). Lower preoperative cardiopulmonary fitness is associated with an increased risk of postoperative complications and ICU admissions (West et al., 2013, Brunelli et al., 2013, Sivakumar et al., 2020). Therefore, preoperative fitness assessments can be used to identify patients at risk for postoperative complications and mortality. Peak oxygen consumption (VO_{2peak}) is the peak volume of oxygen that the body can consume during exercise and can be measured using cardiopulmonary exercise testing (CPET). In lung and colon cancer cohorts, there is a definitive cut-off point to quantify risk. In lung cancer, a VO_{2peak} of <10ml/kg/min is predictive of postoperative morbidity and mortality and

is associated with a four times greater occurrence of PCCs compared to patients with a $VO2_{peak}$ >17ml/kg/min (Licker et al., 2011, Brunelli et al., 2013). In colon cancer, an increase of 1ml/kg/min at oxygen consumption at anaerobic threshold (VO_{2AT}) is associated with an approximate 20% risk reduction in PPCs and an increase of 2ml/kg/min with approximate 40% reduction (West et al., 2013). These findings establish a distinct threshold value for determining the level of risk; however, there are no specific cut-off points for patients scheduled for oesophagectomy (Sivakumar et al., 2020, Sheill et al., 2020b). Regardless of the precise levels of risk associated with fitness for that cohort, a lower level of cardiopulmonary fitness is associated with increased risk of postoperative complications and there is significant interest in proactive interventions to enhance fitness preoperatively, such as prehabilitation.

1.9 Prehabilitation

Surgery results in a physiological and pathophysiological stress response resulting in significant metabolic demands on the body and drop in functional status (ability to perform normal daily activities required to meet basic needs, including self-care and mobility) in the postoperative phase (Durrand et al., 2019, Cusack and Buggy, 2020). The extent of the stress response is directly related to the degree of surgical trauma (Cusack and Buggy, 2020). Prehabilitation is an emerging intervention performed in anticipation of this decline to blunt the impact of surgery. Prehabilitation is a multi-disciplinary intervention, which focuses on enhancing the physiological status of patients prior to surgery to prepare them for the stresses associated with surgery (Thomas et al., 2019, Schier et al., 2020, Durrand et al., 2019). Prehabilitation demonstrates a shift away from reactive care to proactive care, giving patients a role in their recovery and potentially reducing the impact that surgery will have. Interventions focus on modifiable lifestyle factors which can impact outcome in surgery (Carli and Scheede-Bergdahl, 2015). Programmes can be uni-modal or muti-modal, often including interventions such as smoking cessation, dietary optimisation, education, psychological support in addition to exercise (Durrand et al., 2019). Multidisciplinary prehabilitation teams should be patient-centred and include a physiotherapist, dietician, psychologist, anaesthetist and smoking and alcohol counsellor (Durrand et al., 2019). Overall the primary aim of prehabilitation is to enhance patients preoperatively with the goal of reducing postoperative complications, hospital length of stay, burden of cost on the health system and to enhance health related quality of life (HR-QL) (Silver, 2014). Exercise prehabilitation is one component of prehabilitation and involves the participation in an exercise programme following diagnosis and before surgery (Durrand et al., 2019).

Exercise prehabilitation focuses on enhancing preoperative cardiopulmonary fitness and functional capacity (Durrand et al., 2019). The metabolic demands of surgery require a higher oxygen consumption to meet the heightened physiological needs. Therefore, patients with a reduced oxygen consumption capacity preoperatively may face more challenges throughout surgery. Theoretically, patients who take part in exercise prehabilitation will have a higher level of preoperative functional ability and cardiopulmonary fitness compared to patients who do not. This increase provides a buffer, enabling patients to withstand the increased metabolic requirements of surgery and return to baseline level of function more rapidly following surgery (Figure 1.8).

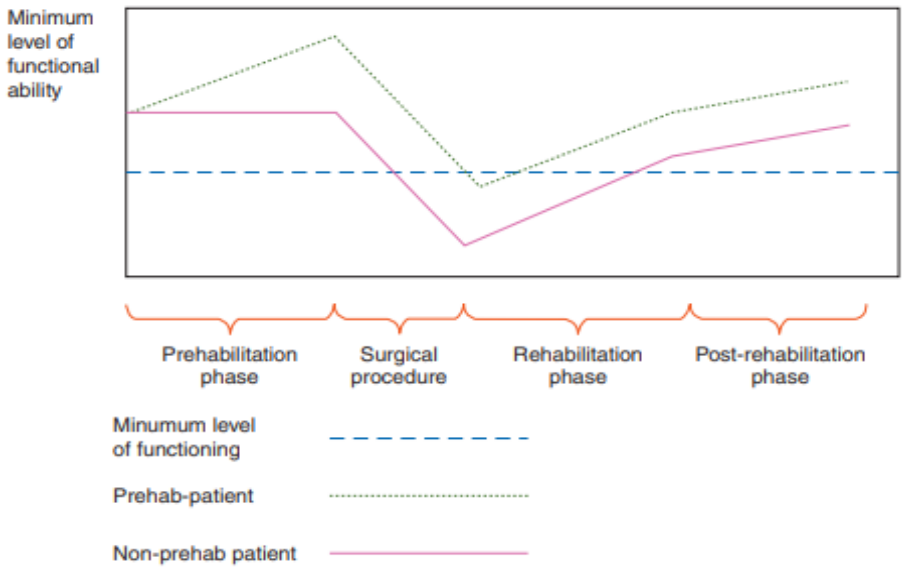

Figure 1.8 Prehabilitation Concept (Banugo and Amoako, 2017)

1.9.1 Physiological Adaptations to Exercise Prehabilitation

The goal of exercise prehabilitation is to target cardiopulmonary fitness as a modifiable factor in preoperative risk. Exercise results in acute and chronic structural, functional and peripheral physiological adaptations (Liu et al., 2020). These adaptations significantly improve oxygen circulation and uptake and enhance physiological reserve of patients, thus improving the ability to tolerate the physiological demands of surgery (Banugo and Amoako, 2017, Laughlin and Roseguini, 2008). This improvement is driven by an increased cardiac output, vascular transport capacity and muscle oxidative capacity (Hellsten and Nyberg, 2015). Exercise results in an increased vagal tone, which leads to a lower resting heart rate. It is this lower resting heart rate which drives an increase in stroke volume (Hellsten and Nyberg, 2015). An increase in stroke volume is characterised by a greater amount of time spent in diastole (Hellsten and Nyberg, 2015). This allows for a greater filling capacity, leading to structural adaptations in the heart such as increased contractibility and

ventricle wall elastic recoil, resulting in a greater ejection fraction (Hellsten and Nyberg, 2015). Overall, exercise results in a more compliant and efficient heart (Hellsten and Nyberg, 2015). The peripheral and vascular changes result in increased blood volume and red blood cells, increased cell mitochondria content and new blood vessels in the muscles resulting in greater oxygen delivery (Laughlin and Roseguini, 2008, Hellsten and Nyberg, 2015, Banugo and Amoako, 2017). This improvement in the delivery of oxygen allows for a significant improvement in skeletal muscle oxidative capacity and therefore greater energy generation within the muscle (Hellsten and Nyberg, 2015). Overall, exercise results in increased cardiopulmonary fitness which supports effective and efficient delivery and use of oxygen around the body.

1.9.2 Evidence for Exercise Prehabilitation

As the need for a preoperative intervention targeting cardiopulmonary fitness becomes evident, exercise prehabilitation has gained significant attention leading to an increased research focus. Most of the evidence in exercise prehabilitation has been collected in abdominal surgery involving cancer and some non-cancer cohorts. In these trials, fitness has typically been measured indirectly as functional capacity using the six minute walk test (6MWT) or directly through cardiopulmonary exercise testing. Systematic review and meta-analyses examining the effect of exercise prehabilitation on fitness report inconsistent results. Some meta-analyses report significant improvements in functional capacity (Waterland et al., 2021, Jain et al., 2023) and significant reductions in postoperative complications (Jain et al., 2023, Hughes et al., 2019, Moran et al., 2016a), whereas others report no change in functional capacity (Lambert et al., 2021, Hughes et al., 2019) and postoperative complications (Waterland et al., 2021, Lambert et al., 2021). None of the meta-analyses report an increase in cardiopulmonary fitness; however, the significant heterogeneity of exercise programmes prescribed may have affected this. Individual studies prescribing high intensity interval training (HIIT) or moderate intensity exercise in combination with resistance training protocols reported the greatest cardiopulmonary gains (Waterland et al., 2021, Lambert et al., 2021, Hughes et al., 2019). This thesis focuses on exercise prehabilitation in lung and oesophageal cancer. The surgical approaches for lung or oesophageal resection are associated with major postoperative risk, as discussed in Section 1.7.1 and 1.8.1. Furthermore, the extent of surgical trauma associated with these approaches places a greater intraoperative metabolic demand on patients (Cusack and Buggy, 2020). This emphasises the need for exercise interventions in advance of these high-risk surgeries to optimise patients physiologically. To date, trials in lung cancer patients have largely been small in scale with many solely focused on feasibility outcomes (Ferreira et al., 2021a, Finley et al., 2020, Bobbio et al., 2008, Jones et al., 2007). These studies supported the feasibility of exercise prehabilitation to target cardiopulmonary fitness within the

lung cancer pathway. Consequently, the number of RCTs and therefore systematic reviews is growing. As with findings from abdominal surgery, the effect of exercise prehabilitation on cardiopulmonary fitness and postoperative complications in lung cancer is unclear. Reviews investigating this question report increase in cardiopulmonary fitness (VO_{2peak}) (Granger and Cavalheri, 2022, Gravier et al., 2022), increase in functional capacity (6MWT) (Granger and Cavalheri, 2022, Gravier et al., 2022), significantly lower incidence of PPCs following prehabilitation (Voorn et al., 2023, Granger and Cavalheri, 2022), lower incidence of postoperative complications (Voorn et al., 2023, Gravier et al., 2022) and shorter length of stay (Granger and Cavalheri, 2022, Gravier et al., 2022). Although these studies indicate that exercise prehabilitation may have positive benefits, study quality is a major issue. This is highlighted by a lack of clarity stemming from the low grade of certainty of evidence generated and the small number of existing systematic reviews and meta-analyses, as outlined in Table 1.2. Consequently, high quality robust trials specifically examining the role of exercise prehabilitation in advance of lung surgery are required.

Table 1.2 Methodological Quality of Meta-Analysis of Exercise Prehabilitation in Lung Cancer

Outcome		Result	Certainty of evidence
Postoperative pulmonary complications	Voorn et al. (2023)	OR 0.31 (0.20 to 0.48)	⊕⊕⊕⊖ Moderate
	Granger et al. (2022)	RR 0.45 95% CI 0.33 to 0.61	⊕⊕⊕⊕ High
	Gravier et al. (2022)	-	-
Postoperative complications	Voorn et al. (2023)	OR 0.37 (0.23 e0.61)	⊕⊕⊖⊖ Low
	Granger et al. (2022)	-	-
	Gravier et al. (2022)	RR 0.58 (0.45 to 0.75)	⊕⊕⊕⊖ Moderate
Length of stay (days)	Voorn et al. (2023)	MD 3.02 (4.82 to 1.22)	⊕⊖⊖⊖ Very low
	Granger et al. (2022)	MD 2.24 (3.64 to 0.85)	⊕⊕⊕⊖ Moderate
	Gravier et al. (2022)	MD 2.29 (3.59 to 0.98)	⊕⊕⊖⊖ Low
Cardiopulmonary fitness (ml/kg/min) CPET	Voorn et al. (2023)	-	-
	Granger et al. (2022)	MD 3.36 (2.7 to 4.02)	⊕⊕⊕⊖ Moderate
	Gravier et al. (2022)	MD 3.43 (2.43 to 4.42)	⊕⊕⊖⊖ Low

Functional capacity (meters) (6MWT)	Voorn et al. (2023)	-	-
	Granger et al. (2022)	MD 29.55 (12.05 to 47.04)	⨁⊖⊖⊖ Very low
	Gravier et al. 2022	MD 37.60 (20.46 to 54.74)	⨁⨁⨁⊖ Moderate

OR= Odds Ratio

As with lung cancer, research into the impact of exercise prehabilitation in patients scheduled for oesophageal resection is still emerging. Evidence to date supports the feasibility of exercise interventions prior to oesophagectomy (Argudo et al., 2021). As with results in lung cancer trials, the impact of exercise prehabilitation on cardiopulmonary fitness is inconsistent (Piraux et al., 2021, Bolger et al., 2019, Tukanova et al., 2022). The quality standards of reviews are inferior to those in lung cancer, lacking meta-analyses and generalisability. This can be attributed to poor methodological design, with heterogeneity in surgical approach across studies (inclusion of oesophagectomy and gastrectomy and gastrectomy-only studies), interventions (inclusion of inspiratory muscle training exercises only) and outcomes in addition to risk of bias, poor quality and underpowered studies (Piraux et al., 2021, Bolger et al., 2019, Tukanova et al., 2022).

Neoadjuvant therapy is another major consideration in oesophageal cancer. Neoadjuvant therapy is the standard of care for many patients undergoing oesophagectomy, with approximately 63% of patients treated with curative intent in St James's Hospital (SJH) receiving neoadjuvant therapy (Donlon et al., 2021). The neoadjuvant therapy period provides a potential window for individualised prehabilitation running concurrently with neoadjuvant therapy to potentially blunt the known impact of treatment on cardiopulmonary fitness and physical function. Furthermore, the deleterious impact of neoadjuvant therapy on physical condition highlights the need for high quality optimisation following neoadjuvant therapy in preparation for oesophagectomy (Donlon et al., 2022, Bor et al., 2021). Exercise prehabilitation may attenuate the effects of therapy on cardiopulmonary fitness and optimise patients' cardiopulmonary fitness following treatment and before surgery; however, robust RCTs are required to clarify its role.

1.9.3 Challenge of Delivering Prehabilitation Programmes in Practice

Prehabilitation is a complex intervention to integrate into clinical care. Lack of knowledge across stakeholder groups regarding the role of prehabilitation, inconsistent evidence to support its role and difficulty providing individualised programmes and logistical challenges of delivering the service within a short and stressful timeframe have been reported as barriers (Heil et al., 2022, Kennedy et al., 2022). Overall, due to the complexity of delivering prehabilitation services, implementation is challenging. One significant challenge is the short timeframes available from diagnosis until surgery. The Irish Department of Health recommends a surgical date within 30 days of the decision to operate and the National Health Service in the United Kingdom mandates a maximum of 31 days from diagnosis of cancer to beginning treatment (Department of Health, 2017, National Health Services England, 2013). Considering 4-8 weeks are required for physiological adaptations to exercise to occur, the short periods (1-3 weeks) available in some of the more time-

sensitive cancers may limit the impact of moderate intensity prehabilitation in increasing O_2 uptake (O'Neill et al., 2018, Campbell et al., 2019, Hellsten and Nyberg, 2015). This has led to significant interest in alternative methods of enhancing cardiopulmonary fitness, such as high intensity interval training (HIIT), to increase oxygen consumption.

1.9.4 Potential of High Intensity Interval Training

HIIT may provide an alternative option to moderate intensity exercise to increase cardiopulmonary fitness in patients who have a limited timeframe available before surgery. High intensity interval training can be defined as 'repeated short to long bouts of rather high intensity exercise interspersed with recovery periods' (Buchheit and Laursen, 2013), or 'intense work periods that may range from 5 seconds to 8 minutes long, and are performed at 80% to 95% of a person's estimated maximal heart rate '(Kravitz, 2014). HIIT has been shown to be a safe and effective intervention for patients across the cancer care continuum (Blackwell et al., 2020, Dunne et al., 2016, Weston et al., 2016a, Palma et al., 2021, Mugele et al., 2019, Wallen et al., 2020). HIIT offers the opportunity to participate in exercise and achieve the benefits.

HIIT is an effective and efficient way of increasing cardiopulmonary fitness (Buchheit and Laursen, 2013, MacInnis and Gibala, 2017, Burgomaster et al., 2008, Gibala et al., 2012, Helgerud et al., 2007). The physiological adaptations elicited are similar and at times superior to moderate intensity training within a shorter time frame (Burgomaster et al., 2008, Gibala et al., 2012, Helgerud et al., 2007, Weston et al., 2016a). These adaptations to exercise are attributed to multiple factors e.g. intensity, duration, frequency, and activity patterns of exercise completed (Gibala et al., 2012). Some factors, such as intensity, have been identified to have a greater influence on certain adaptations regardless of total workload (Gibala et al., 2012, Helgerud et al., 2007). Exercising at higher intensities results in an increased mitochondrial capacity of muscles, increased peripheral vasculature, increased stroke volume resulting in increased exercise performance (measured by time-to-exhaustion) and increased VO_{2peak} (Gibala et al., 2012, Helgerud et al., 2007). Furthermore, not only is HIIT an effective approach to increase VO_{2peak} but it is also efficient, with some improvements in VO_{2peak} and exercise performance noted in as little as two weeks (Gibala et al., 2012). This time-efficient change in VO_{2peak} fits well into treatment pathways for cancer patients requiring major surgery and offers a potential solution to the limited periods available preoperatively. Therefore, prehabilitation interventions using HIIT to increase cardiopulmonary fitness within the short time frames must be assessed considering the important impact on postoperative complication levels it may have. Chapter 2 presents a systematic review and meta-analysis of HIIT interventions for prehabilitation.

1.9.4.1 Acceptability of a Healthcare Intervention

The goal of intervention development is to provide an effective intervention which can be integrated into a clinical pathway. However due to the intervention timing, the clinical populations and the inherent challenges in setting up new services, the implementation of prehabilitation is challenging (Waterland et al., 2021). To support future integration of exercise prehabilitation into a clinical pathway, factors which influence implementation must be considered (Proctor et al., 2011, Kennedy et al., 2022). Acceptability of an intervention is one of the key factors which impacts implementation, with elements of acceptability evident across multiple implementation frameworks (Damschroder et al., 2022, Gaglio et al., 2013, Proctor et al., 2011). In light of the vital role acceptability plays in the implementation of an intervention, evaluation throughout development must be completed (O'Cathain et al., 2019). This may be of additional value in the context of HIIT, considering the intensity of the intervention and the physical effort required.

Acceptability is a complex concept which is poorly described within healthcare interventions. Across the discipline, definitions can vary and comparison between studies is challenging. A 2017 systematic review and a 2012 qualitative study defined acceptability as participants 'willingness and ability' to participate (Frost et al., 2017, Moore et al., 2012). A 2019 study assessing the role of text messages to enhance physical activity in cancer survivors defined acceptability as 'participant's perceived usefulness and satisfaction' (Gomersall et al., 2019). A 2020 review defined acceptability as 'satisfaction among implementation stakeholders' focusing on intervention content, delivery and complexity (Subedi et al., 2020). Furthermore, the primary or secondary outcome of many studies was to assess acceptability; however, many lacked any definition of acceptability at all (Sekhon et al., 2017). The accurate measurement of acceptability has gained significant traction over recent years in healthcare interventions. However, with a lack of standardised definitions and the inconsistency of acceptability measures, comparison of existing data is challenging.

A 2017 study by Sekhon et al. sought to define acceptability and develop a theoretical framework to set a standard for assessment of acceptability (Sekhon et al., 2017, Sekhon et al., 2022). This study used a consensus group of seven research psychologists to review existing definitions, ultimately defining acceptability as 'a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate based on anticipated or experiential cognitive and emotional responses to the intervention' (Sekhon et al., 2017). Following the definition of acceptability, the Theoretical Framework of Acceptability (TFA) was developed using an inductive analysis of current practices and systematic reviews to establish a preliminary theoretical framework. Data was then deductively analysed onto the preliminary

framework and reviewed with healthcare behaviour frameworks for finalisation. The framework consists of seven constructs of acceptability: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy) Table 1.3 (Sekhon et al., 2017).

Table 1.3 Constructs of Acceptability According to the Theoretical Framework of Acceptability

Construct	**Definition**
Affective attitude	How an individual feels about taking part in an intervention
Burden	The amount of effort required to participate in an intervention
Perceived effectiveness	How effective at achieving its goal is the intervention perceived to be
Ethicality	How well the intervention fits into a person's individual value system
Intervention coherence	How well the individual understands the intervention and how it works
Opportunity costs	The extent to which the cost of the intervention is worth it for engagement
Self-efficacy	The person's confidence that they can complete the intervention.

The framework provides a definition and provides a foundation for the measurement of acceptability across healthcare interventions and will be applied in this thesis.

1.10 Aims and Objectives of this Thesis

On consideration of the literature presented, there are major gaps in our understanding of the optimal exercise prescription to elicit maximal gains in cardiopulmonary fitness, particularly amongst some of the most complex surgical resections. As we develop complex interventions during this stressful time in patients' lives, we need to consider how acceptable these interventions are to a variety of stakeholders to inform future implementation into practice.

Therefore, the primary arm of this thesis was to examine the role of exercise prehabilitation prior to oncological resection.

Thesis specific objectives were to:

- Examine the acceptability of exercise prehabilitation prior to oncological resection.
- Examine the role of HIIT prior to oncological resection, in terms of feasibility, effectiveness and acceptability.
- Examine the impact of exercise prehabilitation on postoperative complications.

The primary aims and study specific objectives for each chapter of the thesis is presented in Figure 1.9.

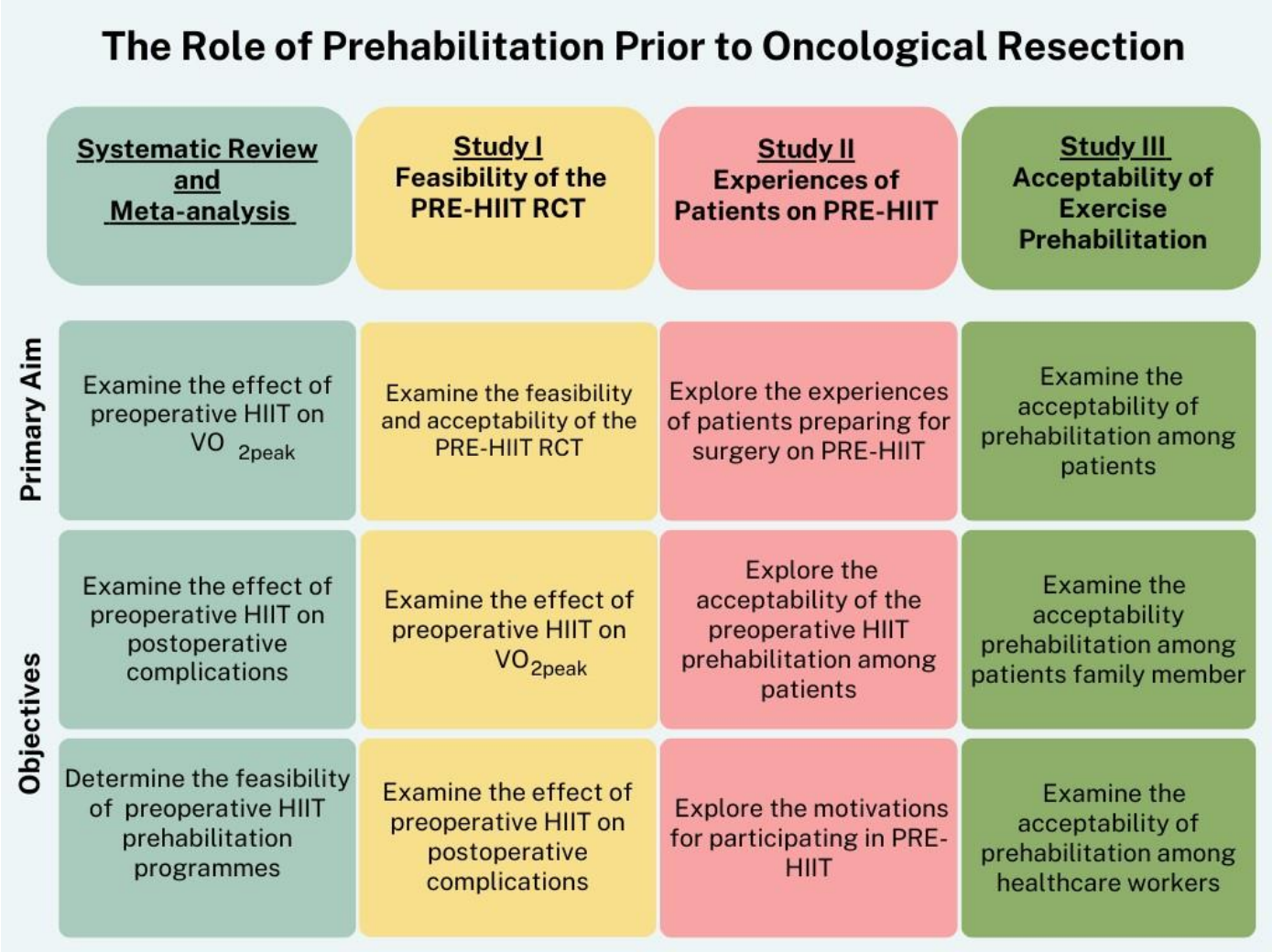

Figure 1.9 Primary Aims and Objectives of Thesis Chapter

1.11 Impacts of COVID-19

The candidate registered for this PhD on March 1st 2020 and consequently all studies completed in this thesis were impacted by the COVID-19 pandemic. The original protocol for Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus (PRE-HIIT), a main component in this thesis, included a face-to-face assessment and intervention in the Clinical Research Facility (CRF) in SJH. Ethical approval was granted in February 2020 and recruitment was set to start in early March 2020. However, on the 12th of March, in response to the COVID-19 pandemic, the government implemented public health restrictions. Due to these restrictions, PRE-HIIT recruitment was unable to commence. Subsequently, there was significant delays to recruitment and many challenges due to the impact of COVID-19 on health service delivery e.g., the need for travel restrictions and major changes to cancer surgery pathways in SJH. As the pandemic progressed, three main challenges became evident:

- Difficulty attending oncology clinics at St. James's Hospital for recruitment.
- Challenges to conducting face-to-face assessments.
- Challenge of carrying out in-person interventions.

Consequently, it became evident that the original plan for PRE-HIIT would require adaptation to address these three significant implementation obstacles. Therefore, PRE-HIIT was adapted. The objectives of the research question for RCT remained unchanged; however, the means of addressing this question required alteration. The following amendments were made to the protocol to address these problems:

- COVID-19 screening of the patient was introduced 24 hours prior to assessment.
- Significant consideration was given to the inclusion of a CPET due to the aerosol-generating nature of the test. However, during the intervention high intensities are reached and ensuring the safety of participants achieving these intensities at home is vital. Therefore, the CPET was kept in the assessment battery with additional safety precautions.
- Spirometry and maximal inspiratory mouth pressures outcome measures were removed from the outcome battery to reduce risk of potential transmission of COVID-19.
- The intervention was amended to be able to be completed at home with supervision via Zoom on an electromagnetically braked cycle ergometer provided on loan to participants for the duration of the intervention.

At the start of the pandemic, exercise via telehealth was a new concept. Therefore, there were problems and concerns regarding hybrid implementation of PRE-HIIT.

These included:

- Concerns about the safety of completing HIIT at home.
- Renting and delivering electromagnetically braked cycle ergometers, which can be programmed to the participant's exact exercise prescription.
- Establishing the feasibility and acceptability of implementing an online HIIT intervention.

The following amendments were made to the protocol to address these problems:

- Inclusion of one home visit by the study physiotherapist. This home visit was considered to be of significant importance for the safety of the participant when using the equipment and to educate the participant on using Zoom and completing the intervention.
- Participants to have a family member at home during HIIT sessions for safety purposes.
- Purchasing of two COSMED E100 electromagnetically braked cycle ergometers, which could be programmed to the participant's exact prescription.
- Addition of a questionnaires addressing the useability of telehealth.

Despite these changes being approved by the Research Ethics Committee in August 2020, recruitment was further delayed until June 2021 as surgeries were relocated from SJH to the Beacon Hospital during subsequent waves of COVID-19. Recruitment was slow as many patients were still anxious with respect to attending hospital appointments. Furthermore, recruitment was paused in early July 2021 until August 2nd 2021 due to malfunction of the indirect calorimeter (the COSMED K4b^2) used to measure gas exchanged during cardiopulmonary exercise testing. The equipment malfunctioned again in February 2022, and consequently the COSMED K4b^2 hired through the Clinical Research Facility at SJH was replaced with a borrowed COSMED QUARK from the Department of Physiology in Trinity College Dublin. Therefore, implementation of PRE-HIIT faced significant challenges in light of COVID-19, impacting both Study I and II.

Study III was designed during the COVID-19 pandemic, with public health restrictions in mind. Regardless of this, recruitment for Study III was also impacted. During Level Five public health restrictions, the patient's family members did not accompany them to hospital for their appointments. This was reported by the physiotherapists distributing the questionnaire as a significant limiting factor for the recruitment of family members. Overall, the completion of this thesis faced significant challenges in light of the COVID-19 pandemic; however, it also presented a

unique opportunity to explore novel concepts and approaches in delivering exercise prehabilitation.

1.12 Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus Randomised Controlled Trial

A primary component of this thesis is Study I, the feasibility of the 'Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus' (PRE-HIIT) randomised controlled trial (RCT). The PRE-HIIT trial is currently being conducted by the Exercise Oncology Research Team, Trinity College Dublin. PRE-HIIT commenced in June 2021 and recruitment is ongoing with an estimated end date of November 2024. The primary aim of this RCT is to examine the effect of a hybrid preoperative high intensity interval training (HIIT) programme on peak oxygen consumption (VO_{2peak}) in patients scheduled for oesophagectomy and major lung resections. The author (Emily Smyth (ES)) was the lead researcher responsible for the management of the PRE-HIIT RCT, leading recruitment, management of all study visits, implementation of the intervention (delivery of the HIIT intervention and home visits), data collection and data analysis for this thesis. Recruitment for the PRE-HIIT RCT is ongoing, with a target accrual of n=78. This target is based on estimates calculated from a pilot study indicating that a sample of size 64 (32 in each arm) is required to detect a mean difference in VO_{2peak} of 1ml/kg/min between the control and HIIT intervention groups. To allow 20% attrition n=78 will be recruited. As the initiation of recruitment was delayed due to the COVID-19 pandemic and resulting amendments to the protocol, an insufficient number of participants were recruited for this thesis to meet the criteria for the power calculation. Therefore, this thesis evaluates the feasibility and preliminary efficacy of this RCT using data from the first 48 participants recruited onto the trial.

Chapter 2 Preoperative High Intensity Interval Training for Oncological Resections: A Systematic Review and Meta-analysis

This systematic review is published in Surgical Oncology.

Citation: Smyth E, O'Connor L, Mockler D, Reynolds JV, Hussey J, Guinan E. Preoperative high intensity interval training for oncological resections A systematic review and meta-analysis. Surg Oncol. 2021 Sep;38101620. doi 10.1016/j.suronc.2021.101620. Epub 2021 Jun 12. PMID 34161894. (Appendix I).

Number of citations: 6, Google Scholar, accessed on 23/08/2023

2.1 Introduction

Prehabilitation is a coordinated multidisciplinary process of enhancing physical, nutritional and physiological resilience to enable the patient to better tolerate the stresses associated with surgery (Thomas et al., 2019, Schier et al., 2020). The principal goal is to reduce surgical complications, length of stay and the burden of cost on the health system, and to enhance recovery of health-related quality of life (HR-QL) (Silver, 2014). Exercise prehabilitation may include cardiopulmonary and resistance training (Moran et al., 2016a, Guinan et al., 2017, Durrand et al., 2019). Cardiopulmonary exercise is a key element and targets an increase in cardiopulmonary fitness before surgery, with an anticipated reduction in postoperative pulmonary complications (PPCs) and improved HR-QL (Moran et al., 2016a, Agostini et al., 2010, Kauppila et al., 2020). Peak oxygen consumption ($VO_{2peak)}$ is a principal metric for surgical outcomes, with an increased VO_{2peak} associated with a reduction in postoperative complications (Sheill et al., 2020b, Licker et al., 2011, West et al., 2013, Sivakumar et al., 2020). Therefore, intuitively it is logical that such a programme may lead to reduced postoperative complications. However, a barrier may exist where the timeframe to effect change is limited, and this is particularly applicable to time-sensitive cancer surgery.

The timeframe for preoperative interventions may also be limited by national policies. As discussed in Section 1.9.3, the Irish Department of Health advises that patients should have a surgical date within 30 days of the decision to operate (Department of Health, 2017). These timeframes may restrict the effect that moderate-intensity exercise can have on the cardiopulmonary system and has led to increasing interest in alternative methods. Accordingly, administration of high intensity aerobic training in a concentrated period may have a pragmatic rationale. High intensity interval

training (HIIT) is defined as 'repeated short-to-long bouts of rather high intensity exercise interspersed with recovery periods' (Buchheit and Laursen, 2013) or 'intense work periods, may range from 5 seconds to 8 minutes long, and are performed at 80% to 95% of a person's estimated maximal heart rate' (Kravitz, 2014). This low volume of high intensity work is an effective method of training in healthy individuals (Buchheit and Laursen, 2013, MacInnis and Gibala, 2017). It can elicit physiological changes similar or superior to moderate-intensity continuous training (Burgomaster et al., 2008, Gibala et al., 2012). It has also been shown to improve aerobic capacity in cancer patients undergoing treatment and in survivorship (Wallen et al., 2020). A 2018 meta-analysis by Blackwell and colleagues reported a mean difference (MD) of 3.38 (95% CI 2.7–4.05) ml/kg/min between HIIT and control groups in less than eight weeks in a population across a number of chronic disease types (Blackwell et al., 2018b). Metabolic adaptations in oxidative capacity and peripheral insulin sensitivity, along with improvements in cardiac and respiratory function, are achieved by the higher intensities reached in each exercise session (Gibala et al., 2012, Weston et al., 2016b). This principle of HIIT achieving physiological benefits fits well into treatment pathways for patients requiring major cancer surgery, either alone or after preoperative chemotherapy or with combination chemotherapy and radiotherapy (Gibala et al., 2012, Weston et al., 2016b).

This systematic review and meta-analysis explores whether HIIT improved preoperative fitness in patients scheduled for oncologic resection, and whether this impacted on postoperative complications. The primary aim of this review was to assess change in preoperative fitness in patients scheduled for oncological resection. Secondary aims were to analyse the impact on postoperative complications and report on measures of feasibility.

2.2 Methods

2.2.1 Design

A qualitative systematic review and meta-analysis was completed. The review was completed following a pre-defined protocol, which was registered prospectively with the International Prospective Register for Systematic Reviews (CRD42020178959).

2.2.2 Eligibility criteria

Eligibility criteria are outlined in accordance with the 'Population, Intervention, Comparison, Outcome'(PICO) format (Table 2.1).

Table 2.1 Inclusion and Exclusion Criteria for Systematic Review and Meta-analysis

Inclusion Criteria	Exclusion Criteria
Types of studies • Randomised controlled trials • Published in English • Published studies only	**Types of studies** • Non-randomised controlled trials • Not published in English • Conference articles or unpublished studies
Population • Patients scheduled for oncological resection	**Population** • <18 years of age
Intervention • Preoperative HIIT prehabilitation programme defined as high intensity intervals at 80% to 95% of a person's estimated maximal heart rate for 5 seconds to 8 minutes	**Intervention** • Moderate or low intensity endurance interventions
Comparison • Active or usual care interventions as a control	
Outcomes • Preoperative fitness • Feasibility outcomes • Postoperative outcome	

Abbreviations: <= less than

2.2.2.1 Types of Studies

Randomised controlled trials (RCTs) measure the cause-and-effect relationship between an intervention and an outcome. As the only effective tool to assess this, they are considered the gold standard of experimental trials. Only studies utilising a RCT design included in this review. The initial search was not restricted by date and included all studies published until March 2020. The search was repeated in April 2021 in preparation for paper publication (search period March 2020 to April 2021) and again in February 2023 in preparation for final thesis preparation (search period April 2021 to February 2023). Only studies published in English were included.

2.2.2.2 Population

Participants were patients who were scheduled for any oncological resection. Patient populations under the age of 18 were excluded.

2.2.2.3 Intervention

Studies prescribing HIIT prior to oncological resection were included. The definition of HIIT varies across the literature. As an umbrella term, HIIT can be defined as *'repeated short-to-long bouts of rather high intensity exercise interspersed with recovery periods'* (Buchheit and Laursen, 2013). Within that umbrella term, the variations in interval intensities and duration can vary significantly. A 2017 systematic review and meta-analysis defined HIIT as interventions with intensities of ≥90% peak oxygen uptake, ≥100% maximal aerobic speed and/or heart rate ≥90% of peak heart rate (Eddolls et al., 2017). Another review defined HIIT as an interval intervention ranging from 6 seconds to 4 minutes at intensities of 85% to 250% of maximum oxygen consumption (VO_{2max}) (Batacan et al., 2017). A 2021 systematic review and meta-analysis completed in breast cancer survivors defined HIIT as *'multiple repetitions of short bursts (≤4 minutes) of high intensity (Tsuji et al., 2021)'*. They defined high intensity as ≥90% of VO_{2max} or VO_{2peak} or rating of perceived exertion ≥18 (Tsuji et al., 2021).

According to the American College of Sports Medicine, HIIT can be defined as interval interventions, where high intensities range from 80% to 95% of a person's estimated maximal heart rate (Kravitz, 2014). The duration of these intervals can range from 5 seconds to 8 minutes long and are interspaced with recovery periods of the same duration at intensities of 40% to 50% of a person's estimated maximal heart rate (Kravitz, 2014). Accurately capturing the true nature of HIIT is important to ensure consistent physiological responses across the studies and analyse if there a true effect of the intervention. The physiological response to exercise (discussed in Section 1.9.1) such as increased cardiac output, increased blood volume, mitochondria content and capillary density are dose-dependent (MacInnis and Gibala, 2017). Exercise intensity is a key factor in the

volume of exercise prescribed and therefore the physiological response to exercise (MacInnis and Gibala, 2017). Higher intensity exercise (defined as >80% to 95% of a person's estimated maximal heart rate) elicits a higher metabolic response when compared to work-matched exercise completed at lower intensities (MacInnis and Gibala, 2017). Therefore, to ensure consistent physiological responses across studies, HIIT was defined as 'interval training with the high intensity interval at 80% to 95% of a person's estimated maximal heart rate for 5 seconds to 8 minutes' and only studies which met this criteria were included (Kravitz, 2014).

2.2.2.4 Comparison

The control group included studies where control participants did not take part in preoperative HIIT programmes. Studies with an active or usual care interventions as a control were included.

2.2.2.5 Outcome

The primary outcome was change in preoperative cardiopulmonary fitness. All outcomes used to measure cardiopulmonary fitness, such as but not limited to cardiopulmonary exercise testing (CPET) were included. The secondary outcome were postoperative outcomes. Studies used standardised outcome measures for postoperative complications including but not limited to the Clavien-Dindo Classification of Surgical Complications, length of stay, costs associated with hospitalisation and postoperative mortality.

2.2.3 Information and Search Strategies

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines were followed (Moher et al., 2015). A search strategy was developed with the subject librarian. Search terms included 'high-intensity intermittent exercise' OR 'high-intensity intermittent training' OR 'high-intensity interval exercis*' OR 'high-intensity interval training' OR HIIT OR HIIE' and 'cancer surgery', 'lung resection' Pneumonectom* OR lobectom* OR segmentectom* OR pneumoresection* OR pulmonectom* were used (see 1 for full search strategy). Forward citing (forward searching of all studies which cited articles identified in the database search), backwards citing (backward searching through all references in articles identified in the database search) were also performed manually. Clinicaltrials.gov was searched for titles of completed and published articles, ongoing trials were not considered for inclusion. The original search was completed in March 2020. This search was updated in April 2021 for publication and updated again in January 2023 in preparation for thesis submission. Each iteration of the search involved a search of all electronic databases listed (EMBASE, PUBMED, OVID Medline, CHINAL and Web of Science) and forwards and backwards citation chasing, all completed in duplicate by two independent reviewers.

2.2.4 Selection Process

Results from the search were imported onto Covidence (https//www.covidence.org/). Covidence is an online screening tool which allows two authors to independently screen citations, abstracts and full texts. This software identifies conflicts between the two authors and enables resolution to identify texts for inclusion. Two authors Emily Smyth (ES) and Louise O'Connor (LOC) in 2020 and ES and Emer Guinan (EG) in 2021 and 2022 independently screened all identified citations and abstracts for inclusion criteria (Table 2.1). Abstracts which did not meet the inclusion criteria were excluded. Conflicts were resolved by discussion with a third reviewer if required. Full texts of eligible or ambiguous abstracts were retrieved and reviewed independently by both assessors.

2.2.5 Data Extraction

A preformatted Excel sheet for data extraction was designed and agreed upon by ES and LOC. Data was extracted independently by two authors and any differences were discussed and resolved with a third author. The 2020 search data extraction was completed by ES and LOC and any differences were discussed with EG. In the updates, data was extracted by ES and EG and any differences were discussed with Juliette Hussey (JH).

2.2.6 Data Extracted

Data extracted included study and sample characteristics, intervention characteristics and results including physiological variables from CPET, feasibility outcomes and postoperative complications outcomes. Three authors were contacted by email to retrieve data to allow for meta-analysis of VO_{2peak}, oxygen consumption at anaerobic threshold (VO_{2AT}) and PPO; however, data was not available from two of these papers.

2.2.7 Risk of Bias

Analysis of the risk of bias is used to identify areas of bias, which may impact on the validity of the results. This gives important context to findings, preventing inappropriate interpretation of the true intervention effect, based on biased results (Higgins et al., 2011). A thorough risk of bias assessment is therefore a key component of a systematic review. Risk of bias was assessed in this review using the Cochrane Collaboration's 'Risk of Bias' (RoB2) tool (Higgins et al., 2011). This was completed independently by ES and LOC in the initial search (March 2020) and updated by ES and EG in April 2021 and February 2023. The RoB2 tool was specifically designed to identify areas of bias within a RCT (Higgins et al., 2011). This tool consists of five domains and an overall risk of bias grade (Higgins et al., 2011). These domains include selection bias, performance bias, detection bias,

attrition bias, reporting bias and other bias (Higgins et al., 2011). Each domain and the overall risk across all domains is judged by the assessor, guided by a standardised algorithm, as 'low-risk', 'some concerns' or 'high-risk of bias'. Domain one, selection bias, assesses the method of randomisation and allocation sequencing of participants within the trial (Higgins et al., 2011). Judgment on randomisation methods considers allocation sequence, concealment of randomisation prior to allocation and presence of significant differences between groups suggesting a problem with the randomisation process (Higgins et al., 2011).

Performance bias assesses the blinding of the research team and considers if the team were aware of intervention allocation. This domain also identifies deviations from intended protocol and considers the presence of deviations and their potential impact (Higgins et al., 2011). The detection bias domain assesses the suitability of outcome measure used, the consistency of use between the groups and the blinding of the assessors to participants allocation (Higgins et al., 2011). Attrition bias identifies if bias was introduced due to incomplete outcome data and reporting bias where selective reporting and selection of measures may introduce bias (Higgins et al., 2011). The overall risk of bias domain allows for the judgment of overall bias based on the five domains and provides an opportunity to add any sources of bias not captured within the other five domains (Higgins et al., 2011).

2.2.8 Methodologic Quality

Assessment of the methodologic quality of included trials is important to determine the quality of evidence or recommendations produced from a review (Guyatt et al., 2008). Therefore, each outcome included in a meta-analysis should be evaluated to ensure a high standard of evidence and prevent inaccurate synthesis of pooled results (Guyatt et al., 2011). All data included in the meta-analysis was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach via the GRADEpro GDT software (https//www.gradepro.org/) (Guyatt et al., 2008, Guyatt et al., 2011). The GRADE approach is an outcome-centred, structured system for grading and presenting the methodological quality of evidence (Guyatt et al., 2008, Guyatt et al., 2011). Quality is graded as high, moderate, low and very low and with different approaches available for RCTs and observational studies (Table 2.2). As only RCTs were included in this review, only this approach to methodological quality assessment will be discussed.

Table 2.2 GRADE Methodological Quality Definition (Guyatt et al., 2008)

GRADE quality	**Definition**
High quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate'
Very low quality	Any estimate of effect is very uncertain

To start, the GRADE approach considers all RCTs as high quality (Guyatt et al., 2008). This 'high quality' score can then be marked down or 'modified down' depending on the presence of five factors which reduce methodological quality (Guyatt et al., 2011, Guyatt et al., 2008). These five factors are 'study limitations, imprecision, inconsistency of results, indirectness of evidence and publication bias'. The first factor 'study limitations' assesses the risk of bias, this is discussed in Section 2.2.7 (Ryan and Hill, 2018). Inconsistency assesses the heterogeneity between studies (Ryan and Hill, 2018). Factors considered include statistical heterogeneity, using the Chi^2 or I^2 statistic; clinical heterogeneity, the difference in study participants; interventions and outcomes and methodological heterogeneity, the differences in study design (Ryan and Hill, 2018). Imprecision is used to assess how precise the effect size is by analysing the size of confidence intervals and the number of people included in the results (Ryan and Hill, 2018). Indirectness determines how well the results of the studies reflect the aims of the systematic review. PICO factors in the studies should be assessed to determine how well they reflect the PICO outlined for the systematic review (Ryan and Hill, 2018). Finally, publication bias covers if the studies included are all of the relevant studies due to selective publication (Ryan and Hill, 2018). While it is uncommon, it is possible that an RCT can be 'graded up' based on three factors which increase the quality of the methodological evidence and confidence in results (Ryan and Hill, 2018). These three factors are '*large magnitude of effect, dose response and confounders likely to minimise effect*'

Figure 2.1).

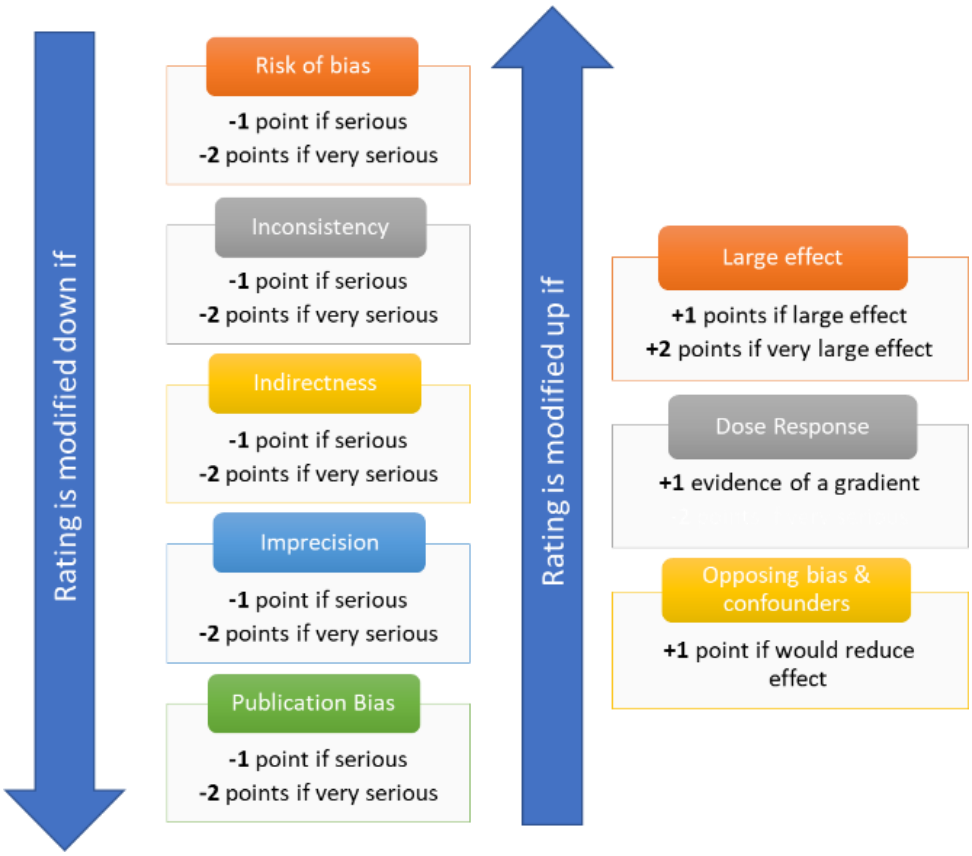

Figure 2.1 Adjusting Grading of GRADE

2.2.9 Meta-analysis

Meta-analysis is the statistical combining of multiple studies results to produce a single summary estimate of the effect (Kirkwood and Sterne, 2010). Meta-analysis can be completed using a fixed effect or random effect approach (Kirkwood and Sterne, 2010). The decision between a fixed or random effect approach should be based on understanding if all studies have a common effect size and goal of analysis (Borenstein et al., 2021). Random effect assumes that in each study included the treatment effect is not equal, therefore an estimated mean effect is calculated (Kirkwood and Sterne, 2010). Therefore, the null hypothesis tested is that the mean effect is equal to zero (Borenstein et al., 2021). The goal of random effect methods is to extrapolate information from the studies to the wider population (Borenstein et al., 2021). The fixed effect method assumes the underlying treatment effect to be the same across study populations and any variation is due to sampling error (Kirkwood and Sterne, 2010). Larger studies carry more importance with a fixed effect method and the null hypothesis is that the treatment effect is equal to zero (Kirkwood and

Sterne, 2010). The fixed effect method calculates the treatment effect within the studied population and is a more valid method when there is a low number of studies (Borenstein et al., 2021). As the aim of the study was to focus on a specific population and considering the small volume of studies included, a fixed effects method was used to examine post-intervention VO^2_{peak} data (expressed by mean difference). Data available for meta-analysis was assessed using RevMan 5 (version 5.3).

2.2.9.1 Heterogeneity

Heterogeneity is the variation of the true effect size across studies (Borenstein et al., 2021). A large heterogeneity means that the effect size differs significantly across studies (Borenstein et al., 2021). A low heterogeneity or heterogeneity of zero assumes that the true effect size is the same across studies and that any variation observed is due to study error (Borenstein et al., 2021). Heterogeneity can be assessed statistically to determine what proportion of the variation is due to real differences in the true mean by testing the null hypothesis that all studies share a common effect size (Borenstein et al., 2021). This can be tested using the chi square test and I^2 statistic (Borenstein et al., 2021). These tests were applied in this thesis.

2.3 Results

Results of the search strategy are presented in Figure 2.2 PRISMA flow chart. In March 2020 a total of 94 titles were identified by electronic database search, four were removed due to duplication leaving 90. No papers were identified in search of trial registry. An additional 428 papers were reviewed through a manual forward and backward citation chasing. After screening of all titles and abstracts, 48 full texts were identified to assess for eligibility. Eighteen papers were excluded due to non-RCT design, only abstract available (n=2), non-cancer population (n=1), HIIT not prescribed (n=18) and not in English (n=2). Seven studies remained for inclusion in the review.

The search was updated in April 2021 for publication following a protracted peer review process. The updated search of electronic databases identified 24 additional papers and forward and backwards citation searching identified 75. After duplicates removal and abstract screening, two full texts were read for eligibility. One was included and one was excluded (non-HIIT intervention). The search was updated in February 2023 in preparation for thesis submission. The updated search of electronic databases identified 30 additional papers. An additional 230 papers were reviewed through a manual forward and backward citation chasing. After screening of titles and abstracts, 13 full texts were identified to be assessed for eligibility and one was included. Five were excluded due to non-RCT design (n=5) and non-HIIT intervention (n=6). One trial included a combination of

oncological and non-oncological resection. The author was contacted by email to clarify the percentage of their cohort who had oncological resection; however, as no response was received this trial was excluded. Of the nine full texts identified for inclusion, three related to The Lung Cancer Rehabilitation Study (LCRS) (Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019). Therefore, seven unique exercise interventions involving 414 participants were identified and included in the systematic review.

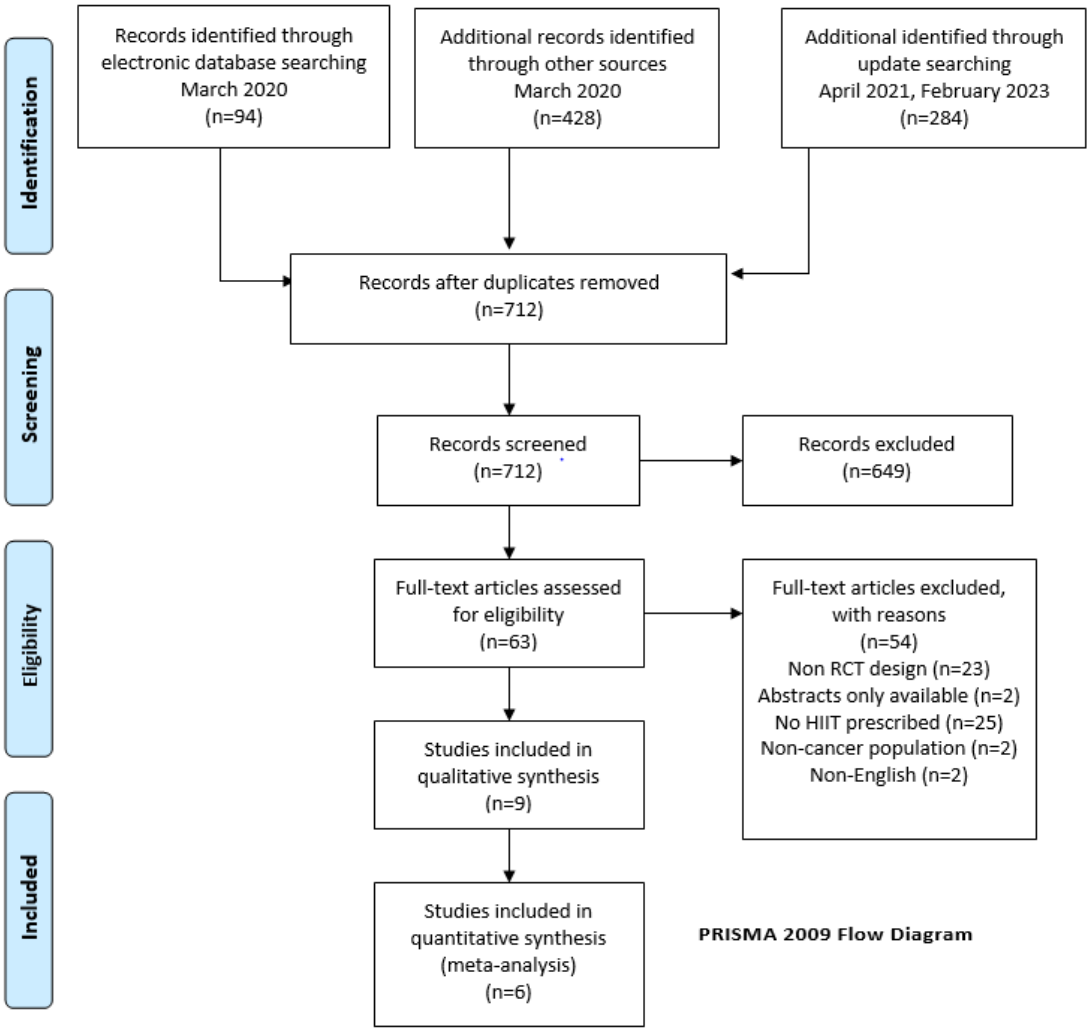

Figure 2.2 PRISMA flow diagram for Systematic Review and Meta-analysis

Types of oncologic resections included lung resection by thoracotomy and video-assisted thoracoscopic surgery (VATS) (Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019, Sebio García et al., 2017), liver resection (Dunne et al., 2016), radical cystectomy, robot assisted or open radical prostatectomy, laparoscopic nephrectomy (Banerjee et al., 2017, Blackwell et al.,

2020, Djurhuus et al., 2023), and laparoscopic colorectal surgery (Minnella et al., 2020). Six interventions reported sources of funding (Karenovics et al., 2017, Licker et al., 2017, Bhatia and Kayser, 2019, Sebio García et al., 2017, Dunne et al., 2016, Blackwell et al., 2020, Minnella et al., 2020, Djurhuus et al., 2023) and one did not (Banerjee et al., 2017). The mean age of participants in each study ranged from 61-72 years. The combined ratio of males to females was 255:127. Mean baseline body mass index of participants ranged from 24.4-29.7kg m^{-2}.

2.3.1 Risk of Bias Assessment

Results are presented in Table 2.3.

Table 2.3 Risk of Bias Assessment Results for Systematic Review and Meta-analysis

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Blackwell et al. (2020)	+	„	+	+	?	„
Dunne et al. (2016)	+	„	+	+	+	„
LCRS	+	„	+	„	?	„
Banerjee et al. (2017)	+	„	+	+	?	„
Garcia et al. (2017)	+	„	„	+	+	„
Minnella et al. (2021)	+	+	„	+	?	?
Djurhuus et al. (2023)	+	+	+	„	+	„

Table 2.4 Legend for Table 2.3

+	Low risk
?	Some concerns
„	High risk

2.3.1.1 Selection Bias

Randomisation techniques: all studies used a valid randomisation technique of either computer-generated lists or random permuted block randomisation held by an independent person. All studies were therefore deemed to have low risk of bias regarding randomisation.

2.3.1.2 Performance Bias

Deviations from intended interventions: all studies described exercise protocols in terms of planned intensity, number of sessions and session duration and recorded adherence as attendance. Additional details describing adherence to each intervention session i.e. actual intensity achieved by participants was described by two studies (Minnella et al., 2020, Djurhuus et al., 2023), with one of those also reporting on dose modifications and early session termination (Djurhuus et al., 2023). Due to the nature of the interventions, all participants and those delivering the intervention were aware of study allocation. The intervention arms in five of the seven interventions were considered high risk of deviation from intended interventions, largely due to lack of reporting rather than intervention design (Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019, Sebio García et al., 2017, Banerjee et al., 2017, Blackwell et al., 2020, Dunne et al., 2016). Two studies were deemed low risk in both the HIIT and control arms due to the reporting of both session attendance and adherence to prescribed intensities (Minnella et al., 2020, Djurhuus et al., 2023) and no reductions or early termination (Djurhuus et al., 2023). The usual care groups were deemed low risk for deviation from the intended intervention. Even if participants assigned to control arms had increased habitual physical activity levels, they were unlikely to have achieved the high intensity training loads prescribed to the intervention arms. Furthermore, in four of the studies patients in both groups were advised to maintain habitual levels of exercise and/ or encouraged to partake in 30 minutes of mobilisation four times weekly allowing for a potential increase or maintenance of aerobic capacity amongst control participants.

2.3.1.3 Detection Bias

Measurement of the outcome: all seven interventions used appropriate outcome measures and measurement timeframes. In five of the papers, assessors were blinded to participant allocation and therefore deemed low risk of bias (Blackwell et al., 2020, Dunne et al., 2016, Banerjee et al., 2017, Sebio García et al., 2017, Minnella et al., 2020). Blinding of assessor for completion of the CPET was not stated in the LCRS trial and one other; therefore, both were deemed high risk of bias due to the lack of reporting (Djurhuus et al., 2023).

2.3.1.4 Attrition Bias

Missing outcome data: one study, which analysed 55% of randomised participants post-intervention and 48% at the three-month follow-up, was considered high risk of bias due to missing outcome data (Sebio García et al., 2017). Furthermore, reported attrition was due to factors which may have had a direct impact on the true value for example addition of neoadjuvant therapy to treatment plan after randomisation (n=1), abandonment of intervention (n=2) and rescheduling of surgery (n=2). One study reported significant drop-out in the HIIT arm (80.95% completing follow-

up assessment in the HIIT arm versus 95% in the moderate intensity arm) (Minnella et al., 2020). The study employed an analysis model to adjust for missing data and was considered low risk (Minnella et al., 2020). Of the remaining five interventions, one analysed >95% (Djurhuus et al., 2023); the remaining all analysed <95% of randomised participants (Dunne et al., 2016, Banerjee et al., 2017, Blackwell et al., 2020, Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019); three analysed >92% of participants (Karenovics et al., 2017, Bhatia and Kayser, 2019, Licker et al., 2017, Dunne et al., 2016, Banerjee et al., 2017); one analysed >85% of participants (Blackwell et al., 2020) and attrition rates were comparable between all arms, and therefore they were considered low risk of bias.

2.3.2 Reporting Bias

Selection of the reported results: four of the seven interventions had trial protocols registered with clinicaltrials.gov (Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019, Sebio García et al., 2017, Dunne et al., 2016, Djurhuus et al., 2022). Of these, three were scored low risk while one (Dunne et al., 2016, Sebio García et al., 2017, Djurhuus et al., 2022), the LCRS, was classified as 'some concerns' due to the secondary outcomes planned in the protocol differing from the final reported study results. One study supplied 'deviations from intended protocol' within their supplementary data (Djurhuus et al., 2022). This criterion was difficult to assess in the other three studies as no published protocols could be found and were therefore considered of some concern (Banerjee et al., 2017, Blackwell et al., 2020, Minnella et al., 2020).

2.3.3 Trial Recruitment and Implementation Metrics

Feasibility was measured as the primary outcome in one trial and was assessed by 'recruitment and attrition; willingness to be randomised; acceptability of the outcome measures; adherence to the intervention; safety and suitability of the exercise dose; and adverse events' (Banerjee et al., 2017). Of 112 potentially eligible participants, 53.5% agreed to participate. All included participants who were willing to be randomised and no objections to the outcome measures were reported. Attrition rates were comparable between study arms and median number of sessions attended was eight (range 1-10). No adverse events were reported.

The other five interventions reported feasibility in terms of recruitment, intervention adherence and adverse events. The LCRS assessed 189 patients for eligibility, of whom 164 were randomised, Dunne and colleagues assessed 193 for eligibility, of whom 115 were eligible and 38 randomised, 76 were deemed eligible for inclusion in a recent study by Blackwell et al. (2020) and 40 were randomised. García and colleagues (assessed 319 for eligibility, excluding 279 and including 40

(Sebio García et al., 2017). One hundred and four patients were assessed for eligibility by Djurhuus et al. (2023) and 75 were excluded: (n=24) did not meet inclusion criteria, (n=29) did not wish to participate and (n=21) other. Therefore, (n=30) were randomised (Djurhuus et al., 2023). Seventy-six were assessed for eligibility by Minnella et al. (2021) and (n=42) were randomised; two participants in the HIIT arm refused to complete preoperative CPET, no reason was reported. Recruitment rates of all studies are presented in Table 2.5.

Table 2.5 Recruitment Rates for Studies Included in Review

Study ID	Absolute recruitment rate (percentage of eligible)
Blackwell et al. (2020)	40 (54.1%)
Dunne et al. (2016)	38 (33.1%)
LCRS	164 (90.6%)
Banerjee et al. (2017)	60 (53.6%)
Garcia et al. (2017)	40 (58.8%)
Minnella et al. (2021)	42 (57.5%)
Djurhuus et al. (2023)	30 (50.5%)

Data is expressed as frequency (percentage)

The LCRS reported an adherence rate of 87% (standard deviation (SD)18%) with a median of eight (inter quartile range (IQR) 7-10) sessions attended. Of the 19 participants randomised to the HIIT intervention by Dunne and colleagues, almost all (n=18) completed 100% of the exercise sessions. Blackwell and colleagues defined adherence as attending more than 10 exercise sessions and reported an 84% adherence rate with a median of 11 (10-12) sessions attended. García et al. reported a median of 16 (range 8-25) sessions attended. Minnella et al. (2021) defined adherence as weekly attendance and percentage of time spent at prescribed work rate. An attendance of 88.5% (standard deviation (19.9%) was reported in the HIIT arm and 92.7% (12.1%) in the moderate intensity arm, adherence to intensity in the HIIT arm was 89.3% (25%) in the HIIT arm and 97% (7%) in the comparator (p=0.282). Djurhuus et al. (2023) reported 100% adherence which was defined as session attendance and adherence to intensity and duration prescribed (Djurhuus et al., 2022). No serious adverse events were reported in any of the interventions. Blackwell and colleges reported two mild adverse events (discomfort with the cycle ergometer seat and mild leg pain post-intervention).

2.3.4 Methodological Quality

Methodological quality was deemed very low; therefore, the quality of evidence produced was deemed very low using the GRADEpro (Table 2.6)

2.3.4.1 Study Limitations

There was a serious risk of bias. All studies scored 'high risk' or 'some concerns' on the ROB2 risk of bias tool.

2.3.4.2 Imprecision

There was no significant statistical heterogeneity, chi-squared (p=0.71) and i2=0%. However, due to heterogeneity in the exercise prescription across interventions, this was scored as a serious risk.

2.3.4.3 Inconsistency of Results

This was scored a serious risk of inconsistency due to the large confidence intervals, which limits interpretation of the true effect (-0.40-2.72).

2.3.4.4 Indirectness of Evidence

Indirectness was scored as a low risk as the aims, population, intervention and outcome measures used for each study reflected the primary aim of the systematic review.

2.3.4.5 Publication Bias

A thorough search strategy was carried out in collaboration with the subject librarian, in addition to forward and backward citation chasing. There was no suggestion that other studies had not published results for previously published protocols and abstracts in this area. Therefore, this was scored low risk.

Table 2.6 GRADEpro Results for VO_{2peak}

Outcomes	Risk with HIIT prehabilitation	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
VO_{2peak} assessed by CPET follow-up range 2 weeks to 8 weeks	The mean VO2 Peak ranged from 18.7-26.73 ml/kg/min[a]	(0.4 lower to 2.23 higher)	340 (5 RCTs)	⨁◯◯◯ Very low	HIIT prehabilitation results in little to no difference in peak oxygen uptake.

Very low certainty we have very little confidence in the effect estimate the true effect is likely to be substantially different from the estimate of effect.

2.3.5 Interventions

Six trials compared HIIT to usual care (Minnella et al., 2020, Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019, Dunne et al., 2016, Blackwell et al., 2020, Banerjee et al., 2017, Djurhuus et al., 2022) and one compared HIIT to moderate intensity exercise (Minnella et al., 2020). The moderate intensity arm completed 40 minutes of exercise three times a week at 80-85% of power achieved at anaerobic threshold (AT) (Minnella et al., 2020). Usual clinical care was not explicitly described in any of the studies; however, three studies instructed the usual care group to maintain habitual levels of exercise (Djurhuus et al., 2022, Banerjee et al., 2017, Blackwell et al., 2020), two advised following clinical recommendations for exercise prior to surgery (Karenovics et al., 2017, Licker et al., 2017, Dunne et al., 2016) and one did not report on any recommendations given (Sebio Garcia et al., 2016).

HIIT interventions varied by intensity prescribed, duration and number of intervals and the number of sessions per week. Intensity was prescribed from baseline CPET using VO_{2peak} or work rate peak (WRp) in six interventions (Minnella et al., 2020, Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019, Dunne et al., 2016, Blackwell et al., 2020, Banerjee et al., 2017, Djurhuus et al., 2022). Four of these five prescribed >90% of WRp or VO_{2peak} (Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019, Dunne et al., 2016, Blackwell et al., 2020, Djurhuus et al., 2022), one prescribed 85-90% of WRp (Minnella et al., 2020) and one prescribed >80% of WRp during periods of high intensity (Sebio García et al., 2017). The seventh intervention prescribed intensity of 13-15 on the Borg Scale of Perceived Exertion reportedly equating to 70-85% of predicted heart rate max (HR_{max}) (Banerjee et al., 2017). Two interventions incorporated HIIT as the aerobic component of a larger multi-component prehabilitation programme (Sebio García et al., 2017, Minnella et al., 2020). In addition to HIIT, the LCRS trial included resistance training exercises prescribed at an individual level; however, details are not provided (Karenovics et al., 2017, Licker et al., 2017, Bhatia and Kayser, 2019). Minnella et al. prescribed individualised resistance training, nutritional interventions and relaxation techniques in both the HIIT and moderate intensity arms of the trial (Minnella et al., 2020). The number of sessions prescribed ranged from two to five per week and number of intervals ranged from six repetitions of five minutes to 30 minutes' worth of 15 second alternating repetitions. The duration of high intensity intervals ranged from 15 seconds to five minutes. The rest intervals were only described in six of the seven studies and consisted of a low-intensity active rest or a 15 second pause (Table 2.8). One study included a progression of 10% of WRp across four periods over the weeks of the intervention (Table 2.8) (Djurhuus et al., 2022).

Four interventions were carried out in a university exercise laboratory (Sebio Garcia et al., 2016, Dunne et al., 2016, Banerjee et al., 2021, Blackwell et al., 2020), one in an outpatient department (Karenovics et al., 2017, Licker et al., 2017, Bhatia and Kayser, 2019), one in a hospital (Minnella et al., 2020) and one did not state the location (Djurhuus et al., 2022). The duration of planned interventions ranged from 31 days to eight weeks. In the intervention arm between baseline assessment and surgery, one study reported median of 30 (27-29,31) days (Blackwell et al., 2020), another reported a median of 26 (21-33) days (Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019), the third study reported a mean of 54.5 (SD15.4) (Sebio García et al., 2017) and the final study reported a mean of 23 (SD 6.5) days (Banerjee et al., 2017). None of the studies reported a significant difference in duration from baseline to surgery between arms. Three did not report the mean time from baseline assessment to surgery (Dunne et al., 2016, Minnella et al., 2020, Djurhuus et al., 2022).

2.3.6 Impact of Preoperative HIIT on Preoperative Cardiopulmonary Fitness

2.3.6.1 VO_{2peak}

A CPET was used to evaluate physiological variables and establish VO_{2peak} in six out of the seven interventions (Table 2.7). VO_{2peak} was defined as the highest VO_2 recorded during the last 30 seconds of the CPET in three of the studies (Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019, Dunne et al., 2016, Banerjee et al., 2017), the last 20 seconds of the CPET in one (Blackwell et al., 2020) and the average values recorded in the last 20 seconds in one (Minnella et al., 2020) and not reported in one (Djurhuus et al., 2023). The mean VO_{2peak} across all studies was >15ml/kg/min therefore falling outside of the high risk category for postoperative complications (Beckles et al., 2003, Licker et al., 2011, Brunelli et al., 2013). However, the mean VO_{2peak} fell into the ‘very poor’ or ‘poor’ fitness category for normative values (Blackwell et al., 2020, Dunne et al., 2016, Karenovics et al., 2017, Licker et al., 2017, Bhatia and Kayser, 2019, Banerjee et al., 2017, Minnella et al., 2020, Djurhuus et al., 2022, Djurhuus et al., 2023, American College of Sports Medicine (ACSM), 2014). Djurhuus et al. (2023) reported the highest baseline fitness with the HIIT group falling within the ‘fair’ category (ACSM, 2010).

Table 2.7 Baseline VO_{2peak} Characteristics for Systematic Review and Meta-analysis

Study	**Baseline VO_{2peak} (ml/kg/min) Usual Care**	**Fitness Category** (ACSM, 2014)	**Baseline VO_{2peak} (ml/kg/min) HIIT**	**Fitness Category** (ACSM, 2014)
Blackwell et al. (2020)	26.4 (5.7)	Poor	24.8 (5.2)	Very poor
Dunne et al. (2016)	18.6 (3.9)	Very poor	17.6(2.3)	Very poor
LCRS	20.4 (5.7)	Very poor	19.9 (5.7)	Very poor
Banerjee et al. (2017)	20.38 ± 5.59	Very poor	19.22 ± 4.80	Very poor
Minnella et al. (2021)	21.70 (18.67 to 24.72)	Very poor	18.53 (15.50 to 21.56)	Very poor
Djurhuus et al. (2023)	31.4 (8.4)	Fair	34.0 (6.4)	Fair

Data is expressed as mean (standard deviation) and median (interquartile range)

Data from these six interventions were included in the meta-analysis of VO_{2peak} post-intervention. Data was analysed using a fixed effect method and presented as MD. Heterogeneity was considered not significant (I^2=0%). There was no significant difference in post-intervention VO_{2peak} in the HIIT group (n=176) compared to usual care or moderate intensity exercise (n=164) (MD 0.83, 95% CI-0.51 to 2.17) kg/ml/min, p=0.12) (Figure 2.3). García and colleagues measured submaximal aerobic capacity using Constant-load Cycle Endurance Test and therefore could not be included in the meta-analysis (Sebio García et al., 2017). This study used time until exhaustion as the primary outcome of aerobic capacity and reported a significant increase of 396.6 seconds (SD 197.9, p<0.001) from baseline in the prehabilitation group. No post-intervention Constant-load Cycle Endurance Test was carried out in the control group.

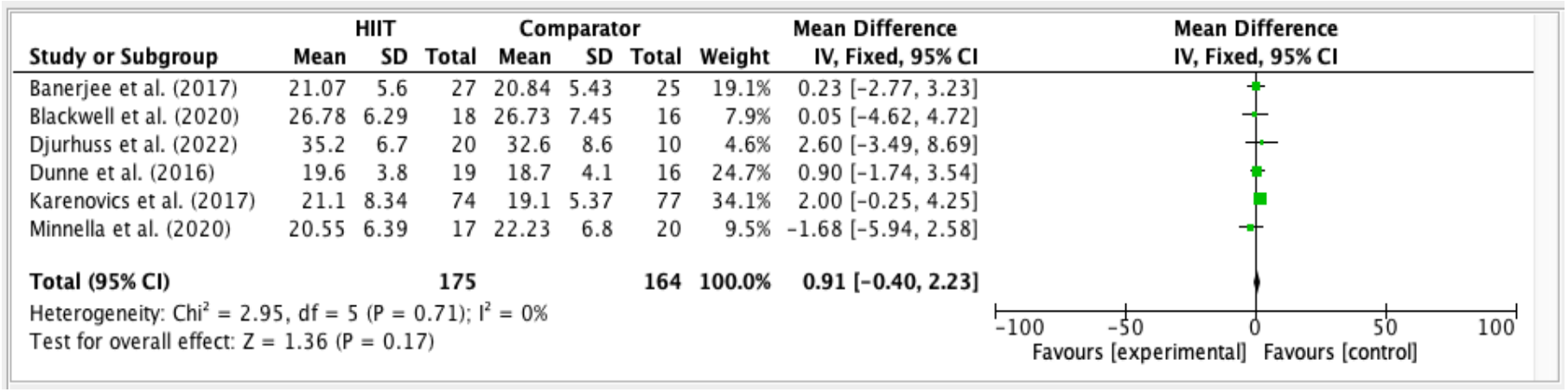

Figure 2.3 Meta-analysis Results

2.3.6.2 Power

Power output was expressed as WRp (wattage at CPET failure) in all seven interventions and all reported a significant improvement in power with HIIT. Dunne and colleagues reported a significant mean difference (MD) between group post-intervention (MD 13 (95% CI 4 to 22) watts, p=0.005). Banerjee and colleagues reported a significant adjusted MD between groups post-intervention (MD 19 (95% CI 10 to 27) watts=0.000). The LCRS reported a significantly greater increase (p=0.021) from baseline in the HIIT group (MC +8 (95% confidence interval (95%CI) 1 to 15) watts in comparison to usual care (Mean change (MC) -4 (95% CI -9 to +1) watts. Blackwell et al. (2020) described a significant increase in preoperative wattage at failure (MD 12.86 (95% CI 5.52 to 20.19) watts. Minnella et al. (2020) reported no significant between group differences for peak work rate following HIIT or moderate intensity interventions (MD 4.74, 95% CI 6.56 to 16.04, p= 0.402) watts but did report a significant increase from baseline in the HIIT arm (MD +12.79 95% CI 4.25 to 21.05) (Minnella et al., 2020). Djurhuus et al. (2020) reported an increase of 11.0 (2.2 to 19.8) watts in the HIIT arm and 3.2 (-9.7 to 16.0) watts in the usual care group in the post-intervention CPET (Djurhuus et al., 2022).

Table 2.8 Intervention Characteristics Table for Systematic Review and Meta-analysis

Study ID	Country	Participants (number and surgery)	Randomisation	Duration	HIIT frequency	HIIT Session duration	High intensity interval	Low intensity interval	Progression	Adherence
Djurhuus et al. (2023)	Denmark	n=30 radicle prostatectomy	HIIT or UC provided and advised to maintain their everyday lifestyle, including physical activity	2-8 weeks	Not reported	20-25min	4–6 cycles of high intensity intervals for 1 min at 100–120% WRp	30% WRp for 3 minutes	Week 1 4x100% WRp, Week 2 4x110% WRp, Week 3+4) 5x120% WRp, Weeks 5–8 6x120% WRp.	100%
Minnella et al. (2020)	Canada	n=42 laparoscopic colorectal surgery	HIIT or moderate intensity training	4 weeks	3x/week	30min	85-90% of peak power output	80-85% power at anaerobic threshold	Not reported	Attendance 88.5±19.9% Adherence to intensity 89.3±25%

Blackwell et al. (2020)	U.K.	n=40, radical robotic-assisted laparoscopic prostatectomy, open prostatectomy, radical cystectomy, laparoscopic nephrectomy	HIIT or UC provided at centre and instructions to maintain habitual physical activity and dietary regimes for the duration of the study.	31 days	3-4x/week	Not reported	5x1min @ 100-115% WRp	Not reported	10% after 6 sessions	84%
Banerjee et al. (2017)	U.K.	n=60 radical cystectomy	HIIT or UC provided at centre. UC group advised to carry on lifestyles in usual way.	3-6 weeks	2x/week	58pprox.. 45min	@ 6 × 5 min perceived exertion of 13-15 on borg scale	2.5 min with light resistance	Not reported	8†sessions(1–10)

Dunne et al. (2016)	U.K.	n=38 liver resection	HIIT or UC provided at centre. No restrictions were placed on either arm of intervention and they were encouraged to follow clinical advice on exercise before surgery.	4 weeks	10 HIIT in total + 2 recovery sessions	30min	>90% per cent VO_{2peak}	<60% of VO_{2peak}	Not reported	18 completed all sessions

LCRS	Switzerland	n=164 lung resection	randomised to HIIT or UC provided at centre. Both groups were given advice on walking 30min 4x/week	3-4 weeks	2-3x/week	2x 10min interspaced by 4min rest period.	15second @ 80%–100% of WRp	15second pauses.	Adjusted during each session to target near-maximal heart rates toward the end of each series of sprints on the basis of the individual's exercise response.	87% ± 18% 8‡ sessions(I7–10)

García et al. (2017)	Spain	n=40 video-assisted thoracoscopic surgery	HIIT or UC provided at centre. No further information reported.	4 weeks	3-5x/week	30min	1min @ 80% of WRp	4 min @50% of WRp f	Not reported	16‡ sessions(8-25)

Abbreviations ±= standard deviation, @= at, x/week = times per week,†=median, ‡= mean, ( )=range, (IQR)=interquartile range, 61pprox..= approximately, min=minutes, n= number of participants, WRp= work rate peak, , VO_{2peak} = peak oxygen consumption.

2.3.6.3 Anaerobic Threshold

Five interventions measured and reported change in VO_{2AT}. Three of these five evaluated VO_{2AT} using the v-slope and analysed ventilatory equivalents (Licker et al., 2009, Licker et al., 2017, Karenovics et al., 2017, Dunne et al., 2016, Banerjee et al., 2017) and two used the modified v-slope and ventilatory equivalents method (Blackwell et al., 2020, Minnella et al., 2020). Dunne and colleagues reported a significant MD between groups post-intervention (MD 1.5, 95% CI (0.2 to 2.9) kg/ml/min, p=0.023). Blackwell and colleagues reported a significant increase in VO_{2AT} from baseline in the HIIT group (MD 2.26, (95% CI 1.25 to 3.26) p<0.0) ml/kg/min and no significant change in the usual care group (data not reported) (p>0.05). No numerical data was reported for the usual care group in this trial. In contrast, two interventions reported no significant effect of HIIT on preoperative VO_{2AT} the LCRS and Banerjee et al. (2017). Minnella et al. (2020) reported a mean change from baseline of 1.97 (95% CI 0.75 to 3.19, p =0.001) kg/ml/min in the HIIT group versus 1.71 (95% CI 0.56 to 2.85, p=0.002) kg/ml/min in the moderate intensity group with no significant difference between groups (MD 0.26 95%CI 1.41 to 1.94 p=0.753) kg/ml/min.

2.3.7 Impact of Preoperative HIIT on Postoperative Outcomes

2.3.7.1 Postoperative Complications

Only the LCRS measured postoperative complications as its primary outcome. The LCRS study assessed the rate of 30-day mortality and number of in-hospital and any complications, which scored greater than two on the Thoracic Morbidity and Mortality System. Postoperative morbidity did not differ between groups (p=0.018). However, the accrual target of 400 was not reached due to a higher than anticipated postoperative complication level, resulting in recruitment cessation. The LCRS did however report a difference in the incidence in PPCs (23% in the control arm versus 44% in the usual care group p=0.018). Garcia et al. (2017) examined postoperative outcomes as a secondary measure and reported no differences in PPCs (HIIT group 50%, usual care group 66%, p=0.361). Results are presented in Table 2.9.

Table 2.9 Postoperative Complication Results for Systematic Review and Meta-analysis

Study Author	**Postoperative Complications**			
	Outcome Measure	**HIIT**	**Usual care/MIE**	**P-value**
Minnella et al. (2020)	Clavien Dindo Classification System (grade (n))	I (3 ±23) II (2±15)	I (6±43) II (2±14)	Descriptive analysis
Blackwell et al. (2020)	Clavien Dindo Classification System (grade (n))	I (2) II (1) IIIb (1) IVb (1)	I (1) II (2) IIIb (0) IVb (0)	Descriptive analysis
Banerjee et al. (2017)	Clavien Dindo Classification System (grade (n))	I (4) ≥ III (1)	I (10) ≥ III(4)	Descriptive analysis
Dunne et al. (2016)	Clavien Dindo Classification System (grade (n))	I (0) II (8) III (4) IV (0)	I (4) II (7) III (0) IV (1)	Descriptive analysis
García et al. (2016)	Melbourne Group Scale (n (%))	5 (50%)	8 (66%)	p = 0.361
LCRS	30-day mortality or any complications with TMM grades of >2 (n (%))	27 (36.5%)	39 (50.6%)	p=0.08

Djurhuus et al. (2023)	Not reported	Not reported	Not reported	Not reported

2.3.7.2 Length of Stay

Hospital length of stay was described but underpowered for statistical analysis in five interventions (Table 2.10). Length of stay was reported by six of the seven interventions, Minnella et al. (2020) reported a median length of stay of 3.5 (3-6) days in the HIIT arm and 4 (3-5) in the control (Minnella et al., 2020). Banerjee et al. (2017) reported a median stay of 7 (4–78) in the HIIT arm and 7 (5–107) in the usual care arm (Banerjee et al., 2017). Dunne et al. (2016) reported a median of 5 (4-6) days in the HIIT arm and 5 (4.5–7) in the control group. Garcia et al. (2016) reported a median of 3 days in the usual care group and 2 days in the HIIT group (Dunne et al., 2016, Sebio Garcia et al., 2016). Banerjee et al. (2017) reported a high dependency unit length of stay of 1 day in both the exercise and control group (range 1–10 and 1– 7 days, respectively, p=0.938). Length of stay in the high dependency unit and intensive care was reported in three studies (Table 2.10). Banerjee et al. and Dunne et al. (2016) reported no significant difference in length of stay in between usual care and HIIT. The LCRS reported a significant difference with 17 (7) in the HIIT arm and 25(10).

Table 2.10 Length of Stay Results for Systematic Review and Meta-analysis

Study	**Length of hospital stay (days)**			**Length of critical care (days)**		
	HIIT	**Usual Care/MIE**	**p-value**	**HIIT**	**Usual Care/MIE**	**p-value**
Minnella et al. (2020)	3.5 (3-6)	4 (3-5)	0.626	n/a	n/a	n/a
Banerjee et al. (2017)	7 (4–78)	7 (5–107)	0.865	1 (1-10)†	1(1-7)†	0.938
Dunne et al. (2016)	5 (4-6)	5 (4.5–7)	n/a	1 (1–2)	1.5 (1–2)	n/a
García et al. (2016)	2	3	0.539	n/a	n/a	n/a
LCRS	10 (8–12)	9 (7–13)	0.223	17(7)	25(10)	<0.001

Data is expressed as median (interquartile range), † = range

2.4 Discussion

There is a logical rationale to suggest that preoperative HIIT may improve cardiopulmonary fitness and impact outcomes after cancer surgery. The results of this systematic review and meta-analysis demonstrate that there is a paucity of research with little evidence currently existing to support this hypothesis. Encouragingly, the evidence in this area is still emerging, with all included trials published in the past six years. Additionally, the existing data supports the feasibility and safety of this approach with low reported numbers of adverse events.

After results pooling, there was no significant MD between HIIT versus usual care or moderate intensity exercise on VO_{2peak} (MD 0.83, 95% CI-0.51 to 2.17) kg/ml/min, p=0.12). However, this should be interpreted in context of the very low GRADE score and the risk of bias. Furthermore, despite a clear definition for HIIT, there was significant variability in the intensities prescribed with two of the studies prescribing lower intensity programmes (Sebio García et al., 2017, Banerjee et al., 2017). It is noteworthy that the two shortest programmes also had the highest intensities and elicited a significant change (Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019, Blackwell et al., 2020). While the effectiveness on VO_{2peak} remains unclear, the positive impact on PPO (all studies included reporting a significant increase from baseline) suggests a positive effect, warranting additional research. These short bouts of intervention in HIIT may provide a more acceptable approach to prehabilitation compared with longer low-intensity sessions in patients where time constraints are a significant barrier (Saggu et al., 2022, Knowlton et al., 2020, Leak Bryant et al., 2017, Lee et al., 2022, Ferreira et al., 2018). As acceptability is a key factor in facilitating the uptake of evidence-based research into practice, evaluation of acceptability of preoperative HIIT should be completed concurrently with assessment of effectiveness. Therefore, there is a sound theoretical basis for additional studies to clarify appropriate protocols within short timeframes and the acceptability of the intervention.

Accurate reporting of mild adverse events that may occur and participant adherence is important in the context of the clinical applicability of HIIT. Reporting deficits feature in six of the seven interventions and are reflected in the risk of bias assessment. Deviation from the intended intervention was considered high risk of bias due to issues with how adherence was reported in these trials. Reporting of adherence to exercise is crucial to ensure accurate representation of the true effect, as exercise is a dose dependent intervention (Hawley et al., 2014). Although overall intervention adherence was defined and reported in each study, a recent paper suggests that when considering adherence to an exercise programme, planned and achieved components should be reported individually (Nilsen et al., 2018). This method advocates documenting intensities achieved

in each session, dose modifications in sessions, early termination of sessions and any interruption to treatment or termination of treatment. This gives a clear indication if the planned exercise doses were achieved by each participant and clearly captures adherence and all adverse events. In all interventions, no serious adverse events were reported. However, only one of the seven studies addressed mild adverse events and captured perceived acceptability of the programme (Blackwell et al., 2020). This absence of reporting is similar to findings in 2020 meta-analysis by Wallen and colleagues (Wallen et al., 2020), which reported HIIT to be a feasible and safe method of improving VO_{2peak} across the cancer care pathway (Wallen et al., 2020). However, only two of the 12 papers in this review explicitly reported mild adverse events (Wallen et al., 2020). Furthermore, measurement of outcomes in the LCRS and the study by Djurhuus et al. (2023), was considered at high risk of bias due a lack of information on assessor blinding (Djurhuus et al., 2023). Considering there is a well-established awareness of the impact of blinding on CPET performance, it is likely that this was due to a reporting oversight as opposed to a protocol error (Hecksteden et al., 2018). Further trials should pay careful attention to reporting factors to ensure the clinical applicability of the intervention and enable integration into clinical pathways.

The impact of preoperative HIIT on postoperative outcome was difficult to determine in the trials reviewed, largely due to small sample sizes; however, no significant benefit was observed. Trials such as the PREPARE-ABC trial, which is powered to examine the impact of exercise prehabilitation on postoperative outcome, cite accrual targets of up to 1146 in contrast to the sample sizes of the studies reviewed (n=38-164) (PREPARE-ABC Trial Collaborative, 2021). The LCRS was the only intervention which evaluated postoperative outcome as its primary outcome and was powered for 400 participants. However, due to higher than anticipated incidence of complications, at a pre-planned interim analysis, recruitment was stopped after 164 participants were enrolled. While insufficiently powered, it is worth noting that there was a reduction of 45% in occurrence of PPCs in the HIIT group. This is similar to the findings of García et al. (2017) who reported 50% of participants had at least one PPCs in the exercise group and 65% in the usual care (Sebio García et al., 2017) group. While these findings are preliminary, they do highlight the need for further analysis given PPCs occur in between 15-40% of patients after thoracic surgery for oesophageal or lung cancer (Feeney et al., 2010, Shirinzadeh and Talebi, 2011, Yang et al., 2019).

2.4.1 Limitations

This review albeit comprehensive has some limitations. The sample size analysed in the meta-analyses and the number of studies included in both the meta-analysis and narrative synthesis were small. Despite a thorough search strategy, only a small number of papers were identified. To

supplement this, a comprehensive manual search which included prospective and retrospective review was carried out. Only six of the nine studies were appropriate for inclusion in the meta-analysis of $VO_{2peak.}$ due to the variation in outcome measures, in addition the meta-analysis needs to be interpreted with caution due to the very low GRADE results and considered in the context of its exploratory purpose at this early stage of research in this area. Additionally, our requests for further data on VO_{2AT} and PPO were not responded to by the authors, therefore meta-analysis was not possible. It is also important to consider that due to the heterogeneity in protocols prescribed, it may not be possible to generalise these results (Viana et al., 2018). Furthermore, in two studies, despite a statistically homogenous baseline VO_{2peak}, the usual care group and the moderate intensity exercise group had a slightly higher baseline VO_{2peak} (Blackwell et al., 2020, Minnella et al., 2020). This between-group difference was not of statistical significance. However, when data was collected for meta-analysis, despite both HIIT groups reporting a significant increase in VO_{2peak} while the comparator did not, the within-group differences post-intervention were not well reflected in the meta-analysis (Blackwell et al., 2020, Minnella et al., 2020). Furthermore, while the intervention carried out by García et al. (2017) satisfied the inclusion criteria, no post-intervention CCPT on the control group was undertaken, limiting its interpretation of the outcomes (Sebio García et al., 2017). The limited studies with variable quality highlights the need to develop a core outcome set for exercise prehabilitation, which would provide a standard battery of outcomes and time-points to make published results more comparable. Finally, considering the varied types of cancer included in this review, it is important to consider that physiological adaptations to HIIT may vary by diagnosis. There is a paucity of evidence in this area; however, considering the physiological implications of different cancer diagnoses and treatments (e.g. direct tumour burden and reduced oxygen diffusion reported in lung cancer or systemic effects of chemotherapy on cardiac function and respiratory muscle strength in breast cancer), response to exercise may be affected (Travers et al., 2008, Yeh Edward et al., 2004).

2.4.2 Conclusion

In conclusion, HIIT is an intense intervention and its feasibility and acceptability must be considered prior to integration into clinical pathways for cancer patients. This systematic review and meta-analysis revealed no significant benefit compared with usual care. Clearly further work is required to fully analyse the role of HIIT programmes and to determine the intensity required to see significant changes over the short preoperative periods.

Chapter 3 Methods

3.1 Introduction

This chapter describes the background and application of the study designs, quantitative methods, qualitative methods and data analysis applied in this thesis. Study designs are procedures or plans for data collection and analysis (Thiese, 2014, Creswell, 2014). Appropriate selection of study design is vital to ensure robust results (Thiese, 2014, Creswell, 2014). There are three main data collection methods: quantitative, qualitative and mixed-methods approach, which utilises both (Thiese, 2014, Creswell, 2014). A mixed-methods approach is applied throughout this thesis to explore the role of exercise prehabilitation in three main studies. Study I used a convergent parallel randomised controlled trial (RCT) design, Study II used qualitative data collection and analysis, and Study III used sequential mixed-methods approach employing a cross-sectional survey and semi-structured interviews (Figure 3.1). The different outcome measures available to collect data are discussed below.

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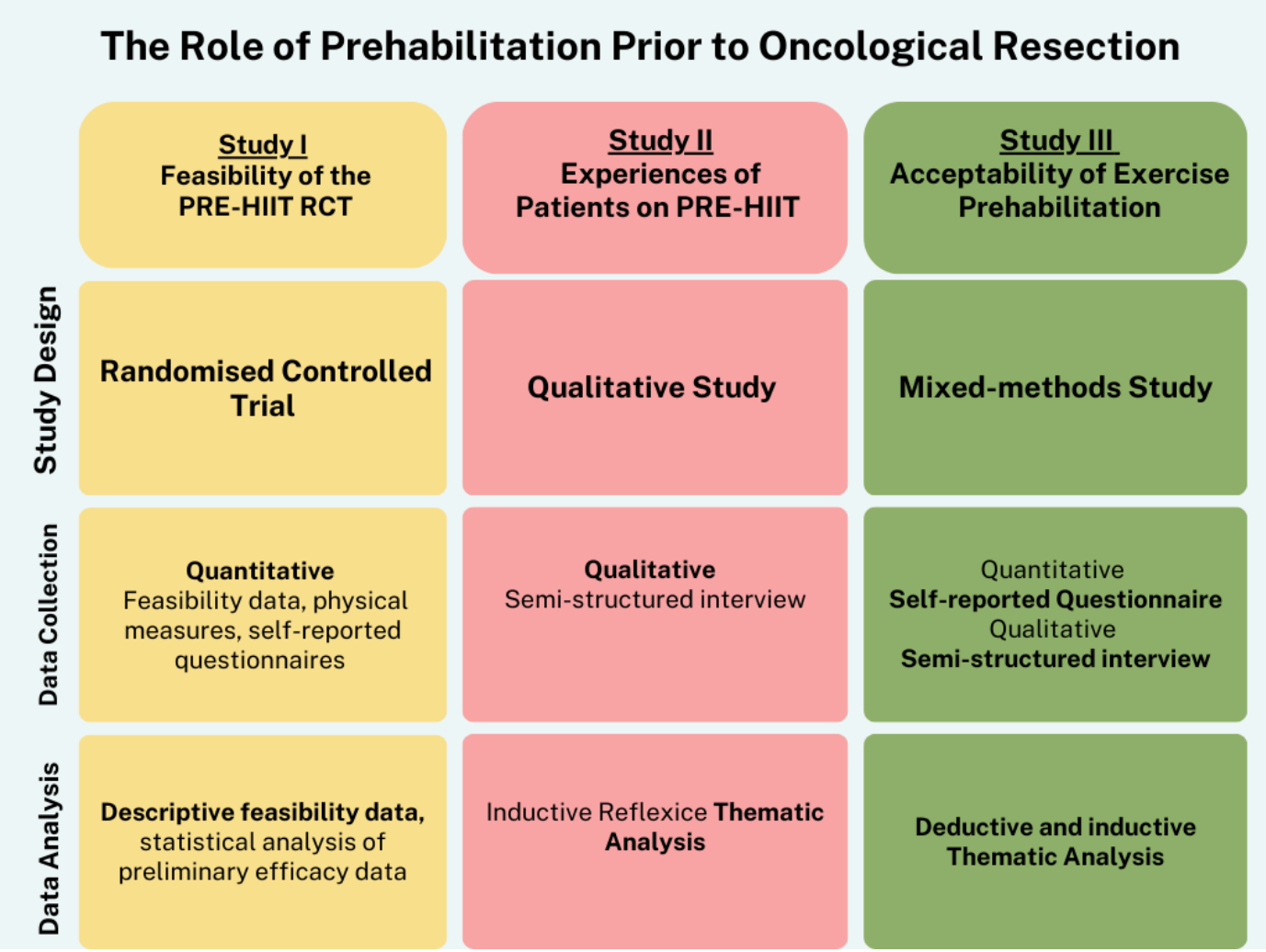

Figure 3.1 Methods Applied in this Thesis

3.1.1 Quantitative Methods

Quantitative research can be defined as 'the processes of collecting, analysing, interpreting' results (Creswell, 2014). The aim of quantitative data collection is to test a hypothesis by analysing the relationship between dependent and independent variables (Creswell, 2014). Data is collected, measured on an appropriate tool and then statistically analysed (Creswell, 2014). Methods of data collection can vary; however, there are two primary methods, questionnaire data collection and experimental data collection (Creswell, 2014).

3.1.2 Qualitative Methods

Qualitative research can be defined as the process of exploring, understanding and analysing peoples' experiences in order to identify meaningful patterns (Creswell, 2014, Vaismoradi et al., 2013). Qualitative research does not use mathematical processes to quantify results, however it is systematic in its approach which captures the unique experiences of individuals (Creswell, 2014, Vaismoradi et al., 2013). It involves the collection of data through various sources such as interviews, free text questionnaires or focus groups.

3.1.3 Mixed-methods

Mixed-methods research integrates both quantitative and qualitative methods within one study (Table 3.1) (Creswell, 2014). This allows analytical evaluation of responses and trends in addition to an in-depth analysis of participants perspectives and opinions (Creswell, 2014, Denscombe, 2008). A mixed-methods approach can be used to enhance understanding through triangulation of different information, combine information from complementary data sources to support results, and compensate for the limitations of a single methods approach (Denscombe, 2008). Data can be analysed using sequential, concurrent or transformative methods (Creswell, 2014). Sequential approach, e.g. an interview following a questionnaire, enables the researcher to use the second method to expand on findings from the first (Denscombe, 2008). Concurrent methods collect both methods of data collection at the same time, data is then combined to provide a comprehensive analysis of the results (Creswell, 2014).

Table 3.1 Quantitative, Mixed, and Qualitative Methods

Component	**Quantitative methods ----------> Mixed-methods <---------- Qualitative methods**		
Methods	Pre-determined	Both pre-determined and emerging	Emerging
Questions	Instrument based	Both open and closed-ended questions	Open-ended
Types of data assessed	Performance data, attitude data, observational data and census data	Multiple forms of data drawing possibilities	Interview data, observation data, document data, audio-visual data
Data Analysis	Statistical	Statistical and text	Text and image
Data Interpretation	Statistical	Across databases	Themes, patterns, interpretation

3.2 Randomised Controlled Trials

Experimental studies assess if a treatment or intervention has an impact on outcome (Creswell, 2014, Eldridge et al., 2016). A RCT is considered the gold standard of clinical trials and the most rigorous way to test a hypothesis (Stel et al., Akobeng, 2005, Nichol et al., 2010, Lee and Kang, 2015). RCTs are a valid tool for assessing cause and effect, therefore allowing the evaluation of the effectiveness of an intervention (Stel et al.). The primary benefit of an RCT is that they eliminate the potential for selection bias and limit the influence of confounding factors on the results (Stel et al., Akobeng, 2005, Nichol et al., 2010). This is achieved through randomisation, concealed allocation and blinding (Stel et al., Akobeng, 2005, Nichol et al., 2010). The Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus (PRE-HIIT) RCT is one of the key studies in this thesis and is presented in Chapter 4.

3.2.1 Sampling

Sampling is an important feature of an RCT to ensure validity and generalisability of results (Kendall, 2003). There are two main types of sampling, probability sampling and nonprobability sampling (Lee and Kang, 2015, Elfil and Negida, 2017). Probability sampling involves random sampling, which can be completed using a simple, stratified, systemic or cluster approach. Simple sampling involves the random selection of participants from the whole population. Stratified sampling involves the random selection of participants from sub-groups within the population based on characteristics. Systemic sampling involves the selection of participants based on a predefined fixed interval and cluster sampling patients are randomly selected based on geographical area. Each of these random sampling approaches can be used where the whole population being assessed is available and means all subjects have an equal chance of being selected therefore ensuring the whole population is represented without introducing bias.

Nonprobability sampling involves three main approaches: convenience, judgemental and snowball. Convenience sampling involves selection of participants based on availability and accessibility. Judgmental sampling involves selection of the participants by the research team based on specific characteristics. Snowball sampling involves accessing other potential participants through current participants. Non-probability that does not ensure equal chances for each subject in the target population and may introduce selection bias. However, nonprobability approaches are economical and convenient, therefore they are often used. The sample size in RCTs is an important factor to ensure there is a sufficient number to give statistical power to results (Lee and Kang, 2015). A common approach used to determine sample size is based on a power calculation to ensure results are not overrepresented or unable to achieve statistical significance based on sample size.

3.2.2 Randomisation

Randomisation is a key feature of an RCT and involves randomly assigning participants to different groups (Lee and Kang, 2015, Moher et al., 2012). This eliminates the potential for selection bias and balances out known and unknown confounding factors adding robustness to results. There are multiple approaches to randomisation: simple, block, and stratified randomisation. Simple randomisation randomly allocates participants to each group. While this approach is effective at random allocation, it may result in an imbalance in numbers across groups impacting interpretation of results. Block randomisation is an alternative approach, which involves random sequencing. This involves randomising patient in blocks of approximately the same size, which contain random sequences of group allocation with 1:1 ratio for each group per block. This approach ensures equal numbers are allocated per group; however, sequences may be guessed if block sizes are too small. Stratified randomisation involves the allocation of participants to a sub-group, based on a baseline characteristic. Participants are then randomised within the subgroup to a treatment group. This ensures that baseline characteristics which may act as a confounder are evenly distributed between the two groups.

3.2.3 Allocation Concealment

Allocation concealment aims to prevent selection bias (Lee and Kang, 2015). This involves the concealment of the allocation sequence from researchers who assign participants to groups. This eliminates the possibility that the research team could consciously or unconsciously influence group allocation by selecting participants to enrol based on a known allocation, therefore introducing selection bias.

3.2.4 Blinding

Blinding of participants and the research team to intervention allocation is a pillar of RCTs and is important to reduce or eliminate performance or measurement bias (Kendall, 2003, Lee and Kang, 2015). Blinding ensures that confounding factors are not introduced after randomisation and that measurement of the outcomes reported are not influenced by knowledge of allocation. Trials may be single-blind or double blind. Single blind involves the participant being blinded to study allocation, this eliminates the impact of the placebo effect. Double blind involves the blinding of both investigator and participant. This approach eliminates the potential for performance or measurement bias. However, in complex interventions such as exercise or dietary interventions, blinding of participants and intervention providers is not possible. Therefore, to ensure that blinding is maintained, assessments can be completed by an assessor, who is unaware of study allocation.

However, RCTs are challenging and expensive to run. Furthermore, while the design of a RCT creates a high internal validity, the strict inclusion/exclusion criteria coupled with the potential differences between patients who choose to take part and those who do not, can limit the applicability of the results into clinical practice (Nichol et al., 2010). Considering these limitations, it is important to examine the feasibility of a RCT prior to implementing one. The primary aim of a feasibility study is to evaluate if it is possible to run a trial which will effectively evaluate an intervention and identify any unforeseen complications (Eldridge et al., 2016). Feasibility studies are complex and encompass various types of studies, among which pilot studies can be classified (Stel et al., Eldridge et al., 2016). Results from feasibility studies assist with decisions on running of future trials and refinements of methodology (Eldridge et al., 2016). Primary feasibility outcomes should focus on areas of uncertainty applicable to the intervention and the logistics of running the intervention (National Institute for Health Research, 2022). Outcome measures include recruitment potential; outcome measures used and data collection instrument; suitability and acceptability of the intervention; willingness to be randomised; and participants perspectives (Eldridge et al., 2016, Orsmond and Cohn, 2015).

3.2.5 Recruitment Potential

Determining the recruitment capability for future studies depends on multiple factors: the appropriateness of the inclusion/exclusion criteria, the recruitment process and the intervention (Orsmond and Cohn, 2015). This can be determined through analysis of screened potential participants to determine the percentage of eligibility and enrolment. Evaluation of these numbers and the accurate reporting of reasons for non-enrolment can indicate areas which require support or adaptation for future studies (Orsmond and Cohn, 2015).

3.2.5.1 Suitability and Acceptability

The suitability of the intervention can be assessed by analysing adherence to the intervention, attrition rates and the number of mild, moderate and serious adverse events (Orsmond and Cohn, 2015). Adherence to the intervention can be measured using standard adherence variables such as number of sessions completed and compliance with the exercise protocol. In addition adherence can be measured using an adapted outcome measure (Nilsen et al., 2018). This novel method recommends measuring adherence based on planned dose of exercise and completed dose of exercise. Reasons for not achieving the planned doses such as dose modification, early session termination, treatment interruption and permanent treatment discontinuation give insight into the factors that influence adherence (Nilsen et al., 2018). Acceptability can be assessed using questionnaires or semi-structured interviews (Sekhon et al., 2017, Sekhon et al., 2022). Recording

of all attrition, mild, moderate and severe adverse events is important. Adverse events can be described using the Common Terminology Criteria for Adverse Events (CTCAE). Grades and their associated definition are presented in Table 3.2.

Table 3.2 Common Terminology Criteria for Adverse Events Definition

Grade	Definition
Grade one	Mild symptoms: clinical observations only, intervention not indicated
Grade two	Moderate symptoms: non-invasive intervention indicated, symptoms limiting age-appropriate activities of daily living (ADL)
Grade three	Severe symptoms: medically significant symptoms but not immediately life-threatening requiring hospitalisation, limiting self-care ADL
Grade four	Life-threatening: urgent intervention indicated
Grade five	Death related to adverse event

The selected outcome measures and procedures should be assessed to ensure the suitability of the instrument for participants and its appropriateness to answer the research question (Orsmond and Cohn, 2015). Qualitative data has a valuable role in feasibility studies. Interviews or open-ended questions offer an opportunity to discuss the experiences of the participant in depth and provides a unique insight, which can guide future work. A semi-structured interview following the intervention provides a rich understanding of their experience.

3.2.6 Quantitative Outcome Measures

3.2.6.1 Questionnaires

Questionnaires are a quantitative tool which measure 'trends, attitudes or opinions' of a representative population (Ponto, 2015). Questionnaires provide the opportunity for insight into individuals' perspectives from a representative population (Alderman and Salem, 2010). They are a reliable and effective method of gathering opinions and perspectives from a large population (Alderman and Salem, 2010). Quantitative questionnaires use numerically rated, closed-ended questions to identify associations or trends (Alderman and Salem, 2010, Ponto, 2015, Bishop and Herron, 2015). A Likert Scale is a commonly used format, which allows for participants' level of agreement with a statement to be quantified (Bishop and Herron, 2015). Questionnaires can be self-administered or researcher administered. Self-administered questionnaires are more reliable than proxy-administered; however, they are still open to error. Recall bias from the passing of time

since an event, or lack of understanding or knowledge about the topic can impact the reliability of responses (Alderman and Salem, 2010). Data collection can be at one (cross-sectional), two or multiple timepoints (longitudinal), depending on the aims of the project.

Questionnaires can be developed and piloted for a specific research question, or a pre-designed questionnaire can be adapted to answer a research question. The selection of the data collection instruments has a direct impact on the potential for measurement error (Alderman and Salem, 2010, Ponto, 2015). Previously validated questionnaires for the population under review, enhance the accuracy of results and enables comparison between studies (Alderman and Salem, 2010). However, validated questionnaires may not effectively answer a specific research question (Alderman and Salem, 2010). Piloting questionnaires is a vital step in the methodology, to evaluate the participants understanding and reduce the potential for measurement error (Ponto, 2015).

3.2.6.2 Physical Fitness Outcome Measures

Physical fitness can be defined as 'the ability to perform daily tasks with vigour' (Wilder et al., 2006, Medicine, 2010). Cardiopulmonary fitness is the ability of the cardiovascular system to supply and utilise oxygen in exercising muscles and the ability of the pulmonary system to remove carbon dioxide. Muscular fitness is a combination of both muscle strength (the ability of the muscle to exert force) and muscle endurance (the ability of muscles to perform repeated contractions). Body composition is the relative measure of the components of the body i.e. fat and fat free mass, and flexibility is the range of movement of joints and muscles (Wilder et al., 2006, Wells and Fewtrell, 2006, Medicine, 2010, Fosbøl and Zerahn, 2015). Accurate measurement of these attributes is recognised as a valuable tool in clinical practice and research (Fosbøl and Zerahn, 2015).

Cardiopulmonary exercise testing (CPET) is the gold standard for assessing cardiopulmonary fitness and is an important clinical tool to evaluate functional capacity (Moran et al., 2016a). CPET is a non-invasive, incremental exercise test, which assesses the cardiopulmonary system during exercise (Cooper, 1999, Chambers and Wisely, 2019). Indirect calorimetry uses breath-by-breath gas analysis of minute ventilation and respiratory gas exchange to calculate oxygen consumption (VO_2) and carbon dioxide (VCO_2) production (Chambers and Wisely, 2019, Albouaini et al., 2007). Multiple physiological variables are derived from breath-by-breath analysis and collected during a CPET (Table 3.3) (Ross, 2003).

Maximal oxygen consumption (VO_{2max}) is the maximum amount of oxygen the body can transport and utilise. VO_{2max} is relative to body weight and is characterised by an absence of an increase in oxygen consumption, despite an increase in work rate (Ross, 2003, Albouaini et al., 2007, Toma et

al., 2010). VO_{2max} is expressed as ml/kg/min and is a commonly reported outcome variable in healthy participants (Ross, 2003, Albouaini et al., 2007, Toma et al., 2010). However, VO_{2max} by definition, requires a plateau in oxygen consumption which is difficult to achieve in a clinical cohort, due to the symptoms associated with maintaining maximal exertion (Albouaini et al., 2007, Noonan and Dean, 2000). Accordingly, peak volume of oxygen consumption (VO_{2peak}), defined as the highest VO_2 reached during the test, is often reported in clinical cohorts as a more accessible measure (Albouaini et al., 2007, Noonan and Dean, 2000). VO_{2peak} can be reported in multiple ways including the average of the VO_2 recorded in last 20 or 30 seconds of the test or the highest VO_2 recorded in the last 30 seconds (Licker et al., 2017, Sheill, 2021, Sheill et al., 2020a). Anaerobic threshold (AT) is the point when aerobic energy production is supplemented by anaerobic mechanisms, i.e. VCO_2 production increases out of proportion to VO_2 (Wasserman, 1986, Smith et al., 2009). AT encompasses the lactate threshold and ventilatory threshold, where lactate accumulation in the blood results in an increase in carbon dioxide levels, therefore stimulating an increase in ventilation (Smith et al., 2009). In healthy untrained individuals this is often recorded at approximately 47-64% of VO_{2max} (Smith et al., 2009). AT can be measured invasively by testing of lactate levels in blood samples to identify when lactate begins to accumulate, and non-invasively by plotting physiological variables derived from breath-by-breath analysis in a CPET (volume of oxygen consumption at AT (VO_{2AT})) (Solberg et al., 2005). The V-slope and modified V-slope methods use computerised linear regression or visual inspection to analyse VO_2 plotted against VCO_2 to identify the point where the data splits (Smith et al., 2009, Schneider et al., 1993). VO_{2AT} and VO_{2peak} are clinically significant outcomes which can be used to predict health outcomes (Wasserman, 1986, Licker et al., 2011, Beckles et al., 2003, Brunelli et al., 2013, Toma et al., 2010).

Table 3.3 CPET Derived Physiological Variables Definitions

Variable	**Definition**
Oxygen uptake (VO_2)	Volume of oxygen uptake (l/min)
Carbon dioxide production (VCO_2)	Volume of oxygen production (l/min)
Expired minute volume	the volume of gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from the lungs per minute
Ventilatory threshold	Oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms
Maximal oxygen uptake (VO_{2max})	Maximum amount of oxygen the body can transport and utilise (ml/kg/min)
Peak oxygen uptake (VO_{2peak})	Peak oxygen consumption attained (ml/kg/min)
VE/VO_2	Ratio of ventilation relative to oxygen consumption
VE/VCO_2	Ratio of ventilation relative to carbon dioxide production
Respiratory exchange ratio	Ratio of carbon dioxide production to oxygen uptake
Heart rate	Beats per minute
Peak power output	Power at test failure
Time to completion	Exercise duration
SPO^2	Oxygen saturation
Blood pressure	The force of the blood against vessel walls

CPETs can be completed on a treadmill or cycle ergometer using an incremental, ramp or standard protocol, depending on the primary outcome of the test and the suitability for the participant (Ross, 2003). Selection of equipment used should be considered carefully as a treadmill test is more influenced by factors such as body weight, use of handrails, pacing, speed and grade of the treadmill (Ross, 2003). Use of a treadmill requires the participant to have higher level of balance and coordination compared to a cycle ergometer (Jones et al., 2008). Furthermore, a cycle ergometer reduces the impact of external artifact from movement, when monitoring blood pressure and ECG throughout the CPET (Ross, 2003). Overall, a cycle ergometer provides a more accurate method for measuring VO_2, and quantification of the external work rate used (Ross, 2003, Jones et al., 2008). Incremental and ramp tests allow for a progressive increase in resistance, therefore challenging the cardiopulmonary system (ACSM, 2010, Noonan and Dean, 2000). Progressive incremental tests, such as on a cycle ergometer protocol involves a three minute warm-up at 0 watts followed by an

increase in work rate every minute (Ross, 2003). Multi-stage tests increase workload every three minutes, however, for some participants the duration of each stage and test may not be achievable (Ross, 2003). A ramp protocol, involves a continuous and gradual increase in workload every 2-3 seconds (Ross, 2003). There is no significant difference reported between ramp versus incremental protocols (Ross, 2003). Ramp and incremental tests workload increase should be calculated based on the participant to ensure the test is appropriate (Ross, 2003).

While maximal CPET is the gold standard for cardiopulmonary exercise testing the process is expensive, time consuming, requires trained personnel and may not be appropriate for all cohorts (ACSM, 2010, Jones et al., 2008). Therefore, alternative options such as sub-maximal exercise may be more applicable (ACSM, 2010, Jones et al., 2008). Sub-maximal exercise testing uses the heart rate response to an exercise test to estimate VO_{2max} (ACSM, 2010). The Astrand and Ryhming Cycle Ergometer Test, Submaximal YMCA Cycle Ergometer Test and Modified Bruce Treadmill Test are different protocols for estimating VO_2 (Ross, 2003). However, despite data reporting correlation between estimated and measured VO_2 in submaximal tests, the prediction method allows for the potential of over or under estimation of functional capacity (Ross, 2003, Bennett et al., 2016, Väisänen et al., 2019).

CPET is considered a relatively safe and effective method of exercise testing (Ross, 2003). A joint statement by the American Thoracic Society and the American College of Chest Physicians (ATS/ACCP) report that the risk of adverse events is two to five per 100,000 tests (Ross, 2003). Within oncology, CPETs are considered a relatively safe and effective test (Jones et al., 2008). However, prior to completion of a CPET, participants should be screened for any absolute or relative contraindications to maximal exercise testing (ACSM, 2010, Ross, 2003). Screening can be completed using a past medical history and screening tools such as the Physical Activity Readiness Questionnaire or American Heart Association/American College of Sports Medicine Health Fitness Facility Preparticipation Screening Questionnaire (ACSM, 2010). Considering the physiological impact of treatments for cancer such as neuropathies, anaemia, immunosuppression, cardiotoxicities, in addition to the age range common in this cohort, additional consideration prior to CPET should be given to oncology patients (Jones et al., 2008, Donlon et al., 2022, Sawaya et al., 2011). If feasible, oncology patients should receive medical approval for participation in CPET prior to completion of the test (Jones et al., 2008).

3.2.6.2.1 Vital Signs Measurement

Blood pressure measurement is a clinically significant outcome which should be measured before, during and following an exercise test (ACSM, 2010, Pickering et al., 2005). Blood pressure can be

measured using a digital blood pressure monitor or sphygmomanometer and Korotkoff sounds technique (Pickering et al., 2005). Blood oxygen saturation can be measured using pulse oximetry (SPO_2) (ACSM, 2010). Heart rate can be measured by counting the pulse beats per minute using pulse oximetry, wrist-based heart rate monitor or with an electrocardiogram (ECG).

3.2.6.2.2 Perceived Rate of Exertion

Perceived level of exertion can be assessed using the modified Borg Rating of Perceived Exertion Scale, a tool for estimating exercise training intensity (Borg, 1982, Arney et al., 2019).

3.2.6.2.3 Muscular Strength Assessment

Muscle strength testing can be used to assess muscle function, evaluate the effect of a muscle strengthening programme or to provide or compare to normative values (Jaric, 2002). Muscle strength can be tested isometrically, isokenitically or dynamically (ACSM, 2010, Grgic et al., 2020). Dynamic muscle strength testing assesses concentric and eccentric muscle contractions throughout a full range of movement across multiple joints against a constant resistance (Jaric, 2002, Medicine, 2010, Grgic et al., 2020). The one repetition-maximum test (1RM) is considered the gold standard for muscle strength testing (Grgic et al., 2020, Seo et al., 2012). This can be defined as the greatest resistance that can be moved through a full range of movement (Grgic et al., 2020, Medicine, 2010). The 1RM test is a safe, effective and reliable method of testing and re-testing muscle strength across healthy and clinical populations (Grgic et al., 2020). It can be completed as a field test, using minimal equipment or in a clinical setting using equipment such as leg press (Grgic et al., 2020). Despite its strengths, 1RM is a time consuming process which should be completed by trained personal (Grgic et al., 2020).

3.2.6.2.4 Body Composition Assessment

Body composition is the measure of the components of the body i.e. the relative measure of fat to fat-free mass (ACSM, 2010). It is a well-established indicator of health outcomes and is an independent predictor for cardiovascular and diabetes related risk and mortality and an important health factor in preoperative cancer patients (Apovian, 2016, Medicine, 2010). Body composition can be measured using bioelectrical impedance analysis (BIA) and is a practical, reliable, inexpensive, safe and observer-independent method of measuring body composition (Fosbøl and Zerahn, 2015). It involves the passing of electric currents through the body, calculating body composition based on the rate of conductivity.

3.2.6.2.5 Acceptability

For the purpose of this thesis acceptability is defined as 'a multi-facetted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate based on anticipated or experiential cognitive and emotional responses to the intervention' due to its comprehensive construction, as described in Section 1.9.4.1 (Sekhon et al., 2017, Sekhon et al., 2022). As this definition of acceptability is newly developed, assessment instruments are evolving.

Quantitative measures include questionnaires and analysis of empirical data (e.g., recruitment rates). For example, Waterland et al. (2020) measured acceptability of exercise prehabilitation using a pilot questionnaire with questions on ' knowledge of prehabilitation', their 'willingness to participate' in exercise prehabilitation and free text data collection which focused on participants', 'specific barriers including cost, perception of use of technology' and facilitators of prehabilitation (Waterland et al., 2020). Qualitatively, focus groups and interviews are a common method of gathering data on acceptability (Ayala and Elder, 2011). These methods offer an opportunity for the concepts to be discussed in depth (Ayala and Elder, 2011). However, these methods are not underpinned by frameworks or theories. This disparity reduces the ability to compare and interpret data across multiple studies. Overall, methods for measuring acceptability lack consistency and validation across the literature. Given these challenges, there has been an increased use of the Theoretical Frame Work of Acceptability (TFA) (discussed in Section 1.9.4.1) as a method underpinning the assessment of acceptability, (Nickels et al., 2020, Bartlett et al., 2021, Timm et al., 2022, Sekhon and van der Straten, 2021). The TFA allows for both quantitative and qualitative data collection which is underpinned by a theoretical framework (Sekhon et al., 2017, Sekhon et al., 2022). Therefore, as the TFA represents the most robust approach for measurement of acceptability, measures of acceptability are underpinned by it throughout this thesis.

The TFA generic questionnaire was designed to create an adaptable tool for researchers to undertake robust and efficient evaluation of healthcare interventions (Sekhon et al., 2022). The design of the questionnaire enables the identification of areas of high and low acceptability and evaluation of overall acceptability. Each question is based on one of the seven constructs of acceptability and one on overall acceptability: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy together with a single-item overall acceptability construct. This tool has been adapted to measure the acceptability of a 'telephone-facilitated health coaching intervention' for the management of type 2 diabetes (Timm et al., 2022). This study applied a 19-item Likert Scale questionnaire, with a range of one to four

questions per construct of acceptability (Timm et al., 2022). A 2019 study applied the TFA as a framework for deductive qualitative analysis of pharmacist acceptability of promoting mental health and care in the community (Murphy and Gardner, 2019). The same method was used to determine the acceptability of a post-natal walking group in a 2020 study (Pavlova et al., 2020). A 2021 study assessing the acceptability of two biomedical HIV prevention approaches used a deductive and inductive approach to qualitative analysis. Data was firstly analysed deductively onto the constructs of the TFA, followed by an iterative analysis of the data within the constructs (Sekhon and van der Straten, 2021). The TFA it is a user-friendly tool which provides a systematic approach to assessing acceptability both qualitatively and quantitatively.

3.2.6.3 Postoperative Complications and Length of Stay

Postoperative complications can be defined as any 'deviation from normal postoperative course' (Dindo, 2014, Manekk et al., 2022). There are multiple approaches to recording postoperative complications, the Clavien–Dindo Classification of Surgical Complications (CDC), Postoperative Morbidity Survey and The Accordion Severity Grading System (Manekk et al., 2022). The most widely used approach is the CDC classification. The CDC is a standardised method which grades complications on a scale of I-IV, based on the level of treatment required (Dindo et al., 2004). The grade and associated definition are presented in Table 3.4. The CDC is a valid and applicable tool for grading postoperative complications.

Table 3.4 The Clavien–Dindo Classification of Surgical Complications Definition (Dindo et al., 2004)

Grade	The Clavien–Dindo Classification of Surgical Complications definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anaesthesia
IIIb	Intervention under general anaesthesia
IV	Life-threatening complication requiring ICU management
IVa	Single organ dysfunction
IVb	Multiorgan dysfunction
V	Death of patient

Length of stay can be described as the number of days spent in hospital. Length of stay in critical care can be defined as the number of days in an intensive care unit or high dependency unit.

3.2.7 Statistical Analysis

Statistical analysis is a method of analysing quantitative data. Statistical analysis can be completed using multiple tools such as IMB SPSS. Choosing a statistical test should be completed during the planning process of a project. There are many different types of statistical tests and the choice of which to utilise depends on the primary aim of the study. Variables, components of the data being measured, can be categorised as categorical or continuous variables (Pallant, 2016). Categorical variables include nominal data (categories of data with no inherent order), ordinal data (categories of data with an inherent order) and continuous data (numerical data with infinite possibilities within a certain range) (Pallant, 2016)

3.2.7.1 Preliminary Analysis

Preliminary analysis is the initial phase of data analysis, involving descriptive statistics. Descriptive statistics allow characterisation of a sample, identification of any violations of assumptions for statistical tests and can be used to answer a research question e.g., in feasibility studies (Pallant, 2016). Descriptive statistics can be presented as frequency and percentage, mean and standard deviation, median and interquartile range or graphs such as box plots and bar charts (Tickle-Degnen, 2013). Distribution is a key factor in the decision to use parametric or non-parametric tests. Normality of distribution can be assessed by analysing histograms, skewness and kurtosis or quantile-quantile (Q-Q) plots. Skewness indicates the symmetry of the distribution with a positive or negative result indicating data is clustered at either end of the graph and a score of 0 indicating data is perfectly distributed. Kurtosis describes the shape of a probability distribution of a random variable, where 0 represents perfect distribution. Visual inspection of bar charts and Q-Q plots are another method of assessing distribution.

3.2.7.2 Statistical Techniques

There are multiple statistical techniques which can be used to analyse data. Two main techniques are parametric and non-parametric tests. All statistical tests have specific assumptions often regarding data type and distribution (Pallant, 2016). Parametric tests are considered the most powerful option; however, these tests make assumptions about the distribution of data which must be met to ensure the validity of results (Pallant, 2016). If these assumptions cannot be met, data can be transformed or a non-parametric test can be used (Pallant, 2016). Transforming data

involves modifying data into new scores which fall into a normal distribution, however this method is controversial, therefore a non-parametric alternative may be a more appropriate option; however, it may be less sensitive (Pallant, 2016).

3.2.7.3 Correlation

Correlation is the measure of the strength and association between two variables (Pallant, 2016). Results are expressed as the correlation coefficient (Rs). Rs can range from -1 to +1, a positive result represents a positive relationship between variables and negative results represents a negative relationship i.e. as one goes up the other goes down (Pallant, 2016). The Rs value indicates the 'strength' of the relationship, a Rs value equal to (+ or -) 0.10 to 0.29 represent a small association, Rs= (+ or -) 0.30 to 0.49 represent a medium association and Rs= (+ or -) 0.50 to 1.00 represents a large association (Pallant, 2016). Pearson's Correlation is one approach. There are four assumptions which should be met in order for Pearson's Correlation to be valid (Table 3.5) (Pallant, 2016).

Table 3.5 Assumptions of Pearson's Correlation

Assumption	**Description**
Assumption 1	Variables must be continuous
Assumption 2	There is a linear relationship between the two variables
Assumption 3	There are no significant outliers
Assumption 4	Data should be normally distributed

If these assumptions cannot be met, a non-parametric test such as a Spearman's Rho Correlation may be more appropriate. T-tests can be used to assess the difference between two means in two groups of data (Pallant, 2016). There are different types of T-tests and the type selected depends on the primary outcome of the study. A paired T-test assess the difference between means in the same groups at different time points and an independent T-test assess the difference between two means in two different groups. There are six assumptions which must be met to use the parametric independent T-test (Table 3.6).

Table 3.6 Assumptions of the Independent T-test

Assumption	Description
Assumption one	The dependent variable is continuous
Assumption two	The independent variable is categorical
Assumption three	Each observation is independent
Assumption four	There are no significant outliers, assessed using visual inspection of data using box plots or histograms
Assumption five	The dependent variable is evenly distributed
Assumption six	There is homogeneity of variances. Variance is the spread of the data points around the mean, this assumption presumes that the variance of the two samples is equal

If these assumptions cannot be met, a Mann-U Whitney Test may be more appropriate. A paired T test assesses the difference between means in one group at two different time points. There are four assumptions which must be met.

Assumption	Description
Assumption one	The dependent variable is continuous
Assumption two	The independent variable is categorical
Assumption three	There should be no significant outliers in the differences between groups
Assumption four	The dependent variable is evenly distributed

If these assumptions are not met, a non-parametric Wilcoxon test can be used (Pallant, 2016).

Significance level for p-values has been set at p=0.05 for this thesis.

3.3 Qualitative Research

Qualitative data can be analysed inductively or deductively following a selected methodology. Deductive analysis is used when there is existing knowledge or theory, and the aim of the study is to test or re-test the theory in a new context (Elo and Kyngäs, 2008, Pope et al., 2000). It involves coding of data into pre-determined categories or a framework (Elo and Kyngäs, 2008). Inductive analysis is a process of 'identifying analytical categories' from the data (Elo and Kyngäs, 2008, Pope et al., 2000). Inductive content analysis involves diverse coding of text, followed by grouping of text into similar categories and finally into a concept which is strongly linked to the data (Elo and Kyngäs,

2008, Braun and Clarke, 2006). The themes or concepts developed in inductive analysis may not directly relate to the questions asked and cannot be driven by the researchers interest (Braun and Clarke, 2006). There are numerous pattern-based approaches for analysis such as grounded theory, content analysis and thematic analysis; however, among all these methods there is significant overlap (Braun and Clarke, 2006, Vaismoradi et al., 2013). Method selection depends on the primary aims of the study and the volume of pre-existing knowledge and frameworks (Elo and Kyngäs, 2008).

3.3.1 Coding

Coding is a key step in the organisation of data to support understanding of diverse text data (Basit, 2003). Coding involves the grouping and categorising of raw text into meaningful segments as 'codes' (Braun and Clarke, 2006). Codes can be defined as 'tags', which 'allocate meaning' to descriptive text data collected (Basit, 2003). Codes refine raw text and enable analysis of descriptive data (Basit, 2003). Coding can be completed manually or using a qualitative analysis software such as Nvivo.

3.3.2 Sampling and Data Collection in Qualitative Research

Qualitative research is exploratory in nature; therefore, the sample size is decided by data analysis. There are various approaches to determining if data collection is complete or not. Data saturation is one approach where data collection ceases once no new information is identified (Braun and Clarke, 2021c). However, the validity and precision of use of this approach is now being questioned. Therefore, when stopping data collection, researchers should consider the focus and goal of the project, the power and diversity of the data collected and the richness of the data generated to determine sample size.

3.3.3 Approaches to Qualitative Data Analysis

3.3.3.1 Grounded Theory and Content Analysis

Grounded theory (GT) is an inductive method, which generates concepts and theories from within the data (Gibson and Hartman, 2013). GT was first presented in 1967 as classic GT (de la Espriella and Gómez Restrepo, 2020, Gibson and Hartman, 2013). The primary aim of GT is to generate theory through three stages of data coding: open coding, axial coding and selective coding (Gibson and Hartman, 2013, de la Espriella and Gómez Restrepo, 2020). GT involves theoretical sampling; therefore, data is analysed as it is collected (de la Espriella and Gómez Restrepo, 2020, Gibson and Hartman, 2013). This often requires the researcher returning to the field to collect more data (de la Espriella and Gómez Restrepo, 2020, Gibson and Hartman, 2013). Since its conception, multiple amendments to the processes have emerged leading to significant debate over the fundamentals

such as the role of the researcher. In classic GT, the research must remain free of prejudice as they 'bear witness' to the emerging data. In newer adaptions of GT researchers' understanding of the topic plays a role in the analysis (de la Espriella and Gómez Restrepo, 2020). GT is a structured and versatile tool, which can yield strong theories (Khan, 2014). The structured and systematic approach allows the researcher to understand complex concepts (de la Espriella and Gómez Restrepo, 2020). However, the primary aim of GT is to generate theory, which does not encapsulate the exploration of experiences.

Content analysis is a method of qualitative analysis, which can be analysed either deductively or inductively (Elo and Kyngäs, 2008). The primary aim of content analysis is to quantify large volumes of words into smaller categories (Elo and Kyngäs, 2008, Vaismoradi et al., 2013). It is an effective way of reporting and identifying common issues (Vaismoradi et al., 2013). Content analysis is completed in three main phases: preparation, organisation and reporting (Elo and Kyngäs, 2008). During the preparation phase, content to be analysed is selected. This includes selection of text or interviews to be coded and decisions on whether latent content is analysed to give additional insights (Elo and Kyngäs, 2008). During the organisation phase, content is coded using open coding and grouping of codes, based on frequency, into categories. In the reporting phase results are reported into a conceptual model (Elo and Kyngäs, 2008). Content analysis also proposes the use of double coding, i.e. when more than one researcher codes the text to assess reliability of the analysis (Vaismoradi et al., 2013). Content analysis is a compressive method of analysing and quantifying qualitative data. However, categories presented are solely based on the frequency of codes and do not account for the relationship to the research question or the researcher's subjectivity and knowledge (Vaismoradi et al., 2013). In comparison in reflective thematic analysis, the researcher's subjectivity is considered a resource (Braun and Clarke, 2021a, Braun and Clarke, 2006).

3.3.4 Thematic Analysis (TA)

Thematic Analysis (TA) can be considered a 'spectrum of methods' which provide a reliable, flexible and useful method to analyse data at an explicit level (Braun and Clarke, 2006, Braun and Clarke, 2021a). Within TA, data can be analysed using an inductive or deductive approach (Braun and Clarke, 2006). Reflexive TA is a systematic analysis of the data to develop comprehensive themes from diverse codes (Braun and Clarke, 2006, Braun and Clarke, 2021a). Coding within reflexive TA is open and is an evolving process, which results in the development of themes reflective of the data (Braun and Clarke, 2021a). Within reflexive TA, the researcher's subjectivity is considered a tool which will identify areas which have the ability to capture what is important for the research

question (Braun and Clarke, 2006). Reflexive TA provides a practical and adaptable guide to qualitative analyse (Braun and Clarke, 2021b). Reflexive TA involves six steps described in Table 3.7.

Table 3.7 The Steps of Reflexive Analysis

Phase	**Description**
Phase one: familiarisation with the dataset	This is a 'process of immersion' and involves reading and rereading of the interview transcriptions or listening to the audio to become thoroughly familiar with the content of the interviews. Comments of interest can be identified for use in later stages.
Phase two: coding	The systematic and diverse generation of initial codes from all data available. Patterns within the text or statements of potential interest are collated into applicable codes.
Phase three: generating initial themes	The codes collected are grouped together based on their relationship into hierarchical levels of themes and sub themes. This offers clearer insight into meaning embedded in the text and understanding of different views on the topic.
Phase Four: reviewing themes	Following collection of the initial themes, a thorough review will refine and consolidate themes. Themes which have insufficient codes to support them can be broken down and codes re-allocated as appropriate.
Phase five: defining and naming themes	Following finalisation of the themes, themes will be named and defined. These names and definition should capture the 'essence' of the theme.
Phase six: producing the report	An in-depth analysis of the developed themes, which represent the story of the data collected. Following analysis, a clear and concise report should be developed, which accurately represents the participants.

3.4 Applications in this Thesis

This thesis used a mixed-methods approach to explore the role of exercise prehabilitation in three main studies. Study I used a convergent parallel study design to assess the feasibility of a two arm RCT examining the effect of preoperative HIIT on cardiopulmonary fitness in patients undergoing complex surgery for cancer of the lung or oesophagus. Study II used qualitative data collection and analysis to explore participants experiences in Study I. Study III used a sequential mixed-methods approach, employing a cross-sectional survey and semi-structured interviews to evaluate the acceptability of exercise prehabilitation in major oncologic resection. The outcome measures used to collect data are discussed below.

3.4.1.1 Questionnaires

Both cross-sectional and longitudinal self-reported questionnaires have been utilised in both Study I and III. Adapted versions of the generic Acceptability Questionnaire are used in Study I and Study III. The Telehealth Usability Questionnaire is used in Study I. Both questionnaires are Likert Scale tools. Educational videos or infographics were utilised throughout to enhance participants understanding of the topic.

The Telehealth Useability Questionnaire (TUQ) is a comprehensive, reliable and valid tool which assesses the 'usability factors' associated with telehealth (Parmanto et al., 2016). The questionnaire has 21 questions, which are divided into five sections of three to four questions, each covering a different usability factor (Parmanto et al., 2016). The usefulness section determines participants' perception of how useful the telehealth tool is at providing a healthcare service (Parmanto et al., 2016). The 'ease of use section' focuses on the learnability and straightforwardness of the interface (Parmanto et al., 2016). The reliability section examines the participants' perception of the reliability of the interface. Interface quality measures the participants' attitudes towards the telehealth interface (Parmanto et al., 2016). Interaction quality measures the participants' attitudes towards the interaction with the healthcare provider through the interface. The final section measures the satisfaction and possibility of future use (Parmanto et al., 2016).

Acceptability was measured using the TFA Acceptability Questionnaire in Study I and Study III. These cross-sectional surveys were adapted from the generic TFA questionnaire to create exercise prehabilitation and PRE-HIIT specific versions (Sekhon et al., 2022). Both were devised based on the constructs of acceptability (affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, self-efficacy and the single-item overall acceptability)

and specific characteristics to ensure the intervention was appropriately represented. The adapted questionnaires were reviewed by two senior researchers in oncology and by Mandeep Sekhon, developer of the TFA, for refinement. Consensus wording for each question was agreed upon for each question. Both surveys comprised of an eight-item Likert Scale questionnaire, with one questions per construct of acceptability and a single-item question reflecting overall acceptability. Each question was scored out of a possible five, where one represents low acceptability and five represents high acceptability, with a total composite acceptability score (the sum all constructs) of 40.

Figure 3.2 Example of Question Adaptation from generic Theoretical Framework of Acceptability Questionnaire

Adaptions to the questionnaires were made by substituting generic terms such as *intervention* or *behaviour* with study specific terms, such as PRE-HIIT or exercise prehabilitation (Figure 3.2). The questionnaire examining the acceptability of exercise prehabilitation, used in Study III, was piloted on 100 participants. Following interim analysis, the questionnaire was amended to include an additional question to enhance participants' understanding (discussed in Section 6.3.4.2).

3.4.1.2 Physical Function

Physical function was a secondary outcome in the PRE-HIIT trial presented as Study I. Physical function was assessed using the Short Physical Performance Battery (SPPB). The SPPB is a reliable measure of physical functioning which evaluates three lower extremities tests: gait speed, chair stand and balance test (Guralnik et al., 1994). The SPPB is scored out of a total of 12, with each test scored out of four (Owusu et al., 2017, Guralnik et al., 1994). Higher scores indicate higher physical function (Owusu et al., 2017, Guralnik et al., 1994).

3.4.1.3 Cardiopulmonary Fitness Assessment

Cardiopulmonary fitness was assessed using CPET as a secondary outcome in Study I. CPET was utilised as it is the gold standard for cardiopulmonary exercise testing (Ross, 2003). Furthermore, due to the high intensities prescribed during the HIIT intervention, the safe completion of a baseline CPET was a requirement for enrolment and outcomes from the CPET (peak power output) were used to prescribe intensity of exercise in the intervention arm. A progressive incremental cycle ergometer protocol was used (4). Increments of work rate progression ranged from 10-25 watts per minute. This was calculated for each participant using predicted unloaded VO_2, predicted VO_2 at peak exercise and height and age using the following equations (Figure 3.3) (Agnew, 2010). The increments were rounded to the nearest five to determine the appropriate protocol.

O2 unloaded in ml/min = 150 + (6 x weight(kg))

Peak VO2 in ml/min = (height(cm) –age(years)) x 20 (sedentary men) or x 14 (sedentary women)

Work rate increment (watts/minute) = (peak VO2 (ml/min) – VO2 unloaded ml/min)/ 100

Figure 3.3 Calculation of Work Rate

Breath-by-breath analysis was completed using the COSMED Quark and COSMED K4b^2. The COSMED K4b^2 is a portable device and the COSMED Quark a stationary indirect calorimeter, which allows for reliable and accurate breath-by-breath analysis. Prior to completion of the CPET, the COSMED devices were calibrated (2)

3.4.1.4 Muscle Strength

Muscle strength was measuring using 1RM. This was a secondary outcome in Study I. As 1RM is considered the gold standard for muscle testing, it was utilised to ensure accurate and repeatable measurement (Grgic et al., 2020). As muscle testing is specific to the muscle group, a horizontal leg press was utilised to assess lower limb muscle strength (5).

3.4.1.5 Body Composition

Body composition was a secondary outcome in Study I. This was measured using the Bioimpedance Analysis. In PRE-HIIT, post-intervention assessors were blinded to study allocation. As there may be a different assessor between the baseline assessment and post-intervention assessment, BIA was selected for use as it is independent measure from the assessor (Fosbøl and Zerahn, 2015) (6).

3.4.1.6 Vital Signs

Resting blood pressure was measured using the 'Welch Allyn' vitals sign monitor. Due to movement on the bike, this blood pressure monitor was not suitable for use during the exercise test. Therefore, blood pressure was measured using a manual sphygmomanometer and Korotkoff sounds. Heart rate was recorded at rest from the finger probe of the vital signs monitor or wrist-based HR monitor (Polar M200). SPO_2 was recorded at rest using pulse oximetry via the finger probe vital signs monitor.

3.4.1.7 Perceived Rate of Exertion

Participants ranked perceived level of exertion at rest using the modified Borg Rating of Perceived Exertion Scale.

3.4.1.8 Postoperative Complications and Length of Stay

The CCD was used to identify and classify postoperative complications. Length of stay was defined as the number of days spent in hospital. Length of stay in critical care, can be defined as the number of days in an intensive care unit or high dependency unit.

Table 3.8 Standard Operating Procedures Available in Appendices

Standard Operating Procedure	Appendix Number
Short Physical Performance Battery	3
Cardiopulmonary Exercise Testing	4
One Repetition Maximum	5
Anthropometry Measures	6

3.4.1.9 Statistical Analysis

Within this thesis, all statistical analysis was completed using IMB SPSS Statistics 26. The statistical analysis approaches used in each study are discussed in their respective chapters.

3.4.1.10 Qualitative Applications in this Thesis

Reflexive TA was used in both Study II and Study III as it provides a systematic approach to data analysis, which validates the role of the researcher in the process. Amendments to the reflexive TA process were made to accurately reflect the aims and objectives of the studies. In Study II, a reflexive TA approach was utilised to explore and understand participants' experiences preparing for surgery on the PRE-HIIT programme. Study III, used both a deductive and inductive approach to analyse data. The primary aim of Study III was to assess and understand the acceptability of exercise prehabilitation among key stakeholders. Therefore, to ensure data analysed was primarily focused

on the acceptability of the exercise prehabilitation, data was deductively analysed onto the TFA constructs. Data collected within each construct of acceptability was inductively coded using a reflexive TA approach to explore participants' perception of each construct. This approach was selected and completed in collaboration with the TFA developer Dr. Mandeep Sekhon (MS), Kings College London. Data collected was coded using Nvivo20.

This theoretical framework and questionnaire has been applied throughout this thesis. A mixed-methods approach underpinned by the TFA has been used to assess acceptability in this thesis. This mixed-methods approach involved an acceptability questionnaire, adapted in collaboration with MS, and a semi-structured interview. Data from the semi-structured interviews were analysed using both a deductive and inductive approach.

Chapter 4 The Feasibility of the Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus (PRE-HIIT) Trial

4.1 Introduction

This chapter outlines the methods, results and discussion of Study I, which examines the feasibility of the 'Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus' (PRE-HIIT) trial. Qualitative results from this study are presented in Chapter 5. PRE-HIIT is a randomised controlled trial (RCT) examining the effect of a hybrid preoperative high intensity interval training (HIIT) programme on cardiopulmonary fitness in patients scheduled for oesophagectomy and major lung resections. This thesis examines the feasibility and preliminary efficacy of this RCT using data from the first 48 participants recruited onto the trial.

As described in Chapter 1, exercise prehabilitation involves preoperative exercise training with the goal of increasing cardiopulmonary fitness to prepare patients for the physiological stresses of surgery (Banugo and Amoako, 2017, Durrand et al., 2019, Silver and Baima, 2013). However, for some of the more time sensitive cancers and high-risk surgeries, the short timeframes available in cancer care coupled with the physiological impact of neoadjuvant therapy may limit the impact that moderate intensity exercise can have. This has led to interest in alternative methods of increasing cardiopulmonary fitness and optimising patients, such as HIIT. HIIT is an effective and efficient way of increasing cardiopulmonary fitness with potential to have an impact in the short timeframe available and optimise fitness in patients who are deconditioned secondary to neoadjuvant therapy prior to high-risk surgeries (Buchheit and Laursen, 2013, MacInnis and Gibala, 2017, Burgomaster et al., 2008, Gibala et al., 2012, Helgerud et al., 2007). However, as discussed in Chapter 2, currently there is insufficient evidence to support its role in exercise prehabilitation and further research is indicated. Therefore, the primary aim of Study I is to examine the feasibility of the PRE-HIIT trial, an RCT designed to assess the impact of HIIT on preoperative cardiopulmonary fitness.

PRE-HIIT is a large RCT funded through the Irish Cancer Society/Health Research Board MRCG Joint Funding Scheme 2018; therefore, it has been completed by a large research team. The author (Emily Smyth (ES)) was lead researcher managing PRE-HIIT, with support from the team physiotherapist, blinded assessor Neil Kearney (NK) and managerial support from Linda O'Neil (LON) and principal investigators Juliette Hussey (JH) and Emer Guinan (EG). The author had responsibility for

recruitment, management of all study visits, implementation of the intervention (delivery of the HIIT intervention and home visits), data collection and data analysis for this thesis. All assessments were performed by the research team (ES, NK). Referrals to usual care were completed by ES and exercise classes were led by physiotherapist Sarah Wade, Clinical Specialist in Exercise Prehabilitation in St James's Hospital (SJH). The background, validity, and reliability of all measures performed have been described in Chapter 3.

4.2 Study Aims and Objectives

The primary aim of this study was to examine the feasibility and preliminary efficacy of the PRE-HIIT RCT in oncological patients scheduled for major lung resection or oesophagectomy.

The study specific objectives were:

- To examine the feasibility of the trial in terms of recruitment rates, suitability of the intervention, suitability of outcome measures and adverse events.
- To assess the change in preoperative fitness, muscle strength and physical function.
- To examine the acceptability of a preoperative hybrid HIIT programme.
- To examine the impact of preoperative HIIT on postoperative complications.

4.3 Methods and Measures

4.3.1 Study Design

This RCT used a convergent parallel mixed-methods 2-arm study design. The intervention group received standard preoperative care in addition to a 2-week HIIT programme, whereas the control group received only standard preoperative care. Study I examined the feasibility of PRE-HIT in the first 48 patients recruited onto the trial. This was examined by analysing recruitment potential, suitability of interventions, suitability of cardiopulmonary exercise testing (CPET) as an outcome measure and participants' perspectives. Secondary measures examined the preliminary efficacy of HIIT on peak oxygen consumption (VO_{2peak}), physical function, muscle strength, postoperative complications and acceptability of the programme.

4.3.1.1 Preoperative Care at St James's Hospital

Standard care at SJH adheres to perioperative ERAS protocols (discussed in Section 1.8.6.1) specific to each surgery type, including preoperative, intraoperative and postoperative management. Preoperative care includes referral to a pre-admission clinic for review by anaesthetics and

advanced nurse practitioners, as well as preoperative education and pharmacist review. Investigations include computerised tomography, positron emission tomography, chest x-ray, pulmonary function tests and/or echocardiogram. Patients with oesophageal cancer are referred to a dietician for preoperative review and all patients are referred to exercise prehabilitation. The hospital prehabilitation exercise class involves standard preoperative exercise advice and exercise classes supervised via telehealth or in-person. The in-person exercise classes are available twice weekly and telehealth classes are available three times weekly. Classes include 20 minutes of moderate intensity cardiopulmonary exercise and 3-5 resistance exercises, targeting the major muscle groups of the body. It is important to note that the protocol for PRE-HIIT was written in 2018, prior to the introduction of an exercise prehabilitation programme.

4.4 Ethical Approval

Ethical approval was granted by the Tallaght University Hospital/ SJH Ethics Committee and the R&I committee in SJH (REC: 2020-02 List 7 – Response to Comments (09)) (7). The PRE-HIIT is registered with Clinical Trials.Gov (NCT03978325). All procedures performed in PRE-HIIT were in accordance with the Declaration of Helsinki (1964) and its later amendments. All the research team involved in PRE-HIIT completed Good Clinical Practice training.

4.4.1 Inclusion Criteria

- Patients who were scheduled for either oesophagectomy (2-stage, 3-stage, transhiatial) or major lung resection for the management of primary oesophageal or lung cancer
- Date of surgery ≥ 2 weeks from baseline assessment (T0)
- Ability to provide written informed consent
- Absence of significant co-morbidities, including metastatic disease, which may adversely impact postoperative outcome
- Successful completion of a medically supervised CPET

4.4.2 Exclusion Criteria

- Meeting the American Thoracic Society/American College of Chest Physicians absolute contraindications for exercise testing (Figure 4.1) (Ross, 2003)
- Pregnancy
- Electrolyte abnormalities
- Orthopaedic impairment that compromises exercise performance

- Any known co-morbidity, which excludes participants from safely completing a CPET or participating in HIIT

- Acute myocardial infarction
- Unstable angina
- Uncontrolled arrhythmias causing symptoms or hemodynamic compromise
- Syncope
- Active endocarditis
- Symptomatic severe aortic stenosis
- Uncontrolled heart failure
- Acute pulmonary embolus or pulmonary infarction
- Thrombosis of lower extremities
- Suspected dissecting aneurysm
- Uncontrolled asthma
- Pulmonary oedema
- Room air desaturation at rest ≤ 85%
- Respiratory failure
- Acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)
- Cognitive impairment leading to inability to cooperate
- Left main coronary stenosis or equivalent
- Moderate stenotic valvular heart disease
- Severe untreated arterial hypertension at rest (>200 mmHg systolic, >120 mmHg diastolic)
- Tachyarrhythmias or bradyarrhythmias
- High degree atrioventricular block
- Hypertrophic cardiomyopathy
- Significant pulmonary hypertension

Figure 4.1 The American Thoracic Society/American College of Chest Physicians (ATS/ACCP) Absolute Contraindications for Exercise Testing

4.5 Sampling and Recruitment

Participants were recruited from SJH, Dublin, Ireland which is the largest cancer centre serving patients nationwide. It is National Centre of Excellence for oesophageal resection in Ireland and completes approximately 65% of national yearly oesophageal resections. Additionally, it is a supra-regional centre for lung resection, completing approximately 50% of national lung resections. Therefore, participants from across Ireland were recruited ensuring nationwide representation. Following multi-disciplinary team discussion, potential participants were identified by the surgical team in collaboration with the research team. Hospital electronic patient records were then

screened by the research team for eligibility. During preoperative treatment-planning appointments at cancer clinics in SJH, eligible patients were introduced to the concept and benefits of exercise prehabilitation by the surgeon or clinical nurse specialist and received a Participant Information Leaflet (PIL) (8). Following a reflection period of 24 hours, eligible participants were contacted by the research team physiotherapist to further discuss participation in the trial and invited to attend a screening assessment. Participants who agreed were scheduled for a screening assessment in the Clinical Research Facility (CRF) in SJH. Written medical approval to participate in PRE-HIIT was obtained from the treating consultant by the research team for each participant prior to baseline assessment. Written informed consent was obtained from all participants at the start of T0 assessment (9).

4.6 Assessment, Randomisation and Blinding

Potential participants attended a T0 assessment approximately 48 hours after receiving the PIL. All assessments were completed in the CRF in SJH and lasted approximately 90 minutes. All assessments were completed by a blinded assessor (i.e., assessments were completed prior to randomisation or by an assessor blinded to study allocation) to minimise performance bias. Participants were enrolled in the PRE-HIIT trial following the successful completion of a CPET and randomised to the HIIT intervention or to the standard care control group using a 1:1 ratio computer-generated randomisation list. Study glow is presented in Figure 4.2. Randomisation was overseen by a co-investigator, independent from the implementation of the trial. Following completion of the intervention and before surgery, participants completed a post-intervention assessment (T1). This was scheduled on the day patients were admitted to SJH for surgery, or as close to that date as possible. Postoperative data (T2) was collected following discharge from the hospital by medical chart and electronic patient record review. Due to the nature of the intervention, programme implementation staff and participants could not be blinded to study allocation.

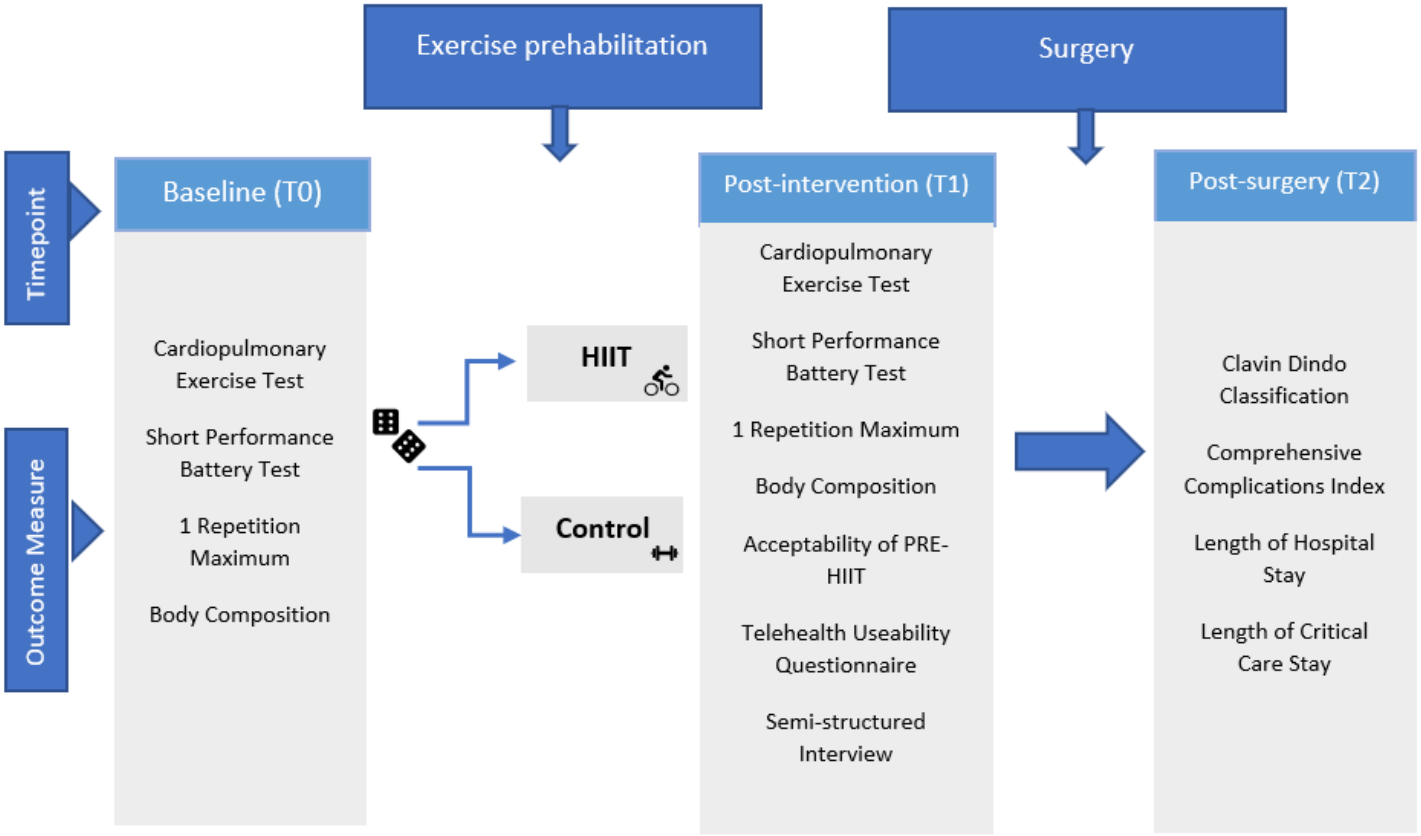

Figure 4.2 PRE-HIIT Flow Diagram

4.7 PRE-HIIT Intervention

Participants who were randomised to the PRE-HIIT intervention group completed an individualised, supervised HIIT programme for a minimum of two weeks preoperatively. All participants randomised to the intervention arm also received standard preoperative care. The PRE-HIIT intervention was a supervised HIIT programme completed for five days a week, for at least two weeks preoperatively. If participants had more than two weeks prior to surgery, the number of sessions per week dropped to three after completion of the second week. All intervention sessions were scheduled at a time convenient to the participant. All exercise sessions were completed on an electronically braked COSMED ergometer and lasted 38 minutes. Intensity was prescribed using peak power output (PPO) achieved during T0 CPET. Sessions included a five minute warm-up at 50% of PPO, 30 minutes of 15 second intervals changing between 100% PPO and 0 watts and a three minute cool down at 30 watts. If exercise tolerance increased during the programme, defined by a failure to reach maximal perceived exertion according to the modified Borg Rating of Perceived Exertion Scale and heart rate maximum, the PPO was increased to elucidate the required exercise response. Exercise prescription is presented in Figure 4.3.

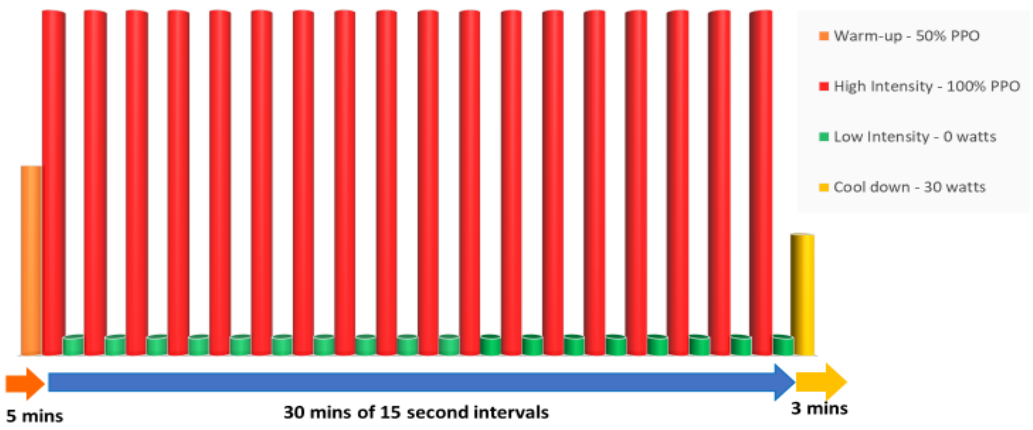

Figure 4.3 PRE-HIIT Exercise Prescription

This intervention was completed either in-person in the CRF in SJH or via telehealth, depending on participants' preference. Each session was supervised by a physiotherapist and lasted approximately 60 minutes. Resting measures for heart rate (HR), blood pressure (BP) and oxygen saturation (SPO_2) were recorded before and after exercise (methods described in 3.4). Vital signs were monitored throughout exercise, using the finger probe from the vital signs monitor. Heart rate and rate of perceived exertion, as per the modified Borg Rating of Perceived Exertion Scale,

were recorded every two minutes. Blood pressure was measured using a manual sphygmomanometer and Korotkoff sounds and recorded every six minutes. Participants completed lower limb stretches of all major muscle groups following the intervention.

Participants who elected to complete the intervention by means of telehealth participated from their home, supervised by the physiotherapist via Zoom. An electronically braked COSMED ergometer was delivered to their home for the duration of the intervention. Following delivery of the electronically braked COSMED ergometer, the physiotherapist completed a home visit. During the home visit, the participant was educated on the use of the Polar M200 watch, Zoom and the COSMED ergometer. The first exercise session was completed during the home visit and all subsequent sessions were completed via Zoom, repeat home visits were scheduled if required. Resting HR was recorded before and after the exercise session (methods described in Section 3.2.6.2.1). Heart rate was monitored and recorded every two minutes during exercise using the Polar M200 wrist-based HR monitor. Perceived rate of exertion was measured and recorded every two minutes using the modified Borg Rating of Perceived Exertion Scale. Lower limb stretching was completed following the intervention.

4.7.1.1 Standard Preoperative Care Control Group

The control group received standard preoperative care in SJH, which involves surgery-specific ERAS protocols, preoperative investigations and referral to exercise prehabilitation (described in Section 4.3.1.1). The hospital prehabilitation exercise class involves standard preoperative exercise advice and exercise classes supervised via telehealth or in-person. The in-person exercise classes are available twice weekly and telehealth classes are available three times weekly. Classes include 20 minutes of moderate intensity cardiopulmonary and 3-5 resistance exercises, targeting the major muscle groups of the body. The standard care control group were not given specific advice regarding exercise beyond that considered usual and were not invited to participate in the HIIT exercise group. Participants were offered recordings of the classes to complete in their own time if they were unable to attend classes. Participants were contacted weekly by the research team to collect data on additional class recordings completed and additional exercise completed.

4.8 Outcome Measures

The background, validity and reliability of all measures performed have been described in Chapter 3. The standard operating procedures that were followed are presented in 3 (see Table 3.8). Consistent with the standards outlined in Chapter 3, feasibility was measured using a range of outcomes including recruitment potential, suitability of interventions, suitability of CPET as an outcome measure and participants' perspective.

4.8.1 Recruitment Potential

Potential participants were screened for eligibility through their electronic patient record and screening outcome was recorded in a standardised screening log. Recruitment potential was defined as the frequency and percentage of eligible patients amongst screened patients. Reasons for ineligibility were documented. All eligible patients were contacted and invited to participate in PRE-HIIT and reasons for declining to participate were recorded.

4.8.2 Suitability of Interventions

Suitability of the intervention arms (HIIT and usual care group classes) were measured using attrition rates, adverse events and adherence (Table 4.1).

Table 4.1 Suitability of Intervention Outcomes

Outcome	**Description**
Adverse events	The frequency, grade and nature of each adverse event for all exercise sessions in both arms were recorded.
Adherence	
Supervised sessions attended	Total number of supervised sessions attended.
Compliant HIIT sessions attended	Total number of supervised aerobic sessions where target intensity was achieved.
Permanent treatment discontinuation	Permanent discontinuation of PRE-HIIT programme.
Treatment interruption	Number of patients missing at least two consecutive supervised PRE-HIIT sessions.
Early session termination	Number of sessions requiring early session termination.
Pre-treatment intensity modification	Number of sessions requiring modification because of pre-exercise screening indications.
Adherence to exercise dose	
Planned cumulative MET-HOUR	Planned intensity of each session was multiplied by the target intensity duration to calculate MET per session. All sessions were summed to derive total “planned” exercise dose.

Completed cumulative MET-HOUR	The actual intensity and duration completed at each session. All sessions were summed to derive total "completed" cumulative (MET-HOUR) per patient.
Relative dose intensity	The ratio of total "completed" to total "planned" cumulative dose, expressed as a percentage.

Abbreviations: MET-HOUR= metabolic equivalent per hour

The frequency and reason for attrition was recorded in both groups. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) presented in Table 3.2 (National Cancer Institute, 2017). Adherence to the exercise intervention was measured using traditional adherence variables i.e., total number of supervised sessions attended and through a more descriptive set of variables recommended for exercise oncology. The frequency of attended sessions in relation to planned sessions (HIIT intervention group) and available sessions (usual care group) was calculated for all modes of intervention delivery (i.e., in-person versus virtual delivery for both HIIT and usual care interventions). Additional adherence measures included compliance to the prescribed exercise protocol, permanent treatment discontinuation, treatment interruption, dose modification, early session termination and pre-treatment intensity modification (Table 4.1). Exercise dose was expressed as the volume of metabolic equivalents per hour (MET-HOUR) completed during sessions. Total planned exercise dose in MET-HOUR was calculated by dividing VO_2 values at exercise levels (taken from baseline CPET) by 3.5 (1MET) and multiplied by appropriate timescale to calculate the volume METs. Total completed exercise dose was calculated by amending the calculation to allow for any reduction in intensity or duration of sessions.

4.8.3 Suitability of CPET as an Outcome Measure

The suitability of CPETs to measure changes in cardiopulmonary fitness preoperatively in patients scheduled for oesophagectomy and lung resection were measured using attendance, attrition, adverse events and completion rates. Outcomes are defined in Table 4.2.

Table 4.2 Suitability of CPET as an Outcome Measure

Outcome	**Description**
Attendance at T1 assessment	The number of planned assessments which were attended.
Attrition rates	The number of participants who withdrew following completion of the exercise intervention but prior to the T1 assessment.

Completion of T1 cardiopulmonary exercise test	Frequency and percentage of CPETs completed during T1 assessment was recorded. Tests which were terminated by the research team prior to participant reaching their reported maximum were considered failed.
Adverse events during cardiopulmonary exercise testing	The frequency, grade (according to CTCAE) and nature of adverse events for all cardiopulmonary exercise testing were recorded.

4.8.4 Secondary Outcomes Measures

Secondary outcome measures are outlined in Table 4.3. The background, validity and reliability of each outcome have been described in Chapter 3. Standard operating procedures are presented in (Table 3.8). Secondary outcomes were collected by the research team at three timepoints: T0, T1 and postoperative period (T2).

Table 4.3 Secondary Outcome Measures in PRE-HIIT

Outcome	**Instrument**	**Timepoint**		
		T0	**T1**	**T2**
Cardiopulmonary fitness	Cardiopulmonary Exercise Testing (CPET)	X	X	
Functional status	Short Performance Physical Battery (SPPB)	X	X	
Muscle strength	Leg-press 1 Repetition Maximum (1RM)	X	X	
Acceptability of intervention	Acceptability of PRE-HIIT Questionnaire		X	
	Semi-structured Interview		X	
Useability of telehealth	Telehealth Useability Questionnaire		X	
Postoperative complications	Clavien Dindo Classification			X
	Comprehensive Complications Index			X
	Length of Critical Care Stay			X
	Length of Hospital Stay			X

Abbreviations: T0= baseline assessment, T1=post-intervention assessment, T2=postoperative

4.8.4.1 Fitness outcomes

Changes in preoperative cardiopulmonary fitness were measured using CPET with breath-by-breath analysis and the procedures followed are presented in 4. Breath-by-breath analysis was completed

using COSMED K4b^2 or COSMED Quark. Physiological outcome variables measured included VO_{2peak}, VO_{2AT}, peak power output (PPO) and time to completion. VO_{2peak} was defined as an average of the VO_2 results in the last 30 seconds of the CPET. AT was measured using the modified V-slope method using visual inspection of VO_2 data derived from CPET and plotted against VCO_2 to identify the point where the data splits. This was completed independently by blinded reviewers.

The following criteria applied to the estimation of VO_{2AT}:

- Two reviewers independently determined $VO_{2AT.}$
- If both points were the same, value was accepted as the $VO_{2AT.}$
- If both points were within 30 seconds of each other, the average of the two values was accepted as the $VO_{2AT.}$
- If both points were more than 30 seconds apart, a third reviewer was assigned.
- If the third reviewer's estimate was the same as one of first two, this value was accepted as $VO_{2AT.}$
- If the third reviewer's estimate was within 30 seconds of one or both points, the average of the closer two points were accepted as the $VO_{2AT.}$
- If agreement is not reached at this point, the three reviewers met and reached agreement by consensus.

Peak power output was defined as the maximum resistance in wattage achieved during the CPET. Time to completion was measured as the amount of time until failure in minutes and seconds. Functional status was measured using the Short Physical Performance Battery (SPPB). Muscle strength was measured using one repetition maximum (1RM) on a leg press (described in Section 3.2.6.2).

4.8.4.2 Acceptability

Acceptability was measured using the using an adapted version of the generic Theoretical Framework of Acceptability Questionnaire (10). The adapted questionnaire was reviewed by two experienced exercise prehabilitation researchers (EG and JH) and by the TFA developer (MS) for relevance and accurate adaptation of the TFA constructs. The survey comprised of an eight-item Likert Scale questionnaire, seven questions reflecting each construct of acceptability and one single-item question reflecting overall acceptability. Each question was scored out of a possible five, where one represents low acceptability and five represents high acceptability, and a total composite acceptability score (the sum all constructs) of 40. Acceptability levels were compared between modes of delivery (online versus in-person) and control versus HIIT intervention.

Correlation between the single-item overall acceptability question and each construct was completed using Spearman's Rank Correlation coefficient.

4.8.4.3 The Telehealth Useability Questionnaire

The Telehealth Useability Questionnaire was used to assess the useability of telehealth to provide prehabilitation (11). The questionnaire is divided into six sub-scales: usefulness, ease of use, interface quality, interaction quality, reliability and satisfaction, and future use. Usefulness, ease of use and reliability have a total possible score of 15, whereas interaction quality, interface quality, and satisfaction and future use have a total possible score of 20. Only participants who attended via telehealth completed the questionnaire. Results were presented as median score for each sub-scale and the percentage of participants who scored each question as one (very poor), two (poor), three (acceptable), four (good) or five (excellent).

4.8.4.4 Postoperative Complications and Length of Stay

Postoperative complications were collected by a review of participants' medical notes following discharge from hospital. The severity of postoperative complications was classified using the Clavien-Dindo Classification (Section 3.2.6.3). The CCI was used to summarise postoperative complications levels in both groups. Length of critical care stay and length of hospital stay are reported as number of days in critical care and number of days in hospital.

4.9 Safety

Prior to baseline testing, written medical approval from the surgical team confirming the participant's suitability for participation was required. Past medical history was updated at the start of each assessment. Patients were only formally enrolled on PRE-HIIT following the successful completion of an ECG monitored CPET. All CPET were supervised by a physician who monitored the ECG throughout. Any cardiac abnormalities identified during or following the CPET were reviewed by the cardiology team in SJH and treated accordingly. All assessments took place in the CRF, which is located within SJH and is covered by the hospital's emergency response team.

4.10 Statistical analysis

Quantitative data analysis was completed using IBM SPSS 26 software. Descriptive statistics (frequency and percentage) and bar charts were used to present feasibility outcomes. Normality was assessed using (1) Skewness and Kurtosis, (2) Shapiro-Wilks and (3) visualisation of histograms and quartile-quartile (Q-Q) plots.

Data was classified as normally distributed when two of the three following conditions were met:

- Skewness and Kurtosis (< ± 1.96) (Kim, 2013).
- Shapiro-Wilks <0.05 (Mishra et al., 2019).
- Normal distribution based on histograms and Q-Q plots.

Equality of variances was assessed using Levene's test. Summary statistics are presented as (i) frequency and percentage, (ii) means and standard deviations for normally distributed data, and (iii) median and interquartile ranges for data which was not normally distributed. Within-group differences was assessed using Paired T-test for normally distributed data and Wilcoxon signed rank test for data which was not normally distributed. Between group differences was assessed using independent T-test for normally distributed data and Mann U Whitney test for data which was not normally distributed. Correlation between the single-item overall acceptability and each construct was completed using Spearman's Rank Correlation.

4.11 Results

In total, n=315 potential patients were screened for eligibility, n=142 were deemed ineligible and therefore excluded, n=125 declined to participate and= 48 were enrolled. Of the 48, n=26 were randomised to the intervention arm and n=22 were randomised to the control (Figure 4.4). Participants recruited travelled from 1.5km to 285km to attend assessments. A detailed analysis of recruitment potential is provided in Section 4.11.2.1.

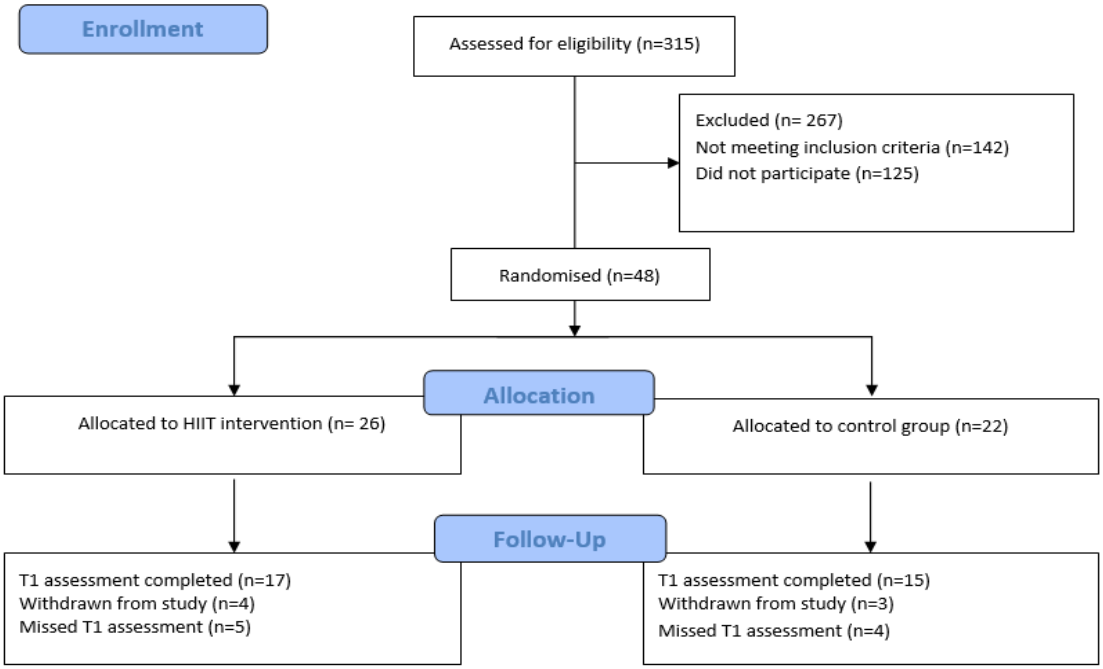

Figure 4.4 PRE-HIIT CONSORT Flow Diagram

4.11.1 Participant Characteristics

Baseline characteristics of all participants are presented in Table 4.4. Baseline characteristics were generally comparable between groups. The majority of participants had oesophageal cancer (52%), were current smokers or had previously smoked (66.6%) and drank alcohol (62.5%). Primary comorbidities present included hypertension (20.8%), gastro-oesophageal reflux disease (GORD) (12.5%) and cardiac arrhythmias (10.4%). More participants on the HIIT arm consumed a higher volume of alcohol per week (13.79 (14.1%) versus 6.25 (7.5%))Table 4.4 PRE-HIIT Baseline Characteristics

Patient characteristic	**HIIT group (n=26)**	**Control group (n=22)**
Age (years)	61.85 (10.5)	63.86 (8.52)
BMI (kg/m$^{2)}$	26.82 (3.55)	27.16 (5.61)
Fat free mass (%)	34 (10)	32.79 (8)
Gender		
Male	17 (65.4)	15 (68.2)
Female	9 (34.6)	7 (31.8)
Oesophageal cancer	14 (53.8%)	11 (50%)
Adenocarcinoma	13 (50%)	6 (27.3%)
Squamous cell carcinoma	1 (3.8)	5 (22.7%)
Lung cancer	12 (46.2%)	11 (50%)
NSCLC adenocarcinoma	7 (23.1%)	8 (36.4%)
NSCLC squamous cell carcinoma	3 (11.5%)	1 (4.5)
Not reported	2 (7.69%)	2 (9%)
Co-morbidities		
Myocardial infarction	0	1 (4.5%)
Coronary artery bypass graft	1 (3.8%)	1 (4.5%)
Cardiac Valve replacement	1 (3.8)	0
Cardiac arrhythmias	4 (15.4%)	1 (4.5%)
Dyslipidaemia	1 (3.8%)	1 (4.5%)
Hypertension	8 (30.8%)	2 (9.1%)
COPD	4 (15.4%)	3 (13.6)
Asthma	2 (7.7%)	2 (9.1%)

Type II DM	2 (7.7%)	1 (4.5%)
Neurological condition	3 (11.5%)	2 (9.1%)
GORD	4 (15.4%)	2 (9.1%)
Total knee replacement	2 (7.7%)	0
Total hip replacement	0	1 (4.5%)
Smoking status		
Never smoked	6 (23.1%)	6 (27.3%)
Stopped >8 weeks ago	12 (46.2%)	10 (45.5%)
Stopped<8 weeks ago	1(3.8%)	3 (13.6%)
Current smoker	3(11.5%)	3 (13.6%)
Alcohol consumption		
Yes	16 (61.5%)	14 (63.6%)
No	7(26.9%)	8 (36.4%)
Units per week	13.79 (14.1%)	6.25 (7.5%)

Data is expressed as frequency (percentage), less than = <, greater than = >, DM= diabetes mellitus, GORD= gastro-oesophageal reflux disease, COPR= chronic obstructive pulmonary disease, NSCLC= non-small cell lung cancer.

Fitness levels were comparable at baseline. All patients were categorised as poor or very poor for preoperative cardiopulmonary fitness based on normative values for age and gender, with the mean VO_{2peak} scores falling in the very poor category for both men and women (ACSM, 2017). Baseline physical measures collected at the T0 assessment are presented in Table 4.5.

Table 4.5 PRE-HIIT Baseline Physical Measures

Baseline Physical Measures	**Intervention (n=26)**	**Control (n=22)**	**p-value**
VO_{2peak} (ml/kg/min)	15.9 (5.1)	19.19 (7.6)	0.169
Fitness category	Poor- very poor	Poor- very poor	n/a
VO_{2AT} (ml/kg/min)	8.6 (2.8)	10 (3.6)	0.157
Peak power output (watts)	116.15 (43.20)	127.27 (48.6)	0.406

Time to completion (mm:ss)	10:51 (02:00)	11:46 (03:07)	0.231
SPBB	12 (1)†	12 (1)†	0.586
Leg press (lbs)	195.42 (60.86)	193 (70.27)	0.903

Data is expressed as mean (standard deviation), † = median (interquartile range), n/a = not applicable

Surgical procedure data was reviewed for 41 (85.1%) participants, n=22 (84.6%) in the HIIT arm and n=19 (86.4%) in the control arm. Surgical data was not collected for the participants who withdrew from the study (n=7). The majority of lung cancer patients underwent lobectomy by video-assisted thoracoscopic surgery (VATS) (n=13) and the majority of oesophagectomies were 2-stage (n=11). One oesophageal resection was abandoned following evidence of metastasis to the pancreas, and the decision was made to close the incision without continuing with the original surgical plan. One planned oesophagectomy was converted to a gastrectomy intraoperatively. Surgical procedures that participants underwent following prehabilitation are presented in Table 4.6.

Table 4.6 PRE-HIIT Surgical Procedures Completed

Surgical Procedure	**Intervention (n=22)**	**Control (n=19)**
Transhiatal oesophagectomy	0	2 (10.5%)
Laparoscopic oesophagectomy	1 (4.5%)	0
2-stage oesophagectomy	7 (31.8%)	4 (21.1%)
3-stage oesophagectomy	2 (9.1%)	3 (15.8%)
Lobectomy by VATS	7 (31.8%)	6 (31.6%)
Lobectomy by thoracotomy	3 (13.6%)	1 (5.3%)
Lobectomy by RATs	0	1 (5.3%)
Total pneumonectomy	0	2 (10.6%)
Did not operate	1 (4.5%)	0
Gastrectomy	1 (4.5%)	0

Data is presented as frequency (percentage)

4.11.2 Feasibility of PRE-HIIT

4.11.2.1 Recruitment Potential

Recruitment began in May 2021. In total, n=315 potential participants were screened for eligibility. Of the 315, n=173 (54.9%) were eligible for inclusion and n=142 (45.1%) were ineligible. Reasons for ineligibility are presented in Figure 4.5. Seven (3.2%) potential participants who were invited to attend a baseline screening assessment did not safely complete the baseline CPET; therefore, were not deemed eligible for participation. All seven participants were referred by the research team to SJH cardiology team for further evaluation and intervention, if required, prior to surgery.

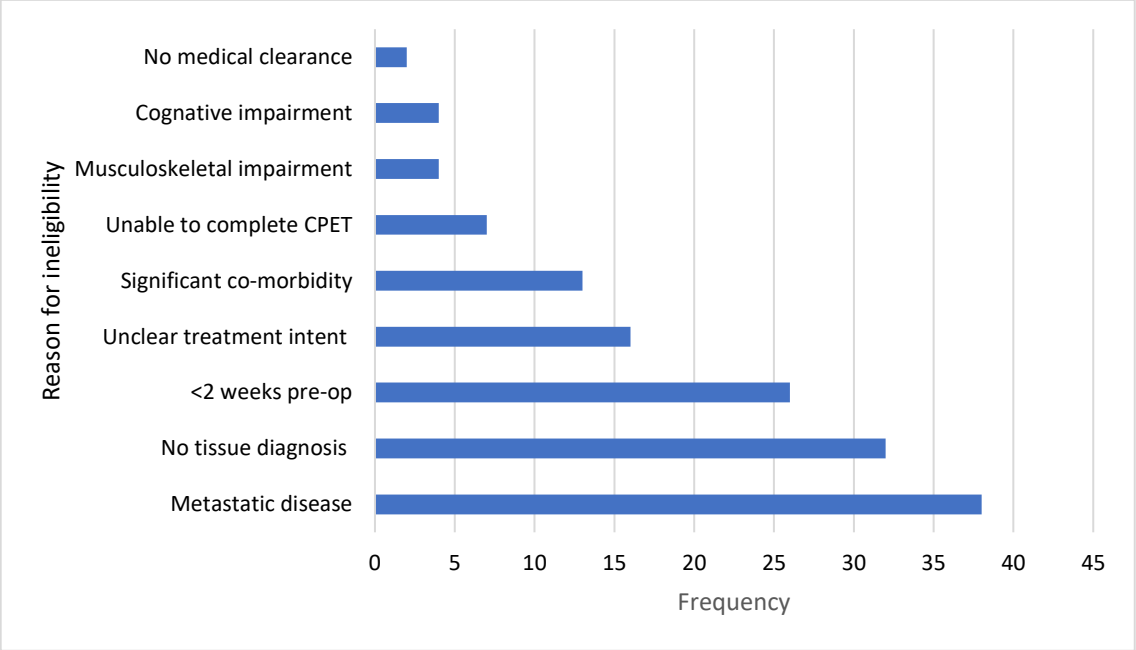

Figure 4.5 Reasons for Ineligibility in PRE-HIIT

In total, n=173 patients were eligible for inclusion; however, due to malfunction of COSMED K4b^2 the research team were unable to invite n=2 to participate. Therefore, n=171 potential participants were contacted for enrolment, n=48 (28.1%) were enrolled and n=123 (71.9%) declined to participate Figure 4.6. The reasons for not participating are presented in Figure 4.7. The primary reasons not participating were travel burden n=43 (34.4%), lack of interest in participation n=21 (16.8%) and inability to contact patient n=15 (12%). Due to a shortage of cycle ergometers available for delivery, telehealth was not available for four patients (2.3%) invited to take part. All four declined to participate due to travel burden.

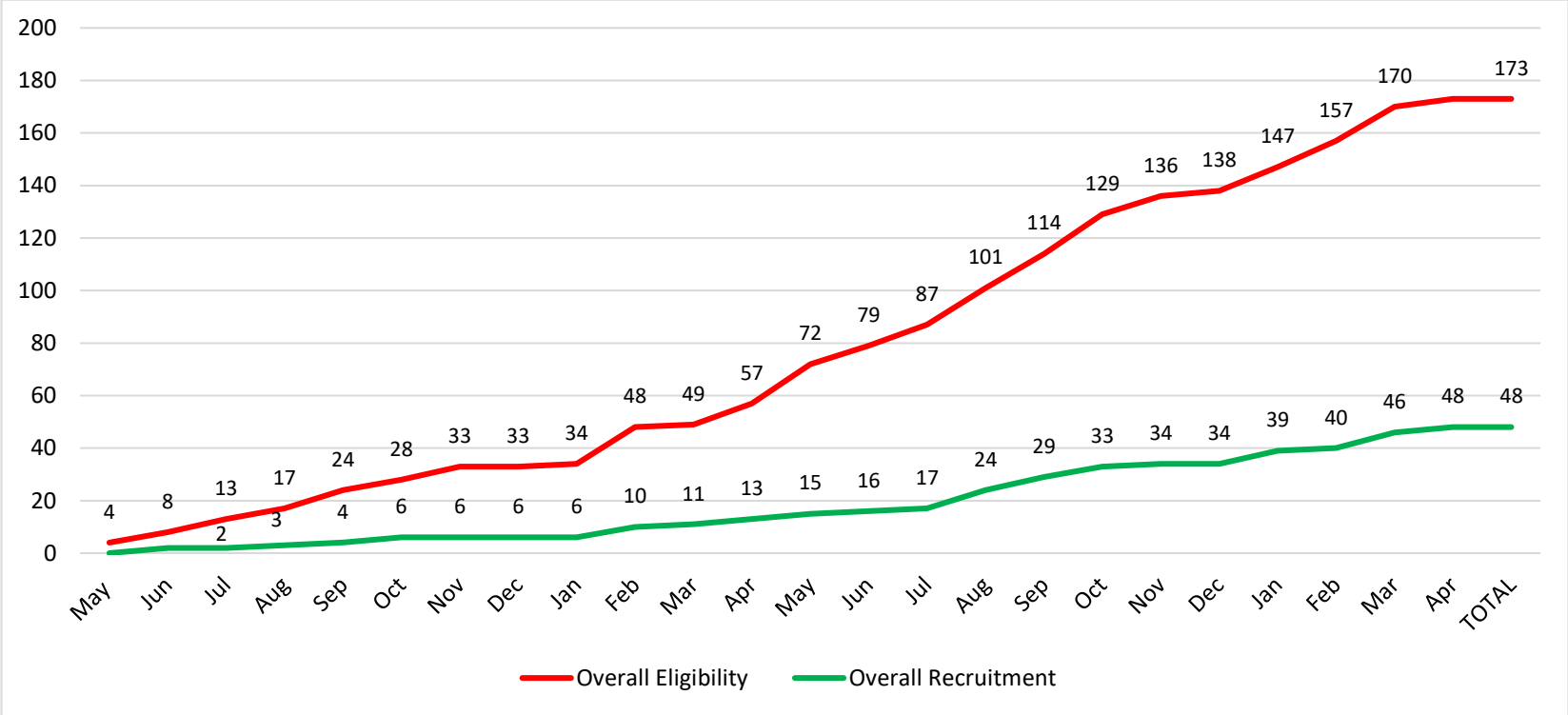

Figure 4.6 Eligible and Enrolled Participants in PRE-HIIT

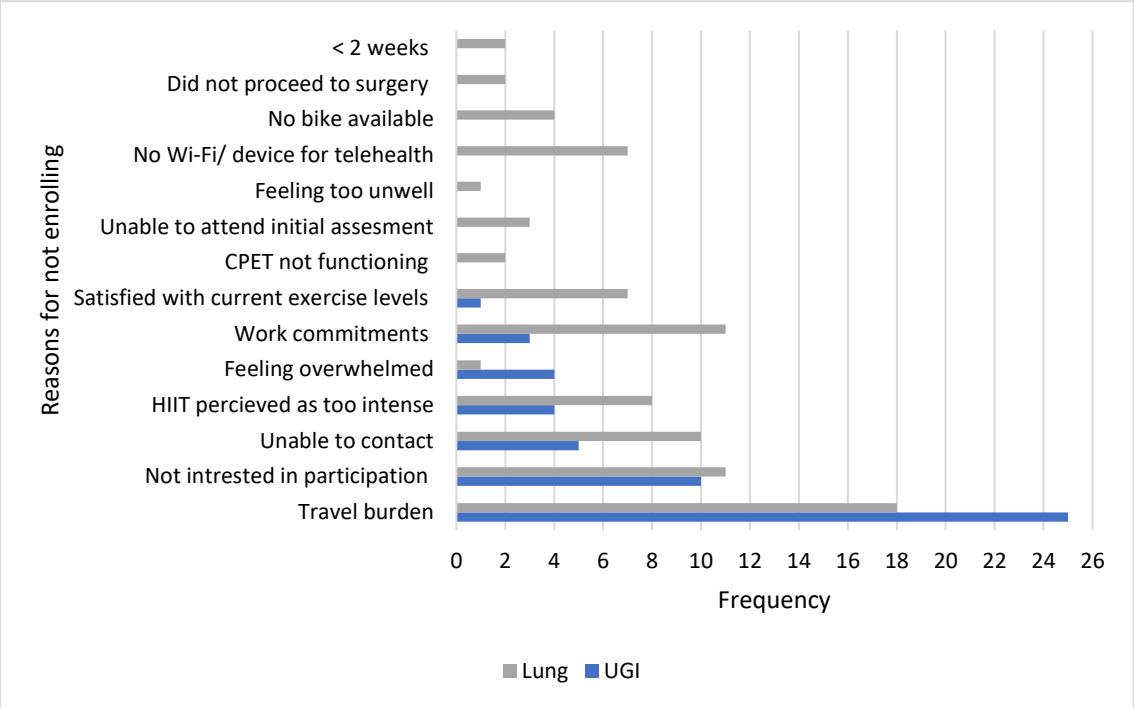

Figure 4.7 Reasons for Not Participating in PRE-HIIT

4.11.2.2 Suitability of HIIT Intervention

Nineteen (73.1%) of the 26 participants randomised to the HIIT intervention completed the intervention via telehealth (Zoom), six (23.1%) completed their exercise sessions in-person and one participant (3.8%) completed 50% in-person and 50% via Zoom. In terms of adherence, the median number of supervised sessions attended was 9.2 (5.1). There was no significant difference in the median number of attended sessions by those completing the intervention in-person 11.5 (7) and those that attended via Zoom 8 (5) (p=0.062). A higher number of compliant sessions were observed by those who completed the intervention in-person 11.5 (7) versus those that undertook it via Zoom 7 (6) (p=0.038). The relative dose intensity was 88.22 (53%), with no significant difference in relative dose intensity achieved between those who completed the HIIT intervention in-person 100% (15) versus those who completed it via zoom 86% (50) (p=0.154). The individual who participated 50% online and 50% in-person attended all planned sessions and achieved 100% of planned exercise dose. Results for suitability of the intervention are presented in Table 4.7 and discussed below.

Table 4.7 Suitability of HIIT Intervention

Outcome	**HIIT (26)**
Attrition	4
Adverse events	
Grade I	3
Adherence	
Number of supervised sessions attended	9.2 (5.1)
Total number of compliant sessions	8.8 (5.3)
Permanent treatment discontinuation	4 (15.3%)
Treatment interruption	1 (4%)
Sessions requiring early session termination	7 (2.9%)*
Pre-treatment intensity modification	21(8.6%)*
Adherence to exercise dose	
Total planned cumulative (MET-HOUR)	437.2
Total completed cumulative (MET-HOUR)	361.8
Relative dose intensity	88.22% (53)

Data is expressed as frequency (percentage), mean (standard deviation), * = percentage of total sessions completed, n/a = not applicable, MET-HOUR = metabolic equivalents per hour

Seven participants withdrew from the PRE-HIIT trial resulting in an overall attrition rate of 14.6%. Four (57.1%) of the seven were in the HIIT arm. One participant withdrew due to an exacerbation of arm pain associated with a history of lymphoedema. Another participant was admitted to SJH during the intervention due to significant worsening of dysphagia requiring parenteral nutrition until surgery, and felt unable to continue. One participant withdrew after failing to attend the first four sessions due a foot injury at home. The participant was subsequently withdrawn following an x-ray which revealed a fracture. Finally, one participant was withdrawn for safety reasons as there was concern that they were under the influence of alcohol.

Participants in the HIIT arm attended a mean of 9.2 (5.1) sessions. The median percentage of planned HIIT sessions which were attended was 100% (33). Planned and attended sessions for each participant is presented in Figure 4.8. The minimum attended sessions was zero (this related to the participant who withdrew due to injury, as described above) and the maximum was 24.

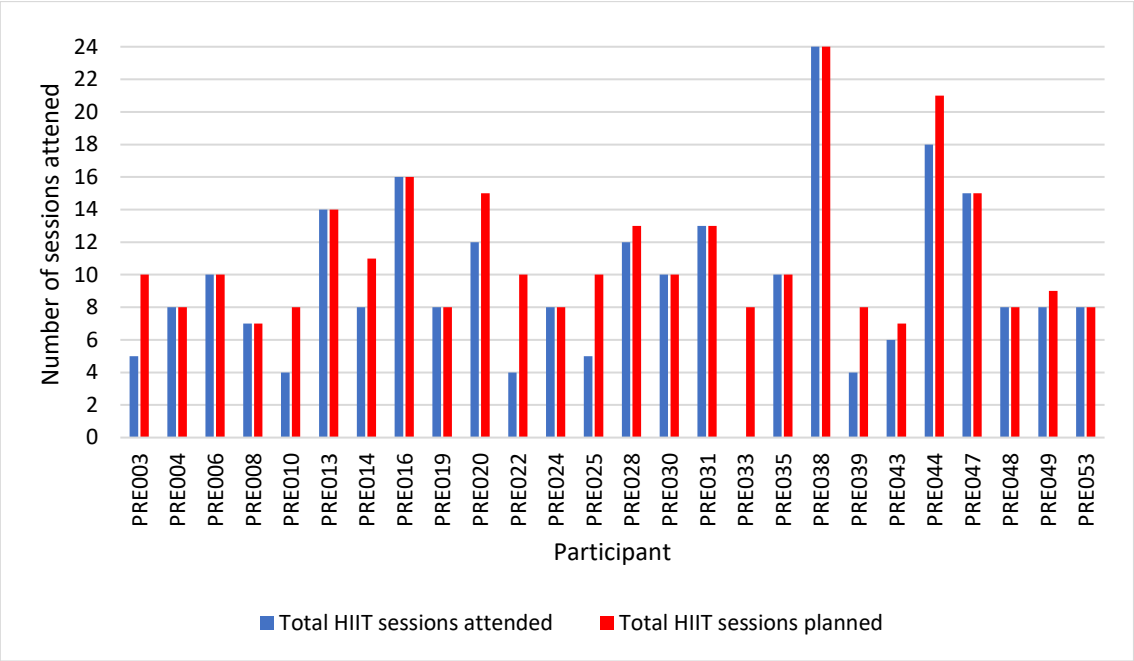

Figure 4.8 PRE-HIIT HIIT Sessions Attended Compared to Planned

In total, 298 HIIT sessions were planned, 245 were attended and 230 were compliant with the exercise protocol. Adherence to planned exercise dose per participant is presented in Figure 4.9. Ten (38.5%) participants completed 100% of their planned cumulative dose. Of those 10, n= 5 (50%) completed greater than the planned cumulative dose. In total, four participants (15%) required pre-treatment intensity modification across n=21 sessions. Intensity was increased for n=3 participants (11.5%) over the course of 15 sessions to increase workload. Intensity was reduced for one patient (3.8%) over six sessions due to knee pain. Seven participants (26.9%) required early termination of the exercise sessions across 10 sessions: three sessions due to exhaustion; three sessions due to knee pain; two sessions due to personal commitments; one session due to regurgitation of stomach contents; and one session due to safety concerns regarding alcohol consumption. One participant in the HIIT arm missed two consecutive sessions due to abdominal pain and personal commitments. The relative dose intensity was 92% (38.5); whole group planned cumulative dose compared to completed cumulative exercise dose is presented in Figure 4.10.

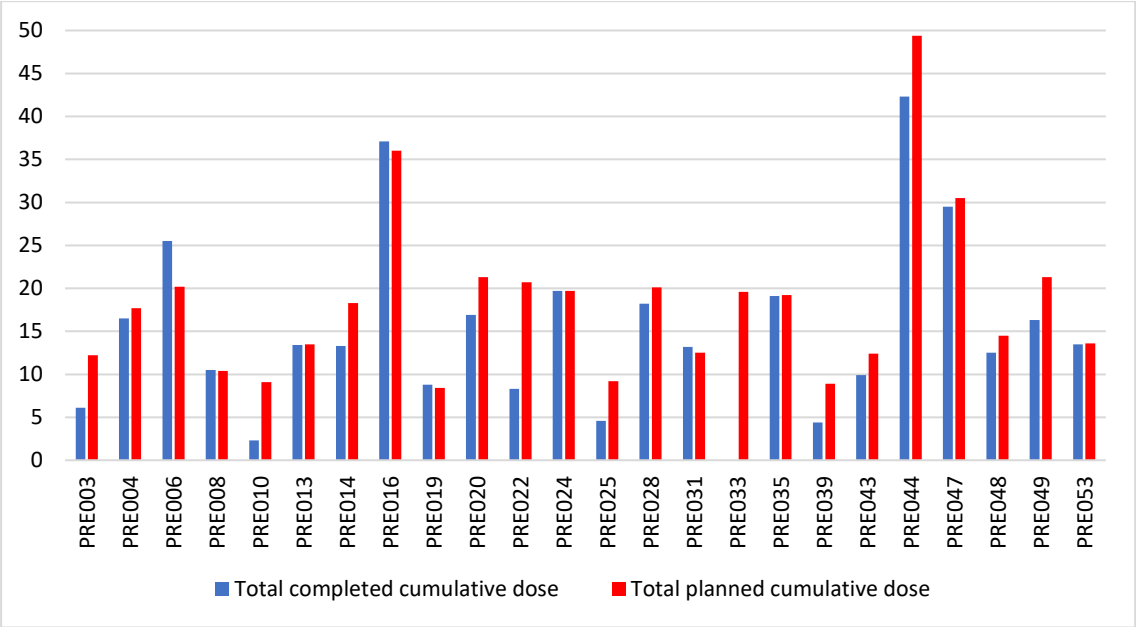

Figure 4.9 PRE-HIIT Adherence to Planned Exercise Dose per Patient in the HIIT Arm

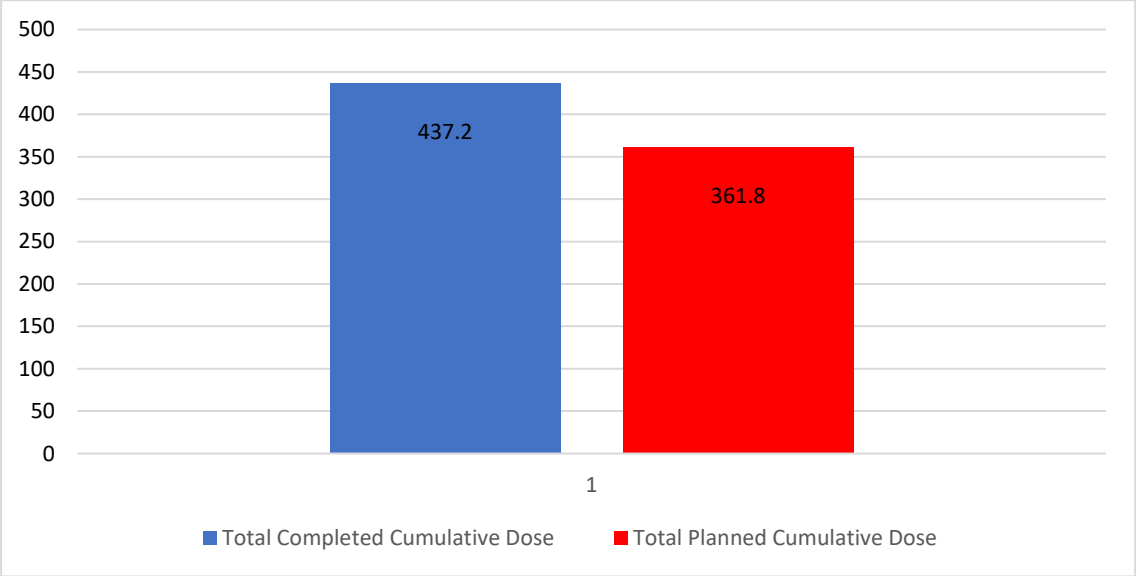

Figure 4.10 Planned and Completed Cumulative Exercise Dose (MET-HOUR)

Three grade 1 mild adverse events occurred in three participants in the HIIT arm. One participant with oesophageal cancer felt unwell and experienced regurgitation of stomach contents during a HIIT session, the session was terminated early. No additional intervention was indicated. One participant reported knee pain, due to long standing arthritis, following each session resulting in early termination of three sessions and one missed session, no intervention was indicated

(discussed in Table 3.2). One patient, with a history of lymphoedema, elected to withdraw after reporting altered arm sensation. No increased arm circumference or swelling was noted; therefore, no intervention was indicated. No adverse events greater than grade one occurred during the exercise intervention.

4.11.2.3 Suitability of Usual Care Exercise Classes

In the control arm n=16 (72.7%) participants attended via Zoom and n=5 (22.7%) attended in-person. The median percentage of available sessions which were attended by those utilising Zoom was 53.4% (87.5) and in the in-person group was 80% (66.6). Results are presented in Table 4.8.

Table 4.8 Results for Usual Care Exercise Classes

Outcome	**Control (22)**
Attrition	3 (13.6%)
Adverse events	
Grade I	0
Adherence	
Adverse events	
Grade I	0
Adherence	
Number of supervised sessions attended	2.8 (2.9)
Total number of compliant sessions	2.8 (2.9)
Permanent treatment discontinuation	1 (4.5%)

Data is expressed as frequency (percentage), mean (standard deviation)

Three (6.25%) participants withdrew from the control group. One participant withdrew following T0 assessment and prior to beginning the exercise programme. This was due to their surgery date being rescheduled resulting in insufficient time to participate in any form of prehabilitation. One participant withdrew following the intervention prior to T1 assessment as their surgery was rescheduled for an earlier date causing the patient to become overwhelmed. One participant was lost to follow-up.

Participants in the control arm attended a mean of 2.8 (2.9) sessions. The median percentage of available sessions which were attended was 25% (54.5) ranging from zero attended to eight. In

total, one session required early termination for one participant due to personal commitments. No sessions required dose modification for any participant. The number of sessions attended compared to available for each participant are presented in Figure 4.11.

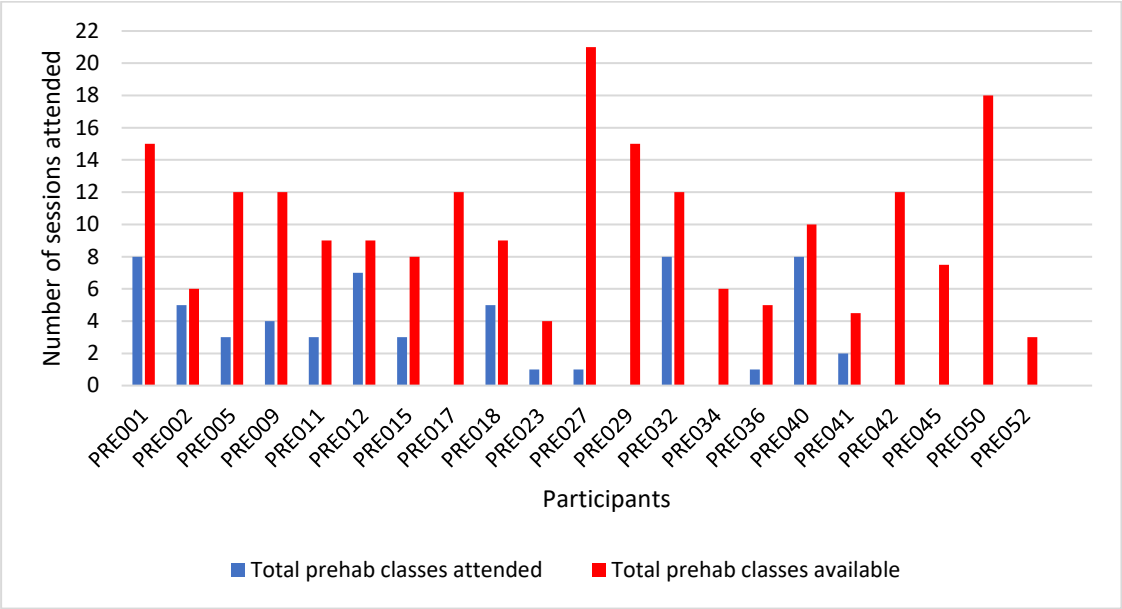

Figure 4.11 PRE-HIIT Control Sessions Attended Compared to Available

Data relating to additional exercise completed at home was collected for n=14 (63.3%). Two (9%) of the 22 participants completed an additional class recording per week (exercise diary available in 12). Three participants (13.6%) reported completing significant volumes of additional exercise. This included a HIIT-like programme and running or cycling three times per week at a moderate to high intensity. Three participants reported completing >150 minutes of moderate cardiovascular exercise per week. Data was not available for 8 (36.3%) participants due to difficulty in contacting them. No adverse events were recorded in the control arm.

4.11.2.4 Suitability of CPET as an Outcome Measure

Of the 48 participants recruited, 33 (68.8%) attended the T1 assessment and 32 (66.7%) T1 CPETs were completed. One CPET was stopped after three minutes due to a possible significant arrhythmia noted by the supervising physician. However, following consultation with the cardiology team, it was determined to be a misdiagnosis and therefore, not deemed an adverse event. Accordingly, no adverse events occurred during CPET.

The first nine patients' CPETs were completed on the K4b^2, one was completed using both the COSMED K4b^2 (T0) and COSMED Quark (T1) and the remainder were completed using the COSMED

Quark. Of the 32 T1 CPETS completed, 31 (96.8%) included breath-by-breath analysis. This analysis was not available for one participant due to COSMED K4b^2 equipment failure. Additionally, there were challenges with interpretation of VO_{2peak} results for five participants (16.1%) due to: (i) differing equipment used to measure each assessment (n=1), (ii) participant interference with mask in the final 35 seconds of CPET, disrupting O_2 measurements and possibly diluting the volume of exhaled O_2 with room air (drop from an average of 10.1 ml/kg/min to 6.9 ml/kg/min in the last 30 seconds)(n=1), (iii) O_2 analyser malfunction resulting in potential underrepresentation of VO_2 levels (n=3). Additionally, one participant had tested positive for COVID-19 10 days prior to T0 assessment and another participant tested positive one day after T1 assessment.

Fourteen (29.1%) T1 assessments were not completed. Seven were not completed due to withdrawal from PRE-HIIT and seven were not attended. Reasons for attrition are discussed in Section 4.11.2.2. The primary reasons for not attending T1 assessments were rescheduled surgical dates resulting in insufficient time to complete assessment (n=3) and uncertainty regarding the time and date of hospital admission for surgery (n=4). Surgical dates and time of being admitted are confirmed at approximately 11am on the day of scheduled admission. However, if no bed is available, admission time or date may be postponed. All four of the patients who did not attend due to lack of confirmation lived a significant distance from the hospital and were unwilling to travel for assessment prior to confirmation of admission.

Atrial fibrillation was identified in one participant at their baseline CPET. However, after discussion with the cardiology team, the participant was deemed eligible for inclusion and was enrolled in PRE-HIIT. Additionally, the participant was referred to Professor Ross Murphy for cardiology review and was managed appropriately prior to surgery.

4.11.3 Preliminary Efficacy of Secondary Outcomes

Preliminary efficacy data for physical measures at T1 are presented in Table 4.9. There was no significant difference in mean change between groups for any physical outcome measure at T1. In the HIIT arm, a significant within-group change was observed in PPO and time to completion. In the control arm, a significant within-group change was observed in time to completion.

Table 4.9 PRE-HIIT Physical Measure Results

Physical Variable	**Baseline**	**Post-intervention**	**Mean change (95%CI)**	**p-value**	**Mean difference between groups**	**p-value**
Fitness category						
HIIT (n=17)	Very poor	Very poor	n/a	n/a	n/a	n/a
Control (n=14)	Very poor	Very poor	n/a	n/a		
VO_{2peak} (ml/kg/min)						
HIIT (n=17)	16.8 (5.9)	17.9 (4.1)	0.2 (-1.7 to 2.1)	0.833	-1.16 (-3.8 to 1.4)	0.359
Control (n=14)	17.5 (7.6)	18.8 (6.7)	1.38 (-0.5 to 3.2)	0.133		
VO_{2AT} (ml/kg/min)						
HIIT (n=17)	9.9 (2.4)	10.18 (2.6)	0.3 (-0.8 to 1.4)	0.559	-0.6 (-2.3 to 1.1)	0.492
Control (n=14)	9.4 (3.5)	10.5 (2.9)	1.5 (-0.2 to 02.5)	0.083		
Peak power output						

(Watts)						
HIIT (n=18)	128.3 (43.5)	143.61 (50.7)	15.3 (5.9 to 24.6)	0.003*	n/a	0.486
Control (n=15)	123 (59.2)	115 (50.9)	7.33 (-5.0- 19.6)	0.221		
Time to completion (mm:ss)						
HIIT (n=18)	11:15 (01:30)	12:34 (01:43)	01:18 (00:34 to 02:02)	0.002*	00:28 (-00:31 to 01.27)	0.34
Control (n=15)	10:53 (02:47)	11:44 (02:55)	00:50 (00:08 to 01:32)	0.022*		
Heart rate peak (bpm)						
HIIT (n=18)	146.5 (29.2)	147.2 (22.3)	0.7 (-7.3 to 8.7)	0.851	n/a	0.864
Control (n=15)	139.9 (19.3)	140 (22.6)	0.3 (-6.9 to 7.5)	0.933		
SPBT (total)						
HIIT (n=18)	12 (0)†	12 (0)†	n/a	0.336	n/a	0.401
(Control n=18)	12 (1)†	12 (0)†	n/a	0.257		
Leg Press (lbs)						

HIIT (n=16)	214 (61.7)	240 (58.4)	25.6 (4.9 to 46.4)	0.019*	n/a	0.904
Control (n=11)	190 (67.7)	214 (71.6)	23.6 (3.9 to 43.3)	0.024*		
BMI (kg/m2						
HIIT (n=18)	27.4 (4.4)	27.7 (4.4)	0.3 (-0.2 to 0.7)	0.240	0.3(-0.3 to 0.9)	0.391
Control (n=14)	26.4 (3.7)	26.4 (3.6)	0.0 (-0.4 to 0.4)	0.979		
Fat free mass (kg)						
HIIT (n=18)	54.8 (10.9)	55.7 (11.5)	0.9 (0.1 to 1.7)	0.28*	-0.4 (-2.4 to 1.7)	0.720
Control (n=14)	47 (12.8)	48.3 (14.2)	1.3 (-0.7 to 3.3)	0.178		

First p-value represents paired T-test results, second p=value represents independent T-test results

4.11.4 Acceptability of PRE-HIIT

The Acceptability Questionnaire was completed by n=36 participants (n=20 in the intervention arm and n=16 in the control arm). Acceptability levels were comparable between groups (0.707) (Figure 4.12).

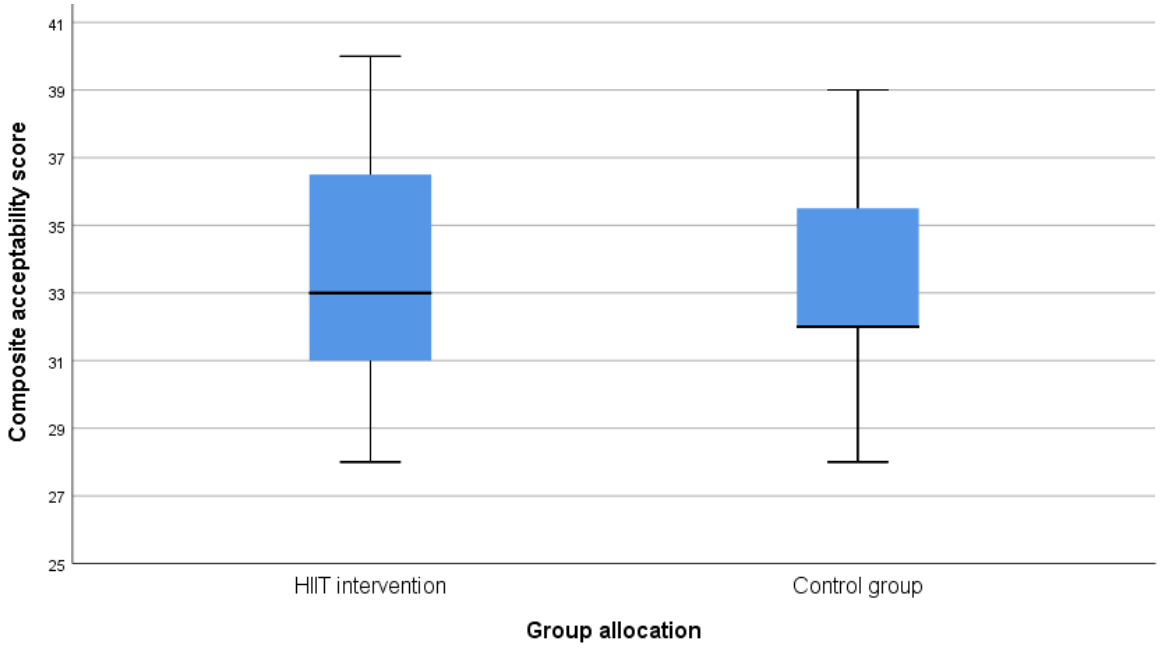

Figure 4.12 PRE-HIIT Composite Acceptability Scores for HIIT and Usual Care

4.11.4.1 Acceptability of Exercise Prehabilitation

Acceptability data from both groups was analysed together to present the overall acceptability of exercise prehabilitation. The mean composite acceptability of exercise prehabilitation was 33.56 (3.4) out of 40. The mean composite acceptability score of exercise prehabilitation using telehealth was 32.92 (3) and 34.7 (3.8) in the in-person group. There was no significant difference between groups (p=0.152, 95% confidence interval (95%CI) -4.3-0.7). Four constructs significantly correlated with the single-item overall acceptability. Intervention coherence (Rs=0.645) and perceived effectiveness correlated moderately (Rs=0.557). Affective attitude (Rs=0.484) and self-efficacy correlated weakly (Rs=0.433) Table 4.10.

The mean composite acceptability score in the HIIT intervention group was 33.75 (3.7). Four constructs had a significant moderate correlation with the single-item overall acceptability construct: intervention coherence (Rs=0.762), affective attitude (Rs=0.684), self-efficacy (Rs=0.630)

and perceived effectiveness (Rs=0.543). The mean composite acceptability score in the control group was 33.31 (3.2). Two constructs, perceived effectiveness and intervention coherence, had a significant moderate correlation with the single-item overall acceptability construct.

Table 4.10 Correlation of the Constructs of Acceptability with Single-item Overall Acceptability

Construct	**All participants**		**HIIT**		**Usual care group classes**	
	Rs	**p-value**	**Rs**	**p-value**	**Rs**	**p-value**
Intervention Coherence	0.645	0.000	0.762	0.000	0.516	0.041
Perceived Effectiveness	0.557	0.000	0.543	0.013	0.566	0.022
Affective Attitude	0.484	0.003	0.684	0.001	0.258	0.334
Self-Efficacy	0.433	0.008	0.630	0.003	0.179	0.508
Burden	-0.15	0.929	-0.213	0.366	0.234	0.384
Ethicality	0.212	0.214	0.64	0.787	0.415	0.110
Opportunity Cost	0.55	0.751	0.031	0.898	0.090	0.739

Data is expressed as Spearman's rank correlation coefficient (Rs)

4.11.5 Telehealth Usability Questionnaire

In total, 20 participants completed the Telehealth Usability Questionnaire (TUQ). The median scores for each subscale are presented in Table 4.11. Results were comparable between groups for five of the six sub-scales. There was a significant difference between groups for satisfaction and future use.

Table 4.11 Median Score for Telehealth Useability Sub-scales

TUQ Sub-scale	All participants	HIIT	Usual care	p-value
Usefulness	15 (1)	15 (1)	15 (2)	0.650
Ease of use	15 (0)	15 (0)	15 (3)	0.143
Interface quality	20 (2)	20 (2)	19 (4)	0.122
Interaction quality	20 (1)	20 (1)	19 (2)	0.203
Reliability	14 (4)	14 (1)	12 (6)	0.162
Satisfaction and future use	20 (0)	20 (0)	19.5 (3)	0.007

Data is expressed as median (interquartile range)

Overall, the participants scored each question regarding the usability of telehealth as poor, acceptable, good or excellent and these results are presented in Figure 4.13. All 'poor' responses related to interface quality and reliability sub-scales. Three questions received a five out of five score by all participants. 95% of participants reported an excellent level of overall satisfaction with telehealth and 5% reported a good level of satisfaction.

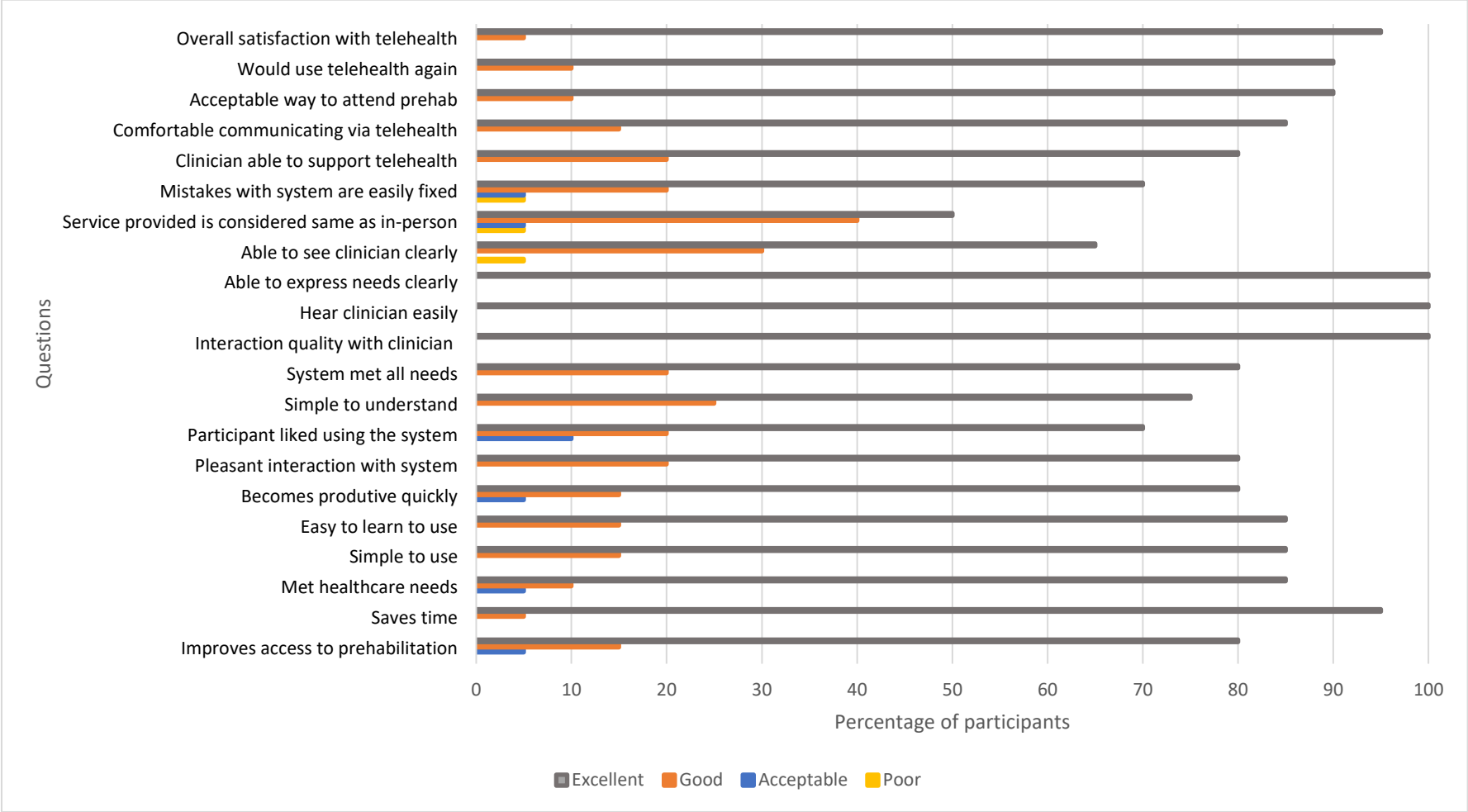

Figure 4.13 Telehealth Useability Questionnaire Results

4.11.6 Postoperative Complications

In total, postoperative complications were collected for 40 (83.3% of total) participants (Table 4.12). Twenty-one patients in the intervention arm and 19 in the control arm experienced postoperative complications. The median first day of mobilising was the same in both groups (postoperative day 1). The median length of stay in critical care (intensive care unit and the high dependency unit) was 6 (8) days in the intervention group and 3 (4) days in the control group (p=0.219). The median length of stay in hospital was 12.5 (28) days in the intervention arm and 9 (7) days in the control (p=0.211). There was no significant difference in CCI scores between groups (p=0.263). The intervention arm had a higher frequency of Grade I and IV complications.

Table 4.12 PRE-HIIT Postoperative Complications Results

Postoperative complications	**Intervention (n=21)**	**Control (n=19)**
Number of patients with complications	19 (90.4%)	13 (69%)
Grade I	5 (23.8%)	0
Grade II	8 (38.1%)	9 (47.4%)
Grade IIIa	2 (14.3%)	2 (15.8%)
Grade IIIb	1 (4.8%)	1 (5.3%)
Grade IV	2 (9.5%)	0
Grade V	0	0
Day first mobilising	1 (2)	1 (1)
Length of stay in critical care	6 (8)	3 (4)
Length of hospital stay	12.5 (28)	9 (7)
CCI	26.7 (18.5)	20 (16.5)

Data is presented as frequency (percentage), mean (standard deviation), median (IQR), POD= postoperative day

4.12 Conclusion & Discussion

High intensity interval training is an emerging preoperative intervention which targets optimisation of patients within short timeframes. This may be of significant value for lung cancer patients, where the short timeframe available limits the potential to enhance cardiopulmonary fitness with moderate intensity exercise. Additionally, HIIT may play a valuable role in the optimisation of oesophageal cancer patients by targeting the preoperative window following completion of neoadjuvant therapy to attenuate the deconditioning effects of treatment. However, the effect of HIIT on cardiopulmonary fitness is not clear and a robust RCT is required to assess the effect. Therefore, Study I examined the feasibility of a hybrid preoperative HIIT RCT in patients scheduled for lung and oesophageal resection, using data from the first 48 participants enrolled on the PRE-HIIT trial.

The overall recruitment rates suggest that recruitment into the PRE-HIIT programme presents a challenge. While a low rate of recruitment onto prehabilitation trials is not unique to PRE-HIIT (27.75%), it represents a difficulty when compared to some prehabilitation trials which achieve significantly higher enrolment (Michael et al., 2021). The reasons reported for declining are consistent with commonly identified reasons in exercise trials in oncology (travel burden n=43 (34.4%), lack of interest n=21 (16.8%) and inability to contact patient n=15 (12%)). (Reynolds et al., 2023). However, COVID-19 may also have had an impact. Recruitment for PRE-HIIT began in May 2021, and for the first ten months public health restrictions due to the COVID-19 pandemic were in place. While this was not specifically identified as a reason for declining to participate, review of recruitment rates suggest it had an impact. Between May 2021-2022, the enrolment rate was 1.5 participants per month. This increased to 3.3 participants per month from June 2022, coinciding with easing of public health restrictions. Another factor that could have influenced recruitment was the existence of an exercise prehabilitation programme offered by SJH. In comparison to other prehabilitation trials, usual care in SJH includes exercise prehabilitation (Blackwell et al., 2020, Licker et al., 2017, Banerjee et al., 2017, Sebio García et al., 2017). Therefore, patients could choose to attend the usual care classes without enrolling in PRE-HIIT. This eliminated the need to travel for assessment while still receiving prehabilitation, the primary reason for not participating in PRE-HIIT (34.4%). The opportunity to prepare for surgery is a significant motivator for participation and travel burden is a well-established barrier therefore, the availability of usual care in SJH may have appealed more to some patients as they still have the opportunity to participate in prehabilitation without the travel burden of PRE-HIIT (Ferreira et al., 2018, Van der Velde et al., 2023, Gillis et al., 2021).

Preoperative HIIT is a feasible and acceptable approach to exercise prehabilitation with high rates of attendance (100% (33)), adherence (92% (38.5)), comparable attrition with moderate intensity exercise (HIIT n=4, control n=3) and no serious adverse events. The HIIT arm had a mean attendance of 9.2 (5.1) sessions and the control arm had a mean attendance of 2.8 (2.9). Several factors may have influenced this difference: one-to-one sessions with a physiotherapist providing individualised support and motivation (Banerjee et al., 2021), potentially greater enjoyment and likeability of HIIT intervention (correlation between affective attitude and single-item overall acceptability Rs=0.684, $p<0.001$) and the flexibility of the HIIT programme. The HIIT intervention provided greater flexibility compared to the control arm, as sessions were scheduled according to patients' availability, accounting for work commitments or hospital appointments and sessions were easily rescheduled. Considering that the large number of hospital appointments and other personal commitments are established barriers to participation in prehabilitation, this increased flexibility may account for this significant difference (Saggu et al., 2022, Knowlton et al., 2020, Leak Bryant et al., 2017, Lee et al., 2022, Ferreira et al., 2018).

Alternative approaches to flexibility were utilised in the control arm, where participants were offered recordings of the classes if they were unable to attend. However only two participants reported completing a recorded exercise class. A mixed-methods systematic review reported that the social aspect of a class, exercising with other people, and encouragement and contact with the supervising healthcare provider are key motivators for participation (Van der Velde et al., 2023). Therefore, while the recordings offer flexibility, patients may not have been as motivated to complete the recordings as they are to attend classes. The higher attendance in the HIIT arm contrasts findings from a recent study examining factors perceived by patients to enhance adherence (Ferreira et al., 2018). This study by Ferreira et al. (2018) reported that the majority of patients were not interested in daily classes and felt a home-based programme with one supervised session per week would be optimal to enhance engagement. However, in PRE-HIIT, adherence and attendance were greater in the HIIT arm, which had five classes per week, compared to the control arm with two to classes per week. In the study by Ferreira et al. (2018), the classes provided were facility-based and travel burden was identified as a significant barrier. Accordingly, it is possible that in PRE-HIIT the option to participate from home, while being supervised via telehealth provides an alternative option and the option may influence this preference. Participants in PRE-HIIT who attended online were satisfied with the telehealth approach; therefore, hybrid classes available daily may provide a superior form of flexibility and enhance patients' ability to attend.

While participants enjoyed preoperative HIIT and felt it was effective at increasing cardiopulmonary fitness, preliminary analysis found no significant difference between moderate

intensity exercise and HIIT in VO_{2peak} (MD 1.16 95%CI -3.8 to 1.4, p=0.359). However, a significant within-group increase was observed for PPO (+15.3 (5.9 to 24.6, p=0.003) in the HIIT arm. When considered in combination with the fact that VO_{2peak} results are preliminary and therefore underpowered, it is reasonable to interpret this increase in PPO as a positive indicator for the effect of HIIT. Furthermore, the limited participant cohort included was exacerbated by attrition, missing T1 assessment, the physiological impact of COVID-19 and equipment failure. The COSMED K4b^2 is a highly sensitive piece of equipment and, despite routine calibration by the research team and standard operating procedures, the O_2 analyser malfunctioned, causing concern as to the validity of five participants' VO_2 results. Cardiopulmonary exercise testing is the gold standard for measuring cardiopulmonary fitness; however, the difficulties experienced with this measure in PRE-HIIT cast doubt on the interpretability of the results generated, highlighting potential challenges with using this outcome measure in trials. Two participants on the HIIT arm (none in the control arm) were affected by COVID-19 infection during the intervention. Data regarding the effect of COVID-19 on functional capacity and cardiopulmonary fitness is emerging. Current literature suggests a significant impact on respiratory and physical function (O'Brien et al., 2022). Furthermore, there was contamination of additional exercise in the control arm with some participants engaging in high volumes of exercise, including a HIIT programme on an assault bike. Controlling for additional exercise outside of the protocol is very difficult, additionally this data is subjective (introducing potential recall bias) and the precise dose of exercise was not calculated. Nevertheless, it can impact the integrity of the cardiorespiratory results, further limiting the interpretation of the effect of HIIT in the intervention arm.

Similarly, results for the effect of HIIT on postoperative complications were underpowered and should be interpreted with caution. There was no significant difference between groups in CCI scores (p=0.263), length of hospital stay (p=0.211) or length of critical care stay (p=219). However, a higher frequency of grade I and III complications were noted in the HIIT arm in comparison to the control.

4.12.1 Limitations

Study I utilised a robust methodological study design, which effectively examined the feasibility and acceptability of the PRE-HIIT trial. Additionally, a significant study strength was recruitment from SJH, a national cancer centre which completes approximately 65% of oesophageal and 50% of lung resections per year and serves patients across the country. However, convenience sampling was used in a single centre which may introduce bias and limit the generalisability of the study results. Secondly, the inclusion of home visits was a strength to the intervention, ensuring the participants took part safely and had confidence using Zoom and the ergometer. However, it placed significant

travel and time burden on the physiotherapist delivering the trial, with distances as great as 550km travelled in one day. Furthermore, only two bikes were available initially, therefore, no more than two participants at a time could be enrolled in PRE-HIIT from home. This resulted in four participants declining to participate due to travel burden prior to the team acquiring two additional bikes, further limiting recruitment. Additionally, the ergometer delivered to the participant was highly specialised to allow provision of the patient specific intervention; therefore, it was an expensive piece of equipment in addition to delivery costs. While these factors are feasible in a research setting, home visits and provision of a highly specialised ergometer may not be feasible in a clinical setting. Finally, data for additional exercise completed outside of planned sessions was collected. Nevertheless, the mode of data collection was subjective and open to recall bias. Alternative options, such as an activity monitor, which would capture an exact dose of additional exercise completed should be considered.

4.12.2 Conclusion

In conclusion, the PRE-HIIT trial examining a hybrid preoperative HIIT intervention is feasible and acceptable among lung and oesophageal cancer patients. However, recruitment onto the PRE-HIIT trial, completion of all assessments and interpretation of VO_{2peak} results may represent a challenge.

Chapter 5 Participants Experiences Preparing for Surgery on the PRE-HIIT Trial

This chapter describes the methods, results and discussion of Study II. This study examines patients' perspectives and experiences preparing for surgery on the Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus (PRE-HIIT) trial. As discussed in Chapter 4, PRE-HIIT is a randomised controlled trial (RCT) examining the effect of a hybrid preoperative HIIT programme on cardiopulmonary fitness. Chapter 4 described the feasibility of the trial, examining recruitment potential, intervention and outcome measures suitability, and adverse events. Participants' perspectives are a valuable component of a feasibility analysis and must be carefully assessed, as they may provide important insights into issues which require amendment. These matters are addressed in Chapter 5.

The preoperative phase is associated with significant stress and anxiety for patients, and as an added burden, a cancer diagnosis is associated with a significant number of hospital appointments. Furthermore, high intensity interval training (HIIT) is a demanding intervention, it is therefore crucial to understand patients' experiences on the trial to determine how they feel about the intervention and explore areas which may enhance their experiences.

5.1 Aim and Objectives

The primary aim of this study was to explore the perspectives and experiences of patients on the PRE-HIIT trial preparing for surgery.

Study specific objectives:

- To explore patients' experiences on the PRE-HIIT trial in preparation for lung and oesophageal resection.
- To explore the acceptability of the PRE-HIIT trial in patients scheduled for lung and oesophageal resection.
- To explore patients' motivation for participating in the PRE-HIIT trial.

5.2 Methods

5.2.1 Sampling

Utilising a convenience sampling technique, all participants in the PRE-HIIT study received a Participant Information Leaflet and were invited to undertake a semi-structured interview at their post-intervention (T1) assessment (13). As this was an exploratory study, there was no set sample

size and the final sample size was determined by data analysis. Data was collected until a rich data set which captured the experiences of participants was identified.

5.2.2 Procedure

Interviews were completed by a research assistant not involved in the delivery of the PRE-HIIT intervention. This approach ensured participants were able to discuss their experiences without being influenced by the presence of the physiotherapists with whom they may have established a working relationship. The interviews took place in-person in the Clinical Research Facility (CRF) in St James's Hospital (SJH), following T1 assessment or by telephone if a participant was unable to attend T1 assessment. All participants provided written informed consent (14).

5.2.2.1 Semi-structured Interview Schedule

The semi-structured interview schedule consisted of 14 broad questions (15). Questions were developed to explore patients' experiences of PRE-HIIT, with several questions reflecting acceptability as per the Theoretical Framework of Acceptability (TFA), experiences on the trial and motivation for participation (Sekhon et al., 2017). All questions were reviewed by senior researchers with experience in qualitative research (Emer Guinan (EG) and Linda O'Neill (LON))

5.3 Data Analysis

Audio files recorded from semi-structured interviews were transcribed verbatim and pseudonymised. Transcripts were imported into NVivo 20 qualitative data analysis management software (QSR International, Melbourne, Australia). Transcripts were inductively coded independently by two reviewers, who coded either 100% (ES) or 40% (LON). Data was analysed following an inductive thematic approach involving data familiarisation, coding of data, searching for themes, reviewing themes, defining and naming themes, and producing the report. This process is described in Section 3.3.4.

5.4 Results

In total, 26 participants completed semi-structured interview. Sixteen (61.5%) of the 26 participants had been randomised to the HIIT arm and 10 (38.4%) to the control group (Table 5.1). The mean age in the HIIT arm was 61.7 (11.6) years and 60.2 (8.6) years in the control arm. Both groups consisted of 50% oesophageal cancer and 50% lung cancer cases. More men than women completed the interview in the HIIT group. Interview length ranged from 4 minutes and 30 seconds to 26 minutes and 15 seconds.

Table 5.1 PRE-HIIT Semi-structured Interview Participant Demographics

Demographics	**Participants (n=26)**
Age (years)	61.1 (11.6)
Cancer type	
Oesophageal	13 (50%)
Lung	13 (50%)
Gender	
Male	16 (61.5%)
Female	10 (38.5%)

Data is expressed as mean (standard deviation) or frequency (percentage)

Three main themes identified were: motivations for participation, a challenging but beneficial intervention and enhancing accessibility of the programme. Within each theme, two or three sub-themes were identified (Table 5.2).

Table 5.2 Qualitative Results PRE-HIIT

Construct / Theme	**Code**	***Quote***
Motivations for participation	Aid with preparation for surgery	*'Well, I suppose two things. From the physical point of view, I hoped that I would become stronger, especially for my lungs, for breathing with the postop in mind. Secondly, I hoped that it would be reassuring and help me psychologically going forward'* (PRE017)
	Altruism	*'So, I just know how important these things are really. You know I think that research is the key to progress'* (PRE044)
	Valued recommendation by the surgical team	*'I was also told by one of the doctors when I was first given the information on it. That it would help with the operation'* (PRE045)
A challenging but beneficial intervention	Enhanced physical fitness	*'I have gained so much from it. I feel better. I feel stronger. I feel more normal'* (PRE012)
	Positive for mental health during challenging time	*'I was doing something with my health that I was in control and you know proactive as opposed to being as passenger or just a patient'* (PRE008)
Enhancing accessibility to prehabilitation	Hybrid delivery	*'Like, everyday travelling. No, that wouldn't have suited me. And I probably wouldn't have done it'* (PRE043)
	Support of physiotherapy team	*It was the access to them, the ease of access, and the fact that you were encouraged to participate no matter what level* (PRE012)

	Flexibility of the programme	*You know, there was good flexibility, cooperation, and responsiveness and mmm yeah certainly a solution focused attitude from the team* (PRE008)

5.4.1 Motivations for Participation

Three main motivations for participation in PRE-HIIT were identified: valued recommendations from surgical team, help with preparation for surgery and altruism.

5.4.1.1 Valued Recommendations from the Surgical Team

Advice and education from the patients' surgical team were identified as key factors in the patient's motivation to take part. Participants highly valued the viewpoints of their surgical team and understood from discussion with their surgeon that participation in prehabilitation would *'help with the operation'* and that it was an important step in the preparation for surgery. Therefore, following recommendations from their surgeon, participants were highly motivated to take part '*the doctor said to me the fitter you are the better the recovery so that was a big push for me to do it'* (PRE048).

5.4.1.2 Aid with Preparation for Surgery

A second motivation identified was the opportunity to prepare for surgery '*I thought that it might actually build you up a bit before the surgery or to feel like you know, you are physically able for surgery'* (PRE036). Participants felt that by participating in PRE-HIIT they had a chance to prepare both physically and psychologically for surgery '*from the physical point of view, I hoped that I would become stronger, especially for my lungs, for breathing with the postop in mind, Secondly, I hoped that it would be reassuring and help me psychologically going forward*' (PRE017). Additionally, patients felt that participation prepared them for the postoperative journey giving them insight - *I'm going to go back after surgery basically to square one* (PRE012) and motivation to tackle the postoperative journey '*I'm actually kinda looking forward now, saying what do I need to do after the op?'*(PRE009).

5.4.1.3 Altruism

Altruism was additionally identified as a key motivator for taking part. Participants understood the importance of research and felt strongly that their participation in PRE-HIIT may have benefits for individuals in the same position in the future *'so, I just know how important these things are really. You know I think that research is the key to progress'* (PRE044).

5.4.2 A Challenging but Beneficial Intervention

Participants, particularly those randomised to HIIT, felt that PRE-HIIT was physically challenging *'every day was very tough, it didn't get any easier*' (PRE043). While some participants were confident about participation, others, particularly those randomised to the HIIT arm, were initially apprehensive '*I was apprehensive about it because when I was in here for my assessment, I said*

this looks like its really really tough' (PRE048). However, participants confidence in taking part and completing the programme grew throughout '*well at start I wasn't very confident, but then as it went on I got more confident and I felt like doing it and you know I felt a lot better about myself*' (PREO28). Overall participants enjoyed taking part in PRE-HIIT and they felt it was an achievable and positive experience. They felt the programme was beneficial in the lead-up to surgery *'all positive, breathing, happiness, fitness going up. That's about it I suppose. Happy enough for it*' (PRE024). Two primary benefits identified were enhanced fitness and benefits for mental health during a challenging time.

5.4.2.1 Enhanced Physical Fitness

Overall, a strong sense that participation in prehabilitation resulted in increased fitness was identified. Participants, particularly those in the HIIT arm, felt that their fitness had improved significantly *'I personally feel much fitter now. More confident. That's being the truth*' PRE030, despite the short timeframe available. Within the participants in the HIIT arm, a sense that HIIT was an effective and efficient way of increasing their cardiopulmonary fitness '*within the two weeks that I was doing it I feel like I've improved*' (PRE045) stands out.

5.4.2.2 Benefits for Mental Health During a Challenging Time

Overall, participants felt that PRE-HIIT offered psychological benefits at a challenging time *'it makes you feel a bit - gives you a bit of a bounce in your step or something'* PRE013. Two elements of PRE-HIIT were identified as playing a primary role in the psychological support: the established benefits of exercise on mental health and a role in their health returning. Participants felt the benefits of exercise directly on their mental health *'actually, it was very good for it. Because exercise is good for stress'.* They felt that not only did exercise help to manage stress, but it was '*very uplifting for your mood*' (PRE012) and provides *'a sense of purpose*' (PRE012). Secondly, a sense that participation in PRE-HIIT gave patients a role in their recovery was identified '*I was doing something with my health that I was in control and you know proactive as opposed to being as passenger or just a patient*' (PRE008). Across both control and HIIT arms, prehabilitation offered participants a stake in their health returning and insight into their role in postoperative exercise self-management *'I've sort of – makes me realise that exercise is important (laughs) so I think there's a greater chance that I'll continue doing exercise afterwards*' (PRE013). A sense that many patients felt that they were playing their part, providing a sense of control was identified '*even, if I had difficulties after I did something that can help me. There's nothing else I can do. So, I think it will be a good thing. And I am glad I did it'* PRE032.

5.4.3 Enhancing Accessibility to Prehabilitation

Accessibility of the programme was highly valued by participants. Three main factors which enhanced accessibility of PRE-HIIT were identified: hybrid approach, support of the physiotherapy team and flexibility of the programme.

5.4.3.1 Hybrid Delivery of Exercise Prehabilitation

The hybrid nature of PRE-HIIT gave participants the opportunity to select the mode of delivery which would suit them best. For some participants, the online approach eliminated the travel burden and provided the opportunity to participate where they may not have done so previously '*Like, everyday travelling. No, that wouldn't have suited me. And I probably wouldn't have done it'* (PRE043). While connecting to telehealth was identified as a challenge for some participants, once this challenge was overcome with education and guidance from the team, participants found it easy to use and time-efficient '*The best possible thing about it was that it was online though…very convenient. That was the single biggest factor*' (PRE044). For others the in-person approach provided a social aspect, motivation and a sense of discipline to complete the full session *'I would have not have been able to do that on my own, or without a mentor, and the 1-to-1 mentor in here was great'* (PRE030).

5.4.3.2 Support of the Physiotherapy Team

Participants valued the support, information, and motivation that the physiotherapy team provided, and these factors enhanced their ability to participate. A clear introduction to the programme was valued by participants '*That's key to it, I think. The explanation, explaining the thing in advance and as you go through explaining what we were going here now. That's all. That's… you couldn't really improve on that because it's going very well'* (PRE009). Participants appreciated the clear communication and positivity that the team provided '*Well, talking to the staff. They were very good. Very, very helpful. Really pushing you'* (PRE014). This motivation and support provided by the physiotherapists across both groups was identified as an important factor to enhance adherence '*The fact that someone was there, that was the big thing to complete it'* (PRE043).

5.4.3.3 Flexibility of the Programme

The flexibility of both programmes was identified as a key facilitator for participants. While participants prioritised participation in PRE-HIIT, the time flexibility of the programme, both HIIT and control was important to participants to enable them to become involved and attend other commitments (family, work etc.). For participants in the HIIT arm, the flexibility of session timing was a valuable factor in enhancing participation '*They were able to facilitate me, there was no problem at all. So, that was very helpful'* (PRE043). Some participants were still working; therefore,

the flexible approach allowed them to continue to work and participate in PRE-HIIT. In the control arm, the opportunity to replay recordings of classes when they were unable to attend in person offered the chance to complete the session regardless of other commitments *'The good thing about them programmes were is that if I did miss the class that morning, I could've repeat it in the evening. So, it was in my own time and schedule'* (PRE034). Overall, participants had other commitments and while participating in PRE-HIIT took time, the flexibility of the programme allowed them to do both.

5.5 Discussion

Exercise prehabilitation is an emerging intervention which targets cardiopulmonary fitness prior to surgery. As the intervention evolves, it is essential to investigate patients' perspectives and experiences to provide valuable insights into their motivation in engaging with prehabilitation. This may be of particular value when examining HIIT interventions, due to their intense nature. Therefore, this study explored patients' experiences while preparing for surgery through exercise prehabilitation and explores their motivations for participation. This information is crucial in understanding their journey and can serve as a guide for future intervention development and integration into a clinical pathway.

Participants felt empowered by the opportunity that prehabilitation provided to prepare for surgery. Participants perceived an improvement in fitness, especially in the HIIT arm, giving them a sense of actively contributing to their recovery by physically preparing their bodies. Additionally, it prepared them mentally and gave them a new insight into the postoperative journey. Preparedness for surgery has been identified as a valuable factor for patients and encompasses factors beyond physiological preparation (Beck et al., 2022). This sense of preparedness was reported to give patients a sense of security and control during a time characterised by lack of control, a sentiment mirrored by participants in PRE-HIIT. Regaining a sense of control has been identified as a significant motivator for participation in prehabilitation and was highly valued by participants in PRE-HIIT (Banerjee et al., 2021, Ferreira et al., 2018). This suggests that the benefits associated with prehabilitation extend far beyond physical fitness. This is an important finding, as enhancing patients physically and psychologically are key pillars of prehabilitation (Durrand et al., 2019). Overall, it is clear that participants felt that taking part in the intervention impacted not only physical preparedness but also psychological well-being.

Receiving recommendations to take part in exercise prehabilitation from the treating surgeon is a multi-faceted motivational factor. Not only is the recommendation highly valued by patients, a factor which has been consistently identified as a motivator in prehabilitation patients, but also it

influences patients' understanding and intrinsic motivation to engage in preoperative preparation (Banerjee et al., 2021, Matthew et al., 2022, Van der Velde et al., 2023). This suggests that the information and how it is conveyed to the patients by the surgical team is an important factor in encouraging patient participation in prehabilitation. This has similarly been identified in other preoperative cohorts where patients value up to date information which is delivered in a comprehensive and empathetic manner (Cuijpers et al., 2022). However, exercise prehabilitation is an emerging exercise intervention in oncological care and while some surgical teams may have a strong knowledge base to advise and refer patients, this may not be true in all clinical settings. In a 2022 scoping review, a lack of knowledge amongst oncological healthcare professionals regarding exercise across the cancer care continuum was identified as a significant barrier to the integration of exercise into oncological care (Kennedy et al., 2022). Areas of uncertainty were the efficacy of exercise across the cancer care pathway and recommended guidelines, safety and uncertainty about how to address behavioural change (Kennedy et al., 2022). Therefore, educating the referring clinicians may be valuable in supporting patient engagement and motivation to participate.

Participants appreciated the opportunity to take part in prehabilitation in a way that was meaningful and easily accessible to them. This depended on personal circumstances such as digital literacy, distance from the hospital and personal preference. This highlights the importance patients place on accessible patient-centred care, which was accessible regardless of their circumstances. Studies have sought to define barriers to exercise prehabilitation, consistently identifying travel burden, scheduling challenges, illness and intrinsic motivation (Kennedy et al., 2022, Van der Velde et al., 2023). However, results from this study indicate that barriers are specific to individuals and what acts as a barrier to some is in fact a facilitator to others. Despite the same barriers being identified across the literature, no one barrier has been identified in 100% of participants. This is similar to results of studies in cardiac rehabilitation, where patients' preferences varied by age, gender, social situation, distance to hospital and access to transportation (Liu et al., 2023). This is a valuable finding and highlights the importance of offering diverse options to cater for various patient needs.

5.6 Limitations

Despite a robust collection and analysis of qualitative data, including completion of the interviews by a third party not involved in delivery of the intervention, double coding and consensus decisions with a third reviewer when discrepancies arose, some limitations exist. The purposeful sampling approach utilised allowed in-dept and relevant analysis of participants experiences, however it may also have introduced selection bias. This may have led to an overrepresentation of patients who

enjoyed and felt the benefits of exercise prehabilitation. Additionally, the results generated have reduced generalisability as they are focused on participants in the PRE-HIIT trial, therefore they may not be easily applicable to other prehabilitation programmes which do not have the same protocols. Therefore, assessment of acceptability across all prehabilitation types would enhance generalisability of results. Finally, as per PRE-HIIT inclusion and exclusion criteria, participants who had significant co-morbidities were excluded. However, this may be the cohort who may face the most challenges to participation in prehabilitation and future research should expand to focus on this cohort, providing opportunity to explore their unique insights.

5.7 Conclusion

In conclusion, participants valued and enjoyed participation in and the benefits of the PRE-HIIT trial. Key factors to facilitate participation identified were recommendations from the surgical team, support from the physiotherapy team and accessibility through multiple mediums. However, an in-depth analysis of acceptability of all prehabilitation types would enhance generalisability of findings.

Chapter 6 The Acceptability of Exercise Prehabilitation Among Key Stakeholders in Oncological Resection

6.1 Introduction

This chapter describes Study III, an exploratory mixed-method study examining the acceptability of exercise prehabilitation as a broad concept amongst key stakeholders. The aim of exercise prehabilitation is to increase preoperative fitness with the goal of reducing postoperative complications, hospital length of stay and healthcare costs and enhance health-related quality of life (HR-QL) (Silver, 2014, Durrand et al., 2019). Development of exercise prehabilitation services and data on its effectiveness continues to emerge. However, its implementation into practice faces challenges due to the timing of the intervention, the clinical populations involved and the inherent difficulties in establishing new services (Waterland et al., 2021). To facilitate integration into a clinical pathway, factors which influence implementation must be considered throughout intervention development (Proctor et al., 2011, Kennedy et al., 2022). Acceptability of an intervention is a key factor with elements of acceptability evident across multiple implementation frameworks (Damschroder et al., 2022, Gaglio et al., 2013, Proctor et al., 2011). Acceptability can be defined according to the Theoretical Framework of Acceptability and its evaluation throughout the stages of intervention development may enhance future uptake of a complex intervention such as exercise prehabilitation (Proctor et al., 2011, Sekhon et al., 2017).

The influence of relevant stakeholders on the successful implementation of a service has been well established (Proctor et al., 2011, Concannon et al., 2019, Damschroder et al., 2022). Different stakeholder groups have different opinions and priorities, and inclusion of all stakeholders in research is vital to maximise impact and understanding. Assessment of acceptability across different stakeholder groups will identify facilitators and barriers within each group, enabling design of more accessible and effective services (Proctor et al., 2011). Therefore, the primary aim of this study was to examine the acceptability of exercise prehabilitation among key stakeholders relevant to surgical prehabilitation and included patients, their families and healthcare providers (HCPs).

6.2 Study Aims and Objectives

The overall aim of Study III was to explore the acceptability of exercise prehabilitation before cancer surgery among key stakeholders including patients, family members and healthcare providers (HCP). The study specific objectives were:

- To develop a specific questionnaire to examine the acceptability of exercise prehabilitation.
- To explore the acceptability of exercise prehabilitation among patients and their families.
- To explore the acceptability of exercise prehabilitation among healthcare providers.

6.3 Methods

6.3.1 Study Design

Study III was a mixed-methods study examining the acceptability of exercise prehabilitation amongst key stakeholders namely i) patients and their family members and ii) health care professionals. Data was collected quantitively by means of the Acceptability Questionnaire and qualitatively through semi-structured interviews.

6.3.2 Ethical Approval

Full ethical approval was granted by Trinity College, Faculty of Health Sciences Research Committee in June 2021 (Ref:210202) and by the Beacon Hospital Research Ethics Committee in November 2022 (Ref: BEA0197) (16). All procedures performed in Study III were in accordance with the 1964 Helsinki declaration and its later amendments. All the research team involved in Study III completed Good Clinical Practice training.

6.3.3 Sampling and Recruitment

A convenience sampling approach was used to recruit stakeholders in oncological resection belonging to one of three groups:

- Patient Group: Patients who were scheduled for or had undergone oncological resection in the last year, referred to subsequently as ‘patients’.
- Family Members Group: Individuals whose relatives were scheduled for or had undergone oncological resection in the last year, referred to subsequently as ‘family members’.

- Healthcare Providers Group: Healthcare providers including any members of the healthcare system involved in the care of surgical cancer patients, referred to subsequently as 'healthcare providers' (HCPs).

Stakeholders were excluded if they were:

- Under 18 years old.
- Non-English speaking.

Participants were invited to participate through multiple channels. Invitation emails were circulated to professional bodies (including The College of Anaesthesiologists of Ireland, The Irish College of General Practitioners, The Irish Society of Chartered Physiotherapists) (18), cancer charities (including The Irish Cancer Society, Marie Keating Foundation, The Oesophageal Cancer Fund) and Community Cancer Support Centres in Ireland (19). The survey was circulated online through various social media platforms including Twitter (X) and Instagram (17). A link to the online survey and Participant Information Leaflet was provided (20). Paper versions of the survey and Participant Information Leaflet were distributed through gatekeepers at surgical oncology clinics and physiotherapy services at St James's Hospital and Beacon Hospital in Ireland (20 & 21). Informed consent and was integrated into the opening section of the survey and was a requirement to proceed with survey completion. The cross-sectional survey concluded with an invitation to provide contact details and participate in a semi-structured interview. Participants provided a second written informed consent prior to completing the interview (22).

6.3.4 Development of Data Collection Tools

6.3.4.1 Measuring Acceptability Using the TFA

Acceptability was measured quantitatively and qualitatively using questionnaires and interview guides underpinned by the TFA. As discussed in Section 3.2.6.2.5, the generic Acceptability Questionnaire is an adaptable survey that comprises eight Likert Scale questions, with seven questions each reflecting one construct of acceptability and one single-item question reflecting overall acceptability (Sekhon et al., 2022). Each question is scored out of a possible five, where one represents low acceptability and five represents high acceptability, with a total composite acceptability score (the sum all constructs) of 40. Correlating each construct with the single-item overall acceptability enables the identification of factors influencing acceptability. This analysis pinpoint areas of both high and low acceptability. Semi-structured interviews, underpinned by the

framework, allow an in-depth analysis of each construct. A mixed-methods approach to assessing acceptability, underpinned by the TFA therefore allows for the triangulation for data providing a rich measure of the acceptability of an intervention.

6.3.4.2 Adapting the Generic Framework of Acceptability Questionnaire

The generic TFA Questionnaire was adapted to focus on exercise prehabilitation (Sekhon et al., 2022). The adapted version was reviewed by two experienced exercise prehabilitation researchers (EG and JH) and by the TFA developer (MS) to ensure the TFA constructs were both relevant and accurately adapted. Consensus was reached to finalise the wording for each question. Demographics including age, surgical timeframes (patient and family group), years of experience (HCPs), experience with exercise prehabilitation and habitual exercise (all stakeholders) were collected to allow identification of demographic trends. To ensure standardised baseline understanding of exercise prehabilitation, participants received information on exercise prehabilitation in advance of completing the survey (discussed in Section 6.3.4.4) (Sidani et al., 2009). Following an interim analysis of data from 112 participants, an additional question was included to optimise clarity regarding the effectiveness of exercise prehabilitation. The new question was reviewed by two patient representatives to ensure readability.

6.3.4.3 Semi-structured Interviews

The semi-structured interview schedule was developed using the same approach as the survey. An initial draft schedule with at least one question per construct of acceptability was devised. The draft was reviewed by EG, JH and MS, amendments were discussed and modified through consensus. The final interview guide consisted of eight questions, each reflecting one construct of acceptability in addition to five questions on demographics. Interviews were completed by telephone or videocall and recorded using a digital audio recorder.

6.3.4.4 Exercise Prehabilitation Educational Information

The acceptability of an intervention is directly impacted by participants' understanding of the intervention. Therefore, participants were provided with standardised educational information regarding exercise prehabilitation prior to completion of the questionnaire comprising either a short education animation or an educational infographic (Figure 6.1). To ensure high levels of comprehension and clarity of the information provided, the same format applied to informed consent was utilised, i.e. a clear description of the nature of exercise prehabilitation, its purpose, the components comprising it and any risks associated (Sidani et al., 2009). All information provided was based on the published literature in exercise prehabilitation.

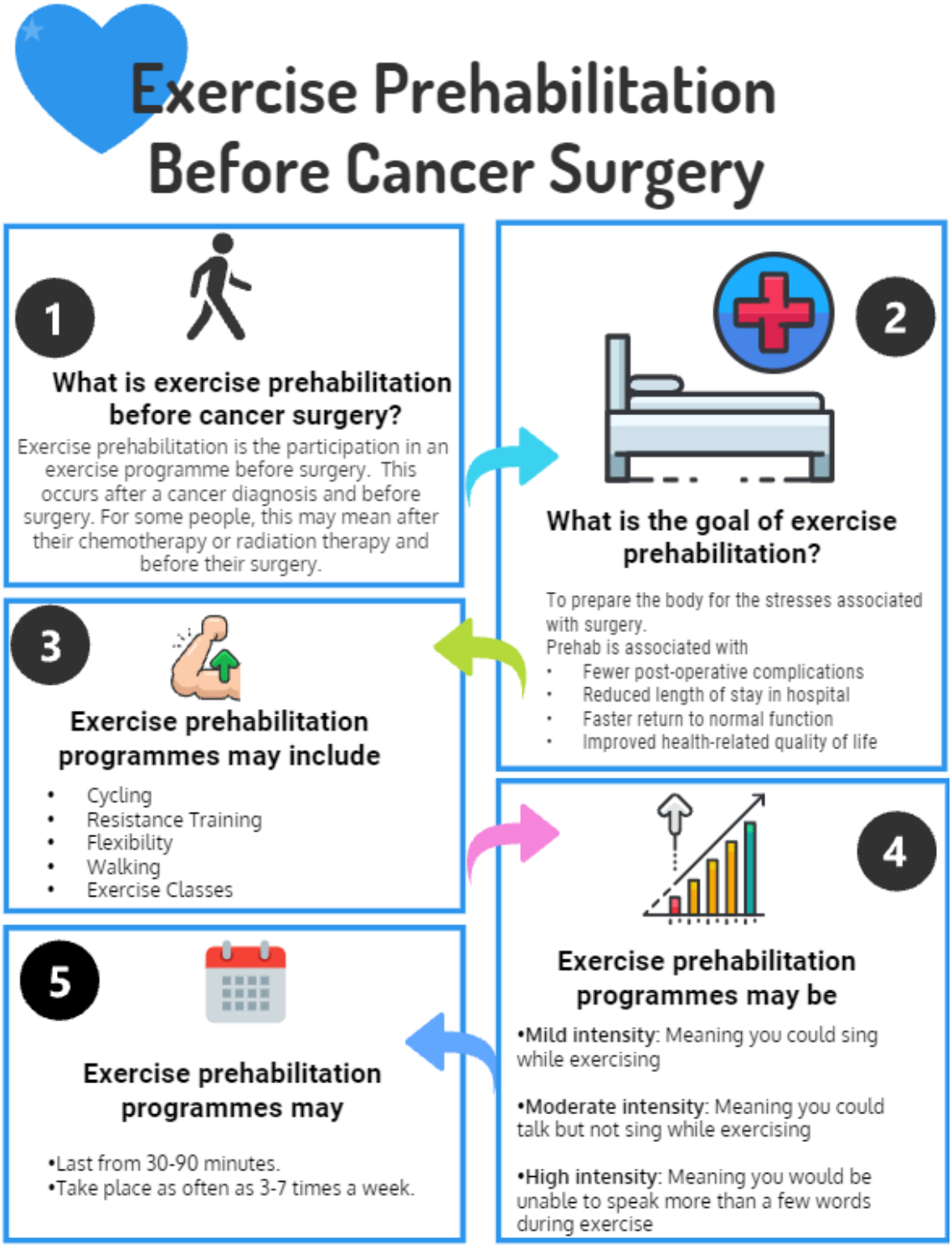

Figure 6.1 Exercise Prehabilitation Infographic

6.3.5 Participant Characteristics

Standardised demographics were collected as appropriate for each stakeholder group (Table 6.1).

Table 6.1 Demographics Collected for Study III

Demographic	Group applicable
Patients and family members groups	Age Cancer types Neoadjuvant chemotherapy and/or radiotherapy Preoperative activity levels Time point in cancer care i.e. preoperative or post operative
Healthcare providers	Years of clinical experience Occupation
All stakeholders	Current activity levels Experience with prehabilitation Experience with exercise prehabilitation

6.4 Quantitative Data Analysis

Data analysis was completed using IMB SPSS 26. Within-group demographics for each stakeholder group was presented as frequency (percentage) for categorical variables, and mean and standard deviation (SD) for continuous variables. Data was analysed for distribution using visual analysis of quartile-quartile (Q-Q) plots, histograms, and Shapiro-Wilk test. Analysis of variance was completed using Levene's test.

Data for the composite acceptability score is presented as median and interquartile range (IQR) across stakeholder groups and within stakeholder groups. Boxplots were used to present median and IQR across stakeholder groups and within stakeholder groups. Between group differences for the composite acceptability score was analysed using ANOVA. Correlation between each construct and the single-item overall acceptability construct was completed using Spearman's Rank Correlation. Significance was set as $p< 0.05$.

6.4.1 Subgroup Analysis

Difference in composite acceptability within the patient and family members groups as one group was compared by timeframes around surgery, exercise levels and experience with exercise prehabilitation. Difference in composite acceptability within the HCP group was compared based

on exercise levels and experience with exercise prehabilitation. Association between composite acceptability score and years of experience (HCPs) and age (patients and family members groups) was noted.

6.5 Qualitative Data Analysis

Audio files were transcribed verbatim and pseudonymised. Transcripts were imported into NVivo 20 qualitative data analysis management software (QSR International, Melbourne, Australia). Transcripts were coded independently by two reviewers, who coded either 100% (ES) or 50% (LB) of transcripts and a subset by MS to ensure accurate mapping onto the framework. Following data familiarisation, data was analysed using a hybrid (deductive and inductive) thematic analysis process. Firstly, using a deductive approach transcripts were coded into seven predetermined themes based on the seven constructs of acceptability. Secondly, data within each deductive theme was analysed using an inductive thematic approach to identify a range of related topics (codes) within each TFA based theme. Codes were agreed between E.S and L.B with any differences resolved by a third-party (E.G), quotes were selected to represent each code.

6.6 Results

Participant demographics are presented in Table 6.2. Between June 2021 and April 2023, n=244 participants completed the questionnaire and n=31 participated in semi-structured interviews. Of questionnaire respondents, n=100 (41%) were HCPs, n=101 (41.4%) were patients and n=39 (16%) were family members.

6.6.1 Patient Group

In total, n=101 patients participated in the questionnaire with a mean age of 54.9 (13.7). The majority had received adjuvant or neoadjuvant treatment n=60 (59.4%). Breast cancer was the most common cancer type n=38 (38%). Most patients had undergone surgery n=67 (66.4%) at the time of questionnaire completion and n=30 (29.7%) were awaiting surgery. Only n=22 (21.8%) had participated in exercise prehabilitation, although 50.5% of patients reported achieving 60-150 minutes of exercise per week before surgery. At the time of completing the questionnaire, n=47 (46%) of patients reported achieving 60-150 minutes of exercise per week.

Twelve patients took part in the semi-structured interview, breast cancer was the most common diagnosis n=5 (41.6%) and only one participant had taken part in exercise prehabilitation.

6.6.2 Family Members Group

In total, n=39 family members (whose relatives were scheduled for or had undergone oncological resection in the last year) participated with a mean age of 41.2 (15.1). The majority of the

participants in the family member group had relatives who had undergone surgery already at the time of questionnaire completion n=36 (92.3%), and n=29 (74.4%) had received neoadjuvant or adjuvant therapy, the most common cancer diagnosis was breast cancer n=10 (25.6%). Ten participants reported that their relative had participated in exercise prehabilitation and 16 (41%) reported that their relative was active (60-150 minutes of exercise per week) prior to surgery.

Five family members participated in the semi-structured interview, only one participants' relative had participated in exercise prehabilitation and all had different diagnoses.

6.6.3 Healthcare Providers

In total, n=100 healthcare providers participated in the questionnaire, n=37 (37%) were doctors. This was comprised of a combination of surgeons n=9 (9%), anaesthetists n=3 (3%), and physicians n=25 (25%). The balance was made up of nurses n=26 (26%), allied health professionals n=32 (32%), hospital management n=3 (3%) and n=2 (2%) did not report their occupation. Healthcare providers had a mean of 10 (12) years' experience. Of the 100 participants, n=37 (37%) had experience with exercise prehabilitation. The majority n=83 (83%) of HCPs were achieving between 60-180 minutes of exercise per week.

Fourteen HCPs participated in the semi-structured interviews: n=5 (36%) were anaesthetists, n=5 (36%) were physiotherapists, n=3 (21%) were general practitioners and n=1 (7%) was an intensive care physician. Healthcare providers who completed the interviews had a mean 21 (12.6) years' experience and n=5 (36%) had direct experience with exercise prehabilitation. Of the five who had experience with exercise prehabilitation, n=4 were physiotherapists working in the area and n=1 was a consultant anaesthetist.

Table 6.2 Participant Demographics for Survey and Semi-structured Interview

Total Sample		**Survey respondents (n=244)**	**Semi-structured interview participants (n=31)**
Stakeholder group	Healthcare provider Patient Family member	100 (41%) 101 (42%) 39 (16%)	14 (45%) 12 (38%) 5 (16%)
Patients and Family Members Demographics		**Survey respondents (n=140)**	**Semi-structured interview participants (n=17)**
Age (years)	Patient Family member	54.9 (14) 41.2 (15)	n/a n/a
Patient and family members cancer type	Breast Lung Colorectal Uterine Gastric Ovarian Prostate Other	49 (35%) 21 (14.8%) 11 (7.7%) 8 (5.6%) 6 (4.2%) 7 (4.9%) 5 (3.5%) 35 (25%)	5 (29%) 1 (6%) - 1 (6%) 2 - 1 (6%) 8 (47%)
Patient group: habitual exercise	Inactive <60 minutes 60-150 minutes	19 (14%) 64 (45%) 47 (34%)	- 8 (47%) 9 (52%)

Patient group: timeframe around surgery	Waiting on surgery <6 months post-op 6-12 months post-op	30 (29.7%) 35 (34.7%) 32 (31.7%)	3 (25%) 3 (25%) 6 (50%)
Patient group: experience with exercise prehabilitation	Yes No Not reported	22 (21.8%) 77 (76.2%) 2 (2%)	1 (6%) 16 (94%) -
Patient group: preoperative exercise levels	Inactive <60 minutes 60-150 minutes	12 (11.9%) 36 (35.6%) 51 (50.5%)	5 (41.6%) - 6 (50%)
Family members group: relatives' timeframe around surgery	Waiting on surgery <6 months post-op 6-12 months post-op	2 (5%) 16 (41%) 20 (51%)	1 (20%) 1 (20%) 3 (60%)
Family member group: relatives' exercise prehabilitation	Yes No	10 (26%) 29 (74%)	1 (20%) 4 (80%)
Family member group: relatives' preoperative exercise levels	Inactive <60 minutes 60-150 minutes	8 (20.5%) 14 (35.9%) 16 (41%)	2 (40%) - 3 (60%)
Family member group: participants current exercise levels	Inactive <60 minutes 60-150 minutes	6 (15.4%) 8 (20.5%) 25 (64.1%)	2 (40%) - 3 (60%)
Healthcare Providers		**Survey respondents (n=100)**	**Semi structured interview participants (n=14)**
Years of experience		10 (12)	21 (12.6)

Occupation	Surgeon	9 (9%)	-
	Anaesthetist	3 (3%)	5 (36%)
	Doctor	25 (25%)	4 (28%)
	Nurse	26 (26%)	-
	Physiotherapist	25 (25%)	5 (36%)
	Dietitian	5 (5%)	-
	Occupational Therapist	2 (2%)	-
	Hospital Management	3 (3%)	-
	Other	2 (2%)	-
Experience with exercise prehabilitation	Yes	37 (37%)	5 (36%)
	No	63 (63%)	9 (64%)
Habitual exercise habits	Inactive	1 (1%%)	-
	<60 minutes	16 (16%)	5 (35%)
	60-150 minutes	84 (83%)	9 (64%)

Data is expressed as frequency (percentage) and mean (standard deviation), <=less than, post-op =postoperative

6.6.4 Composite Acceptability Score

The median composite acceptability score across all stakeholder groups was 29 (4) out of a maximum of 40 (Figure 6.2). There was no significant difference in composite acceptability score between stakeholder groups (HCPs 29 (4), patients 29 (6), family members 28 (5), p=0.466).

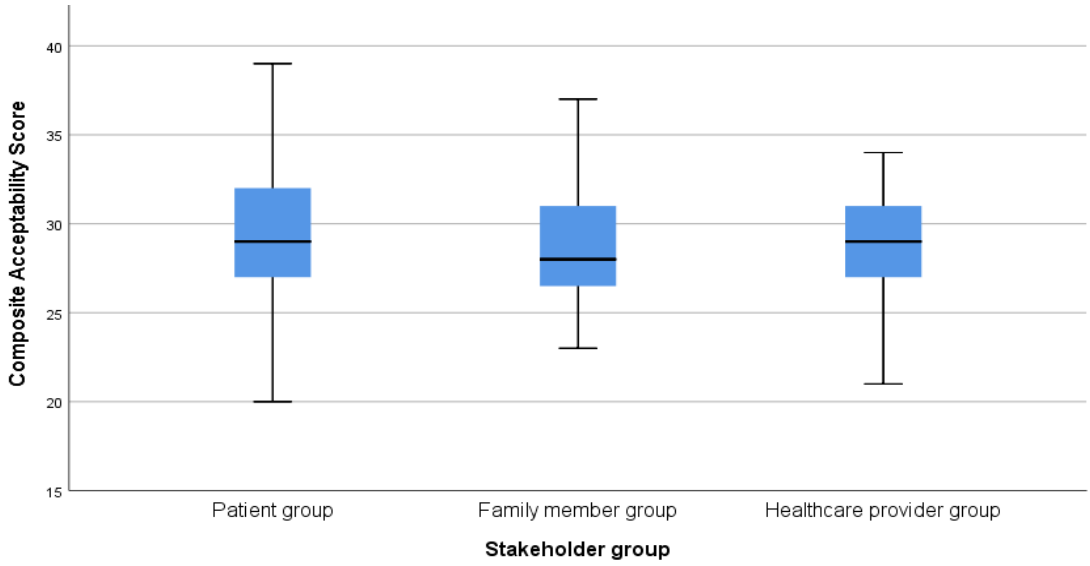

Figure 6.2 Composite Acceptability Score Across Stakeholder Groups

6.6.5 Correlation Between the Single-item Overall Acceptability and Constructs of Acceptability

Four of the seven constructs correlated significantly with single-item overall acceptability. Affective attitude has a moderate positive correlation (Rs= 0.453, p< 0.001). Self-efficacy has a weak positive correlation with overall acceptability (Rs= 0.399, p< 0.001), effectiveness for fitness had a weak correlation with overall acceptability (Rs= 0.340) ethicality has a weak positive correlation with overall acceptability (Rs= 0.298, p< 0.001) and intervention coherence has a weak positive correlation (Rs= 0.281, p< 0.001).

Table 6.3 Correlation Between Single-item Overall Acceptability and the Constructs of Acceptability

Construct	**The Spearman's rank correlation coefficient**	**p-value**
Affective attitude	0.453	<0.001
Self-efficacy	0.399	<0.001
Effective for fitness	0.340	<0.001
Ethicality	0.298	<0.001
Intervention coherence	0.281	<0.001
Burden	-0.033	0.608
Perceived effectiveness	-0.071	0.275
Opportunity costs	-0.123	0.057

6.6.6 Subgroup Analysis

Composite acceptability scores were significantly higher in patients and family members in the preoperative phase 31 (7), compared to 29 (6) less than six months and 28 (4) 6-12 months postoperatively (p=0.016). Mean difference in composite acceptability scores pre- and post-surgery increased with time from surgery (preoperative and <6 months; MD 1.88 (95%CI 0.17-3.16) p=0.031; preoperative and 6-12 months MD 2.471 95%CI (0.17-3.16) p=0.005) (Figure 6.3).

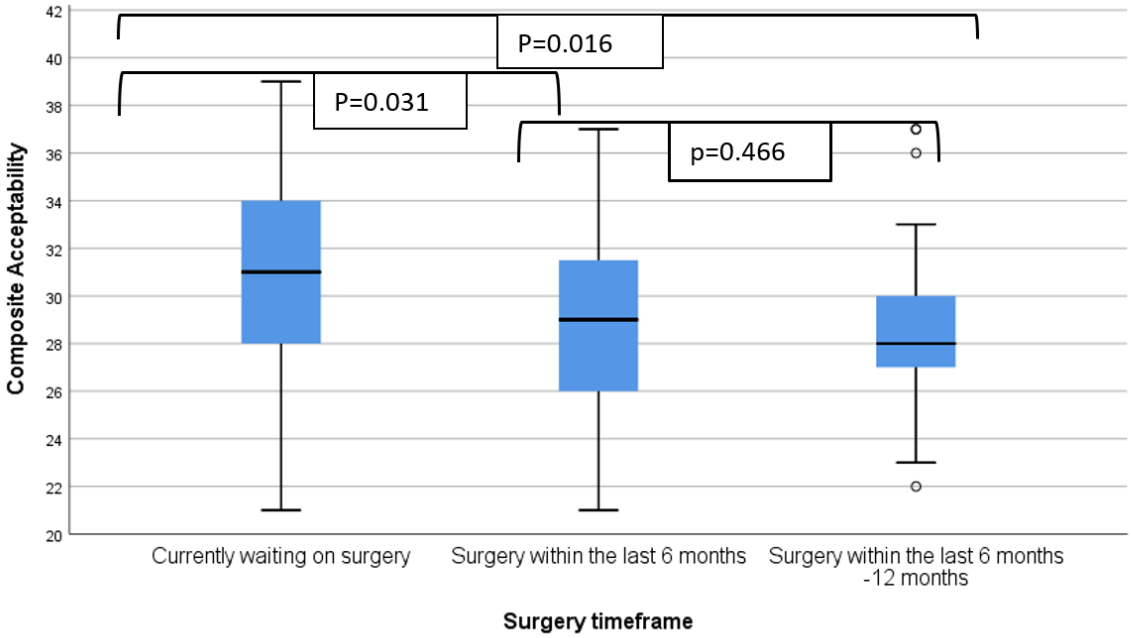

Figure 6.3 Composite Acceptability Based on Timeframes Around Surgery

Composite acceptability scores were comparable in the patients and family member group in respect of habitual exercise levels (inactive 29 (3), <60 minutes 29 (6), 60-180 minutes 29.5 (5), p=0.536); preoperative activity levels (inactive 27 (6), <60 minutes 29 (5) and 60-180 minutes 30 (5), p=0.141); and having experience with exercise prehabilitation and those who did not (29 (5) versus 29 (6), p=0.237).

Composite acceptability scores were comparable in HCPs based on habitual exercise levels (inactive 29 (11), <60 minutes 29 (13), 60-180 (29 (4), p=0.058). Healthcare providers who had experience with exercise prehabilitation had a significantly greater composite acceptability score than those who had no experience (mean difference 1.557 95% CI 0.422-2.692, p=0.008) (Figure 6.4).

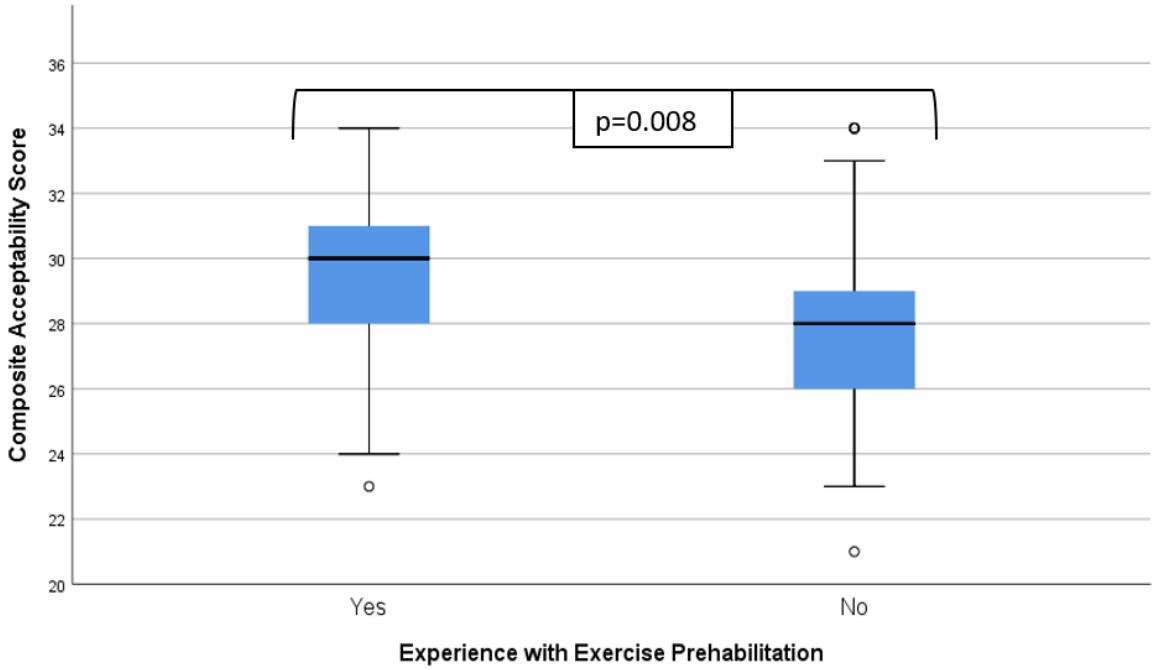

Figure 6.4 Composite Acceptability in Healthcare Providers Score Based on Experience with Exercise Prehabilitation

6.6.6.1 Sub-group Correlation Analysis

There was no significant correlation between age and composite acceptability score (p=0.810) or years of experience and composite acceptability score (p=0.285).

6.6.7 Qualitative Results

In total, 31 participants completed the semi-structured interview. Of those, n=14 were HCPs, n=12 were patients and n=5 were in the family members group. Within the patient group, one participant was also a healthcare worker (occupational therapist) and within the family group one participant was also a healthcare worker (physiotherapist), these two patients were not included in the HCP group. The themes identified in each construct are presented in Table 6.4. Participants are presented by stakeholder group and ID number (HCP: HCP (number), family member: FM (number) and patient group PT (number)).

Table 6.4 Theme & Coding Structure for Acceptability of Exercise Prehabilitation

Construct	Inductive code	Sample quotes
Affective Attitude	Positive feelings towards prehabilitation Psychological benefits • Improve mood • Reduce stress	*' it would have been lovely to have a regime or something that I could work you know give me something you know a targeted goal something I should be working towards if that makes sense'* PT2
Burden	Worthwhile commitment despite burden Minimal effort for physicians to support • Clear referral pathway needed	*'It certainly is a commitment, but I think for a lot of patients it's a welcome focus to have at that time point'* FM2
Ethicality	Role in patients' recovery In line with the health systems values	*'I think that they will do anything they can to improve the outcome for themselves so high motivation at a time like that'* HCP9
Intervention Coherence	Strong coherence in HCPs • Components involved in prehabilitation • Benefits of participation • Literature on prehabilitation Patients & family required an introduction	*'I was looking at poster presentations that intervention before major risk surgery like oesophageal cancer reduced time in ICU and reduced mortality and I guess that's the bottom line'* HCP11
Opportunity Costs	Physiotherapists are under-resourced Patients' personal commitments may impact ability to prioritise • Work commitments • Family commitments • Large number of appointments	*'it's just getting the framework up and running and actually it's the admin support that's nearly the hardest bit and then it would be time from physio'* HCP7
Perceived effectiveness	Effective on outcomes Effective at reducing hospital stay	*'Because all the problems that could arise afterwards your better to spend the money before and to try and prevent rather than deal with it afterwards I think'* PT3

Self-Efficacy	Individulised prehabilitation is appropriate for all patients **Facilitators:** Ability to perform may be enhanced by • A planned and patient focused programme • Clear, educational and empathetic introduction • Accessible to all **Barriers:** Varying levels of ability to perform may be impacted by • Socioeconomic status • Physiological wellbeing • Travel burden	*'Look, it's going to be difficult for a lot of people if you have cancer, but it really it's the approaches, the protocols, the benefits. It's how it's presented to the patient it's the crucial thing'* HCP6

6.6.7.1 Affective attitude

All stakeholders positively perceived exercise prehabilitation. Healthcare providers believed that exercise prehabilitation would be a positive intervention, which might enhance patients' outcomes-'*from an anaesthetics perspective I think its brilliant to have your patients in their fittest possible state before they go for their surgery, their outcomes are better'* HCP4*.* Physiotherapy participants were particularly passionate about the prospect of exercise prehabilitation, HCP7 reported being '*incredibly excited*'. Patients had less experience around exercise prehabilitation and therefore their positive feelings were more modest. However, from their understanding there was a sense that it would be a positive intervention, which could provide support and guidance - '*I actually think it's probably a very good idea'* (PT1). Additionally, participants, particularly HCPs, were aware of the **psychological benefits associated** with exercise to improve mood and reduce stress at a challenging time- '*there's several benefits to that I think first and foremost that we know there's a huge body of evidence that says that exercise helps to decrease stress and anxiety'* (HCP10)*.*

6.6.7.2 Burden

A sense of burden was associated with exercise prehabilitation. This burden may be more evident in certain cohorts, such as those who are new to exercise *'I think if it's somebody who's going from zero exercise, it would certainly be more'* (PT4) or those being treated with neoadjuvant treatment. Overall, while burdens exist, they do not necessarily deter individuals from wanting to participate. One patient stated *'it would have been a lot of effort I think I do feel it would be a lot of effort but I would have done it'* (PT3)**. Additionally, HCP were aware of the burden and financial cost required to establish the service** '*it's just getting the framework up and running and actually it's the admin support that's nearly the hardest bit*' (HCP7). Despite the initial workload involved, HCPs felt if funding was received it *'would be well worth everyone's while'* to support the delivery of the service. Some participants were concerned that appointments were time-limited and that prehabilitation '*may not necessarily be the first thing you discuss with them'*, however they felt that once a clear pathway was established, it would reduce the effort involved and the process would easy to support *'but I don't think it would take that much work, I don't think the volume of work for us would be too intense'* (HCP9).

6.6.7.3 Ethicality

Exercise prehabilitation may give patients a valuable role in their recovery. At a time when patients are experiencing a loss of control, all stakeholders and particularly HCPs, felt that patients would be willing to do whatever it took to help *'they would do handstands if they thought it would*

help them get better' (HCP3). Similarly, patients valued the opportunity to contribute to their recovery journey *'I would probably have jumped at anything that possibly would have helped me in my quest to get better, you know'* (PT7) and exercise prehabilitation presented this opportunity. Furthermore, HCPs felt prehabilitation had potential to be **very valuable in the postoperative phase and enhance their ability to provide medical care** *'I think certainly all anaesthetists would be one hundred percent supportive, anything that is going to make our job easier'* (HCP1).

6.6.7.4 Intervention Coherence

Healthcare providers had a strong understanding of what prehabilitation involves and the potential benefits. Healthcare providers mentioned literature they had read, suggesting HCPs are actively engaging in the concept of prehabilitation and interested in it *'obviously it makes the patients fitter and stronger and eh it certainly improves their short-term outcomes'* (HCP6). Patients were on board with the idea of exercise and being physically fit before surgery however, **the formal concept of prehabilitation was new to them** '*I know the benefits of exercise overall, and I know the benefits that I've had, and again, I thought that would be useful to get it explained*' PT4. There was a desire for introduction and guidance from HCPs to inform and motivate them *'I would loved to have had a like if you can get to here it will really benefit you or you may not even know that but if there was some way of setting a goal to work towards it might motivate me more if that makes sense* (PT2).

6.6.7.5 Opportunity Costs

Physiotherapists felt that services were under-resourced *'at this time every employee has a job role to do'* (HCP11). They expressed concern that running exercise prehabilitation programmes without additional staff would have knock-on impacts on other services and physiotherapists' personal time '*…because there was no resources but she said she can't do that going forward she was doing it in the evenings on her own time'* (HCP11). Furthermore, the concern was recognised that initiating the process while still under-resourced would impact the longevity of a prehabilitation programme *'I think you have to resource something otherwise it is being set up to fail'* (HCP11). Additionally, participants were aware of the significant number of hospital appointments and work or family obligations which may impact patients' ability to prioritise prehabilitation '*how many responsibilities you have got at home, if you have got a heap of kids and nobody to look after* them' (HCP2). To avoid patients missing out, programmes should be flexible, and prescribed/designed around the patient's individual needs *'I can see that actually there can be quite a bit of work around somebody's lifestyle and thinking about how does this fit into their lifestyle and how likely is it that they are going to comply with this'* (PT1).

6.6.7.6 Perceived Effectiveness

Participants across all stakeholder groups felt exercise prehabilitation would increase fitness and in turn may have a positive impact on their outcomes - *'build up that system before it takes the big blow of surgery and hopefully in doing that that would minimise the complications that the patients would have'* (FM2). Overall HCP's felt that patients who participate in exercise prehabilitation are likely to spend less time in ICU or hospital and that this in turn would have a positive outcome on the economic impact of hospitalisation.

6.6.7.7 Self-Efficacy

Stakeholders felt that *'everybody can do some form'* (HCP1) of exercise prehabilitation. While the level may vary from person to person, everyone should be given the opportunity -*'I think everybody should be offered some level of exercise that they are being empowered to maximise their possibilities'*(HCP11). Facilitators and barriers which impact ability to participate were identified. Facilitators included provision of a structured, flexible, and individualised prehabilitation programme, which is introduced to patients in a clear and empathetic way. Barriers included travel burden, illness and lower socioeconomic cohort. Additional inductive coding was completed for the facilitators and barriers to fully explore them.

<u>Structured and individualised prehabilitation programme</u>

Across all groups, participants felt that a planned and patient focused programme would encourage and enable patients to participate *'I think it needs to be individualised care that people need to feel that they are getting something that is designed for them and for their life'* HCP9. Participants felt that a flexible prehabilitation programme may motivate patients to exercise despite other commitments. Additionally, guidance and education from HCPs would support patients to take part at a level that is appropriate for them. Overall, the concept that the programme must be patient-centred and adaptable to their life was clear *'if were not listening to the patient were not setting them up for success'* HCP10.

<u>Clear and empathetic presentation</u>

The importance of how the programme is presented and introduced to patients was identified. All stakeholders felt that the introduction of prehabilitation and '*how it's presented to the patient*' was '*the crucial thing'* HCP6. A clear description of the components involved and education was important *'if patients understood how beneficial and how worthwhile it would be that there will be a good uptake'* HCP5. Overall, the feeling that this is a highly distressing time for patients came

across and the delivery of clear information is vital to ensure patients feel confidant and empowered to take part.

Accessibility

Finally, participants felt that it was important that the services should be easily accessible for all patients '*you just have to make sure that its em you have to make sure that its something that is easily accessible to them'* HCP11. Challenges to accessibility such as geographical location and numerous medical appointments were identified as concerns *'the travel aspect is a significant factor'* FM3. It was considered very important that the services should be easily accessible for all patients, so alternative options like telehealth or satellite programmes should be discussed.

Lower seriocomic cohort

Participants, particularly HCPs, expressed concerns that patients who were in a lower seriocomic cohort may struggle with participation more due to the financial cost of travel or the ability to take time off work '*if you have the same amount of motivation, I think it probably depends on how well off you are, so how easy it is to get the exercises'* HCP2.

Physiological wellbeing

The physiological wellbeing of patients may act as a significant barrier to participation in prehabilitation. Co-morbidities and side effects from neoadjuvant treatments were identified as potential factors that stakeholders thought may limit their ability to participate *'Well obviously the physical limitations to chemotherapy and radiotherapy…..they can have low anaemia, low white cells etc, they are very deconditioned'* HCP1.

6.6.8 Discussion

There is a growing body of evidence to support the effectiveness of exercise prehabilitation to enhance preoperative fitness and influence postoperative outcomes (Durrand et al., 2019). Assessment of acceptability is vital to identify the barriers and facilitators that can affect the adoption and long-term sustainability of the service (Proctor et al., 2011, Damschroder et al., 2022, Gaglio et al., 2013). This study integrated results from a cross-sectional survey and semi-structured interviews to gather rich information on the acceptability of exercise prehabilitation among key stakeholders including patients, family members and HCPs. The findings indicate that exercise prehabilitation is acceptable to stakeholders: they are positive about exercise before surgery, value its role and feel it is an effective intervention. While exercise prehabilitation is associated with a sense of burden, it was considered a worthwhile commitment, which could be facilitated by

enhancing accessibility, flexibility and individualisation of the programme to ensure all patients have the opportunity to take part.

Composite acceptability scores in this study were comparable across groups, suggesting that all groups are equally positive regarding exercise prehabilitation. This is an important finding, as patients in this cohort are heavily dependent on support and guidance from their family and HCPs (Beck et al., 2021, Waterland et al., 2020, Daun et al., 2022, Banerjee et al., 2021). Healthcare providers play a particularly vital role and have been identified as a key motivator to patients' engagement in prehabilitation (Waterland et al., 2020, Ferreira et al., 2018, Banerjee et al., 2021). Results from the semi-structed interviews similarly emphasised the value of introduction of exercise prehabilitation from HCPs. However, participants placed greater emphasis on the approaches taken by these HCPs to disseminate the information. This indicates that patients and their family members not only desire an introduction from HCPs, but also consider the way the topic is addressed as vital to enhancing engagement. These results are consistent with other studies, which found recommendations from HCPS, specifically doctors, were a primary motivator for participation, and significantly increased patients' willingness to take part in exercise prehabilitation (Waterland et al., 2020, Ferreira et al., 2018, Banerjee et al., 2021). The valuable role of the approach to dissemination was similarly recognised, with an emphasis on education as a tool to motivate patients (Ferreira et al., 2018).

The TFA questionnaire is a new tool, robustly developed through consensus. However, normative data about quantitative scores is only emerging thus limiting interpretation of the raw quantitative scores. Several studies are underway which plan to use this acceptability tool (Samuel et al., 2023, Petrovic et al., 2023, Kathyrn et al., 2023, Whitaker et al., 2023). However, current data from an acceptability study examining the acceptability of a healthy lifestyle programme in primary caregivers of children suggest that the quantitative scores presented indicate high levels of acceptability (Bell et al., 2023). This is reinforced by corroboration from existing literature and the qualitative component of this study, suggesting that stakeholders in the context of exercise prehabilitation have indeed demonstrated high levels of acceptability (Beck et al., 2021, Ferreira et al., 2018, Waterland et al., 2020).

Results of this study indicate that exercise prehabilitation, like all exercise programmes, is inherently associated with burden (Saggu et al., 2022, Knowlton et al., 2020, Leak Bryant et al., 2017, Lee et al., 2022, Rodrigues et al., 2017, Chao et al., 2000). The specific burdens identified, such as travel burden, number of hospital appointments, illness are consisted with current literature (Saggu et al., 2022, Knowlton et al., 2020, Leak Bryant et al., 2017, Lee et al., 2022,

Ferreira et al., 2018). However, as the results illustrate, the burden associated with exercise prehabilitation is complex. The lack of clarity in the correlation results for burden and discrepancies between perceived and actual burden highlight the unique position of exercise prehabilitation. Participants in the semi-structured interviews expressed concerns that patients who did not regularly exercise at the time of diagnosis may struggle to participate in exercise prehabilitation. However, this is not supported by the quantitative data, where composite acceptability scores are comparable between habitually active and inactive patients and family members. Analysis of the demographic characteristics of participants who expressed this concern revealed that all were HCPs or postoperative patients, and all identified as being habitual exercisers. There is an established link between previous experience with exercise and motivation to participate in survivorship (Weller et al., 2019, Ormel et al., 2018). Therefore, the opinion that inactivity was a barrier to engaging in prehabilitation was largely an assumption, based on current circumstances or observations of other's (i.e. patients') behaviour. This may lead them to perceive low levels of habitual activity as a burden for others, despite it not truly being one. This disparity between perceived burden for others and actual burden may result in a reluctance to address or refer to exercise prehabilitation based on assumptions. These results, along with the minimal impact of actual burden on motivation, highlights the importance of addressing exercise prehabilitation with all patients, regardless of preconceptions, allowing the identification of individuals barriers and empowering them to take part.

Prehabilitation which is delivered between cancer diagnosis and surgery brings challenges and considerations for implementation. For patients and family members, pre- or post-surgical status had a clear impact on the acceptability of exercise prehabilitation. Composite acceptability scores were highest in the preoperative group, with levels dropping significantly in the 0-6 months postoperative group and further again in the 6-12 months group. This suggests that patients and family members in the preoperative phase are most motivated and on board with the idea of exercise prehabilitation compared to other timepoints. This higher acceptability aligns with the '*teachable moment*' concept, often described as an event leading to changes in a person's health behaviours (Lawson and Flocke, 2009, Karvinen, 2015, Flocke et al., 2014). This supports the hypothesis that the preoperative phase may represent an important opportunity not only to participate in exercise, but to educate patients and family members on the role of preoperative and postoperative exercise, at a time of highest motivation (Durrand et al., 2019). This approach is used in smoking cessation, with education and intervention starting following diagnosis with the aim of continuing into survivorship (Villebro et al., 2008, McBride and Ostroff, 2003). In the semi-structured interviews, high levels of preoperative motivation to participate in prehabilitation were

attributed to a sense of control, at a time where patients felt they had no control. The preoperative phase is associated with fear, isolation and anxiety and participants valued the opportunity for patients to have an active role in the preparation for surgery, a desire consistently identified in pre-treatment oncological cohorts (Beck et al., 2021, Matthew et al., 2022, Gillis et al., 2021, Van der Velde et al., 2023, Brahmbhatt et al., 2020). This desire to contribute to preoperative preparation, in addition to the potentially higher capacity to modify health behaviours at this critical time, suggests that the preoperative phase is an opportune time to introduce, educate and motivate patients about exercise.

While the mixed-methods approach generated rich data and enabled in-depth analysis, this study has several limitations. A strength of this study is the inclusion of family members as their voices are frequently not heard in research, therefore bringing a novel perspective to this area of research. However, despite a comprehensive recruitment strategy involving professional and patient representation groups, social media and in-person recruitment at two clinical sites, family members were underrepresented in the overall sample, which may lead to an under-representation of their views on the acceptability of exercise prehabilitation. Additionally, the mean age in the questionnaires may limit the generalisability of these results to older adults. Furthermore, the participants in the semi-structured interviews were self-selected, which may introduce bias as they may have had a greater interest or motivation towards exercise prehabilitation. Finally, while a strength to the study was the use of a theoretical framework to add rigour to the analysis, currently there are no standardised cut-off points for composite acceptability, making quantification of acceptability levels challenging. However, the study was underpinned by a theoretical framework across quantitative and qualitative elements, providing a clear platform for triangulation of results and enhancing the robustness of the results. Furthermore, the publication of multiple protocols utilising this approach will increase the availability of data for comparison, thereby enhancing the ability to compare acceptability levels (Samuel et al., 2023, Petrovic et al., 2023, Kathyrn et al., 2023, Whitaker et al., 2023).

In conclusion, stakeholders are positive about exercise prehabilitation, and they understand its goal and support the provision of the service. However, consideration should be given to execution of the service to enhance implementation. Therefore, three recommendations have been generated (Figure 6.5):

Introduction of the service should be comprehensively designed and clearly presented. The discussion should be approached in a supportive and accessible manner, discussing potential

barriers and empowering patients to participate. The information should include a concise outline of the components of prehabilitation and potential benefits.

Prehabilitation programmes should be patient-centred and prioritise accessibility for all. Programmes should be designed in collaboration with patients, addressing specific needs and goals and enabling them to overcome barriers. Therefore, programmes should be flexible, accommodating of other commitments, and accessible through multiple mediums.

Service must be appropriately resourced with a clear referral process to ensure the longevity of the prehabilitation programme.

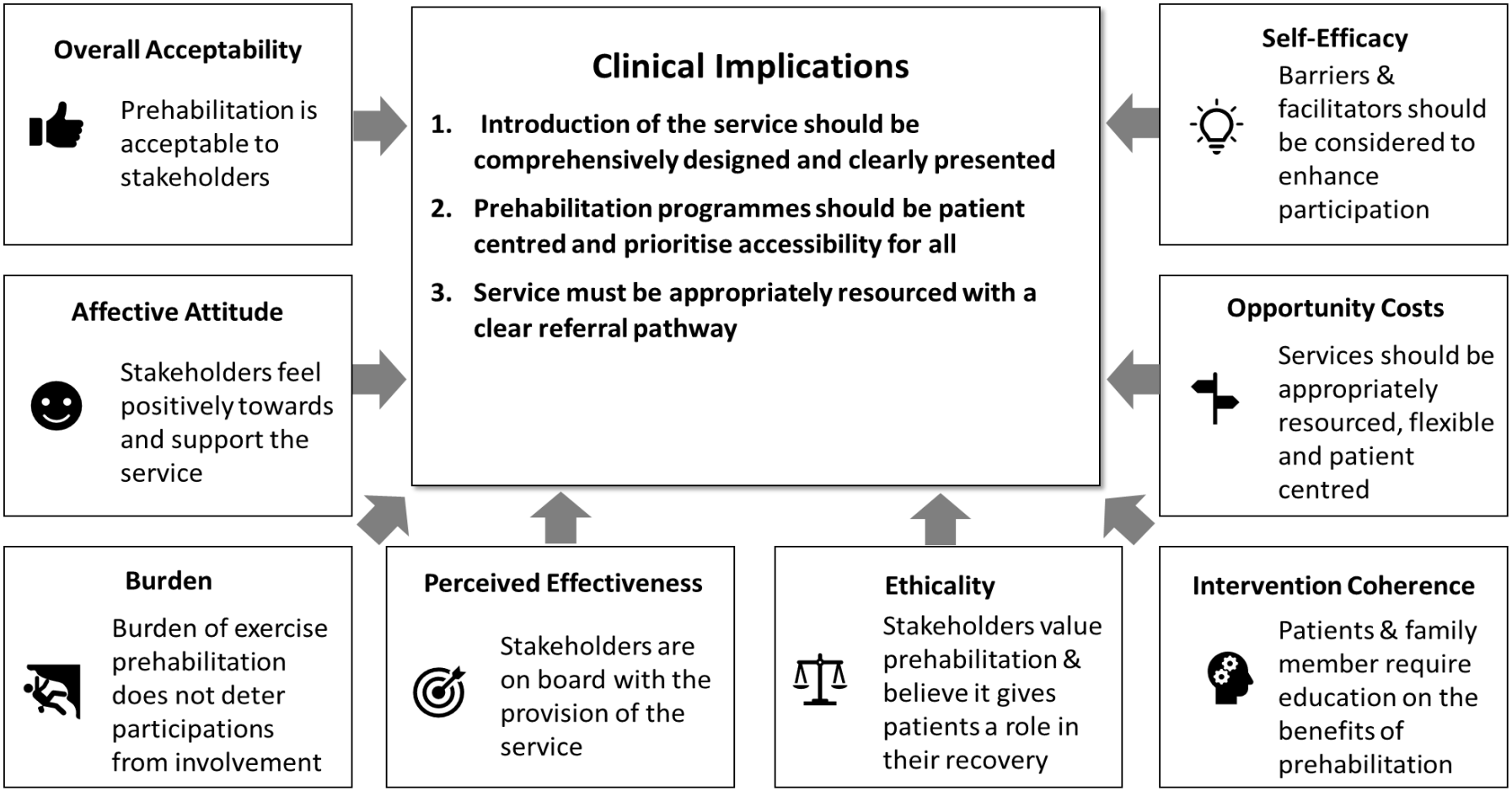

Figure 6.5 Clinical Implications of Study III

Chapter 7 Discussion

7.1 Introduction

Exercise prehabilitation is an emerging intervention targeting preoperative fitness in order to improve patients' outcomes. As prehabilitation evolves, it is clear that there are many difficulties associated with delivering effective interventions over a short time period. Consequently, there is a need for clarity on the role of exercise prehabilitation to identify the most meaningful approach to elicit an increase in preoperative cardiopulmonary fitness within a short period. Additionally, there is a need to examine intervention acceptability among key stakeholders to support integration into clinical pathways and enhance engagement. Therefore, the aims and objectives of this thesis were to examine the role of exercise prehabilitation prior to oncological resection. The specific objectives were to assess the acceptability of exercise prehabilitation prior to oncological resection: evaluate the feasibility, effectiveness, and acceptability of high intensity interval training (HIIT) as a prehabilitation approach and explore the impact of HIIT prehabilitation on postoperative complications.

In order to address the aims and objectives of this thesis, one systematic review and meta-analysis and three studies were completed. Firstly, a systematic review and meta-analysis examining the impact of preoperative HIIT on cardiopulmonary fitness and postoperative complications in patients scheduled for oncological resection was completed. Secondly, Study I examined the feasibility of a RCT evaluating the impact of a hybrid preoperative HIIT programme on cardiopulmonary fitness in patients scheduled for lung and oesophageal resection. Thirdly, a qualitative analysis was completed on a sub-set of patients from the Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus (PRE-HIIT) trial to explore patients' motivations to participate and their experiences preparing for surgery on the PRE-HIIT trial. Finally, a mixed-methods study, underpinned by the Theoretical Framework of Acceptability, was carried out to examine the acceptability of exercise prehabilitation among patients, family members (i.e., relatives of patients) and healthcare providers. Collectively, these studies contribute to a comprehensive understanding of the role and effectiveness of exercise prehabilitation in the context of oncological resection. The main findings from this thesis are presented in Figure 7.1 and discussed in detail in this chapter.

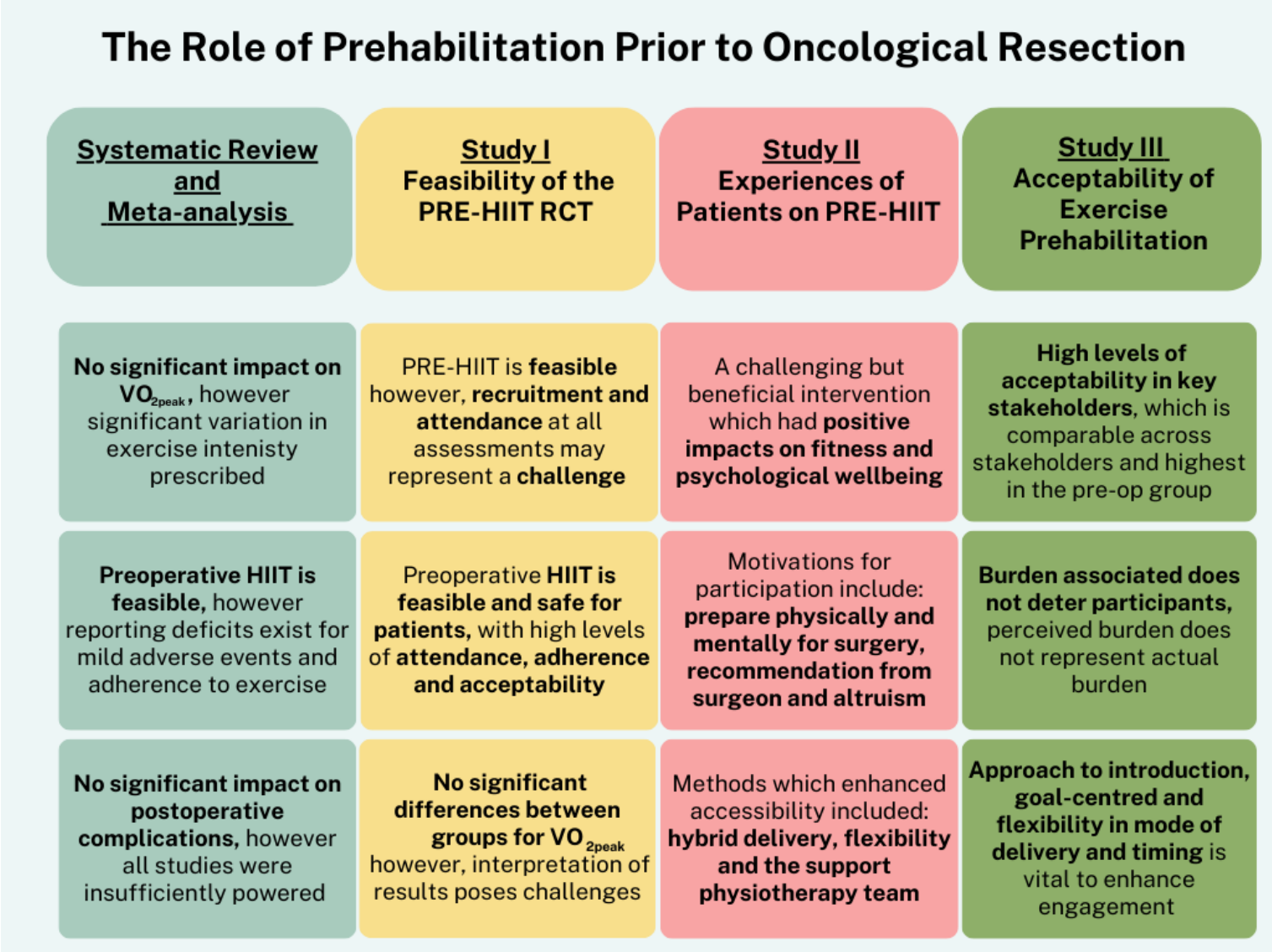

Figure 7.1 Main Thesis Findings

7.2 Analysis of Key Points

7.2.1 Feasibility of Exercise Prehabilitation

Exercise prehabilitation, including HIIT is a feasible, safe and enjoyable intervention for patients prior to lung or oesophageal resection. In Study I, the HIIT arm showed high levels of attendance at planned sessions (median 100% (33)), comparable levels of attrition with moderate intensity exercise (HIIT n=4, control n=3) and no serious adverse events. This was comparable to attendance, attrition rates and adverse events noted in studies in the systematic review and meta-analysis in Chapter 2 and in current literature (Machado et al., 2023, Dronkers et al., 2010, Santa Mina et al., 2018). Drawing on insights from Chapter 2, Study I adopted an enhanced reporting approach, particularly in relation to adherence and adverse events (Nilsen et al., 2018). HIIT had high levels of adherence to the exercise dose (relative dose intensity 92% (38.5)), and a low requirement for pre-exercise intensity reduction (2.4% of all completed sessions) and a low-level need for early session termination (4% of all completed sessions). The value of reporting adherence to exercise dose should not be overlooked and is arguably one of the most valuable outcomes to report in an exercise study. Exercise is a dose-dependent intervention and the physiological outcomes depend on the volume of exercise completed (Hawley et al., 2014). Therefore to accurately assess the effect of the intervention, it is vital to accurately report adherence to the protocol (Sterne et al., 2019). As evident in Chapter 2, neglecting to report these factors introduces bias and complicates interpretation of the true effect due to potential deviations from the intended protocol, which attenuate the effect of exercise. Although Study I was not powered to determine the effect of HIIT on cardiopulmonary fitness, it showed the feasibility of collecting this data which will support the interpretation of results in an appropriately powered cohort. Additionally, the adverse events which occurred were mild as they required no intervention (National Cancer Institute., 2017). This comprehensive dataset, in addition to patients' positive experiences on PRE-HIIT presented in Study II, offers a deep understanding of influencing factors and offers a compelling rationale for the feasibility of a preoperative HIIT intervention.

The feasibility of delivering exercise prehabilitation is multi-faceted and influenced by complex evolving factors. Several challenges relating to delivering an effective prehabilitation programme that were discussed in this thesis include the short timeframe to surgery, travel burden, large number of hospital appointments, digital-literacy, co-morbidities and physiological well-being (Saggu et al., 2022, Knowlton et al., 2020, Leak Bryant et al., 2017, Lee et al., 2022, Ferreira et al., 2018). However, PRE-HIIT faced additional challenges associated with the COVID-19 pandemic. Throughout the pandemic elective surgeries were often subject to last-minute rescheduling and confirmation of surgical admissions was frequently delayed until the end of the day of planned

admission therefore limiting the time for completion of assessments. This resulted in withdrawals from the study (n=2) and non-attendance at post-intervention (n=7) assessments. Incomplete follow-up assessments are not uncommon in this cohort and reasons often involve illness or injury, loss to follow-up or disease progression, often the reasons are not justified by participants (Van Wijk et al., 2022, Ferreira et al., 2021b, Carli et al., 2020, Santa Mina et al., 2018). However, the national catchment of St James's Hospital (SJH) coupled with the disruptive impact of COVID-19 on admissions presented a new challenge, as many patients were reluctant to travel for assessments without the assurance of surgical admission.

Centralisation of cancer services in Ireland occurred in 2007 with the goal of optimising outcomes and improving survival (NCRI, 2019). SJH is the National Centre of Excellence in Ireland for oesophageal resection and a supra-regional centre for lung resection (SJH, 2023., NCRI, 2019). In both cases, SJH is one of four centres in Ireland for surgical treatment of lung and oesophageal cancer serving large geographical areas across the country. Therefore, patients travel considerable distances to reach the hospital, with the greatest distance recorded in the PRE-HIIT study being 285km. While this represents a significant strength to PRE-HIIT sampling, ensuring the generalisability of the results and representing a wide variety of patients, it concurrently posed a recruitment and completion challenge exacerbated by the impact of COVID-19. Travel burden associated with the assessment was the primary reason for declining to participate in the trial, and the patients' unwillingness to travel for assessment prior to confirmation of admission for surgery was the primary reason for missed assessments. This finding is mirrored in Study III and current literature, which described travel burden as a significant barrier to participation in prehabilitation (Van der Velde et al., 2023). This indicates that the accessibility of cancer services in Ireland has a direct impact on the feasibility of prehabilitation programmes and should be considered when interpreting results.

Centralisation of care for surgery is crucial for optimising outcomes. However, it presents recruitment challenges for rural patients and contributes to the under-representation of this population in research (Levit et al., 2020, Copur et al., 2016). Provision of hybrid prehabilitation programmes to enhance accessibility for patients is one of the key recommendations derived from Study III. This approach was adopted in the PRE-HIIT trial and enabled patients to participate, who previously would have declined due to the daily travel burden. In PRE-HIIT when patients had the opportunity to choose their preferred approach to delivery of prehabilitation (face-to-face or online) acceptability, attendance and adherence levels were comparable between groups. This suggests that one approach is not more appropriate than the other, rather it is dependent on personal preference. Therefore, the mode of delivery is a flexible factor which can be adjusted

based on patients' preferences, ultimately promoting a higher level of commitment and engagement. Recent prehabilitation trials have focused on enhancing engagement by delivering telehealth interventions and so removing travel burden (Machado et al., 2023, Wu et al., 2021, Blumenau Pedersen et al., 2023). However, different barriers exist for each mode of delivery (online: digital literacy and internet access, face-to-face: travel burden and accessibility). Limiting the provision to one option could restrict opportunities for patients to participate, highlighting the value of a hybrid approach to exercise prehabilitation.

Although the hybrid approach enhances accessibility, travel burden for participation in a trial remains a barrier. The hybrid approach to the intervention demonstrates comparable levels of attendance (in-person 80% (66.6) and online 53% (87.5), p=0.25), adherence to exercise dose (in-person 100% (15) and online 86% (50), p=0.154) and composite acceptability (in-person 34.7 (3.8) and online 32.92 (3), p=0.152) as well as the occurrence of no serious adverse events in either approach. However, challenges remain to optimising attendance at assessments and accommodating those unable to attend in-person in SJH or at online classes. It is reasonable to hypothesise that in the absence of the barrier of accessibility, the recruitment, retention and assessment completion rates would have experienced a significant increase. Therefore, a potential solution would be to implement access in a rural satellite centre, allowing patients to complete assessments and/or exercise sessions in a regional referral centre. This approach of linking academic centres to a qualified body of community-based health care providers to enhance recruitment was piloted by the US National Cancer Institute (NCI) Community Cancer Centres Program (Clauser et al., 2009). The satellite research centres enhanced recruitment onto trials from 3.2% to 23% (Copur et al., 2016). Furthermore, this approach is in line with the National Cancer Strategy for Ireland, which proposes that patients have their planning sessions in the cancer centre, while receiving some of their treatment closer to home (Department Of Health, 2017). Satellite centres offer a potential solution to key accessibility barriers identified in our findings, further enabling us to provide high quality preoperative care to all patients and ensuring all are given the opportunity to participate in clinical trials. However, while this concept may appeal, there are many challenges such as training of staff in skilled techniques and use of equipment, clinical support and funding.

Although the PRE-HIIT trial faced unprecedented challenges due to the COVID-19 pandemic, the lower recruitment levels reported in PRE-HIIT (27.75%) are not unique to this population. There is significant variability in recruitment rates in prehabilitation studies (Michael et al., 2021). Similar to the extent of variability reported in a systematic review and meta-analysis by Michael et al. (2021) (36.5% to 100%), recruitment levels in Chapter 2 varied from 30.4% to 100% (Michael et al., 2021).

However, only one of the trials in the systematic review and meta-analysis specifically described the recruitment approaches. This is similar to current literature where reporting of recruitment approaches is often limited to location, how patients were identified and the means of receiving participant information leaflets (i.e., in clinic or by post) (McIsaac et al., 2022, Brahmbhatt et al., 2020). However, studies often fail to report how patients were introduced to the concept of prehabilitation and by whom, at what timepoint in relation to diagnosis patients received that information, if the person who introduced the concept of prehabilitation also recruited them for the trial and the average travel distances patients had to cover to attend appointments. Although this is a common approach to reporting in clinical trials, considering the variability in rates of enrolment and the value placed on the approach of introduction identified in Study III, it is worth considering that detailed inclusion of recruitment procedures would enable the replication of effective approaches in future clinical trials or settings (Reynolds et al., 2023, Moher et al., 2012). Elements of enhanced reporting were used in a review of the feasibility and outcomes of a real-world regional lung cancer prehabilitation programme in the UK (Bradley et al., 2023). This review included additional information on methods of recruitment, including the education of referring clinicians on the benefits of prehabilitation and strategies to communicate this to patients (Bradley et al., 2023). This UK service had a high recruitment rate (80.5% attending baseline assessment and 64.5% appropriate for inclusion), and the comprehensive reporting of their strategies provides an evidence-based solution to problems new service developers may encounter. Therefore, comprehensive reporting of all trial components is crucial to support the interpretation of clinical applicability and enable translation from research settings into clinical settings.

7.2.2 Acceptability of Exercise Prehabilitation

Exercise prehabilitation is an acceptable intervention for patients, their family members and healthcare providers. As discussed in Chapter 6, stakeholders demonstrated high levels of acceptability of exercise prehabilitation with even higher levels evident in Study I, and strong positive corroboration from the qualitative components in Study II. In Study III, surgical status (preoperative or postoperative) had a clear impact on the acceptability of exercise prehabilitation amongst patients and their family members. Specifically, scores were found to be the highest in the preoperative group, with levels dropping significantly in the 0-6 months postoperative group and further again in the 6-12 months group. This suggests that motivation and willingness to engage with the concept of exercise prehabilitation amongst patients and their family members in the preoperative phase is greater compared to other timepoints. It is plausible to suggest that the

higher composite acceptability scores observed in Study I is potentially due to the proximity of participants' scheduled surgery and survey completion.

Higher acceptability in the preoperative phase aligns with the '*teachable moment*' concept often described as an event leading to changes in a person's health behaviours (Lawson and Flocke, 2009, Karvinen, 2015). This supports the hypothesis that the preoperative phase may represent an important opportunity not only to participate in exercise, but to educate on the role of preoperative and postoperative exercise, at a time where motivation is at its highest. This approach is used in smoking cessation with education and intervention starting following cancer diagnosis with the aim of maintaining impact into survivorship (Villebro et al., 2008, McBride and Ostroff, 2003). Preoperative smoking cessation interventions are effective, with high cessation rates maintained in lung cancer patients even two years after their surgery (Villebro et al., 2008). Participants in PRE-HIIT noted this phenomenon in the qualitative component, citing new insights and motivations to exercise following surgery (Section 5.4). While no data on postoperative exercise levels were collected in this thesis, the literature suggests that this approach has been effective in smoking cessation and therefore has potential to work in exercise (Villebro et al., 2008, Lee et al., 2015). Therefore, the potentially greater capacity to modify health behaviours at this critical time suggests that the preoperative phase is an opportune time to introduce, educate and motivate patients about exercise. However, as discussed in Chapter 6, the way in which the introduction is carried out is crucial for improving engagement. As evident from the apprehension prior to participation in PRE-HIIT, this aspect becomes even more significant when considering HIIT.

Despite the comparable levels of acceptability observed after participation, initial apprehension regarding the intensity and concerns prior to participation may represent a challenge to engagement. HIIT is feasible and safe across the cancer care continuum, however cancer survivors and patients tend to gravitate towards moderate intensity exercise (Wong et al., 2018, Gurunathan et al., 2023, Wallen et al., 2020). Notably, Study I found that 10% of the patients who declined to participate in PRE-HIIT attributed it to the intensity of the programme. Additionally, many participants randomised to HIIT reported an initial apprehension towards participation due to intensity. However, following completion of the programme, composite acceptability scores were comparable between HIIT and moderate intensity exercise. This finding is also consistent with previous research, which reported comparable or higher levels of enjoyment with HIIT compared to moderate intensity exercise in multiple cohorts (Stork et al., 2017, Reljic et al., 2021). Furthermore, the correlation analysis in Study I revealed significant results for affective attitude and self-efficacy, isolated to the HIIT arm. The enjoyment of HIIT is additionally noted in Study II, with emphasis placed on enjoyment associated with the challenge and the perception of enhanced

preparation for surgery. Given these findings and considering that a primary motivation for participating in prehabilitation is a desire to feel prepared and physically fit for surgery (Brahmbhatt et al., 2020), HIIT may represent a more enjoyable approach which builds additional confidence in patients prior to surgery. However, for HIIT to be successful in this patient population, the concerns expressed by patients prior to participation (Study II) need to be addressed to help facilitate engagement. These concerns are not just isolated to our findings but have been reported among HCPs and caregivers in other cohorts (Martland et al., 2021, Hannan et al., 2018). Consequently, a crucial question arises regarding how best to address these concerns proactively before patients engage in the programme, so the number of potential patients lost in the early stages can be limited.

As described in Study III, the approach to introducing prehabilitation is the key to supporting patient engagement. Recommendations from the surgical team were similarly identified as a primary motivator in Study II and is well described in the literature (Waterland et al., 2020, Ferreira et al., 2018, Banerjee et al., 2021). The approach to introducing the role of prehabilitation is pivotal, which may be more crucial when higher intensity exercise is proposed. Therefore, a patient-focused discussion, which aims to alleviate apprehension and support patients to engage regardless of the intensity of the exercise is important. However, the use of HIIT in healthcare is still novel. Concerns regarding the appeal of the intensity of HIIT for inactive and overweight patients has been identified by HCPs working in mental health (Martland et al., 2021). Furthermore, HCPs perception of non-acceptance of HIIT in patients has been identified as a barrier in cardiac rehabilitation (Hannan et al., 2018). Results from Study I in this thesis show that acceptability of HIIT is comparable to moderate intensity training in patients scheduled for oncological resection. However, HCPs' preconception may represent a barrier. Dissemination of these findings is important to ensure HCPs do not avoid referring patients based on assumptions.

7.2.3 Benefits of Exercise Prehabilitation

Lower preoperative cardiopulmonary fitness is associated with an increased risk of postoperative complications. Concerningly, participants in PRE-HIIT baseline peak oxygen consumption (VO_{2peak}) were categorised as very poor or poor for normative values. Similarly five of the six studies included in the meta-analysis in Chapter 2 reported poor or very poor baseline values. As VO_{2peak} defines a metric that is associated with risk in surgery, these results indicate that participants were at risk for postoperative complications, emphasising the critical need for intervention to address this fitness deficit. However, uncertainty remains around the effect of preoperative HIIT to increase cardiopulmonary fitness. Two recent meta-analyses reported HIIT to be effective at increasing cardiopulmonary fitness across the cancer care continuum and in other clinical populations

(endocrine, cardiovascular, respiratory and psychiatry) (Wallen et al., 2020, Blackwell et al., 2018a). However, after pooling of results in Chapter 2, there was no significant MD between usual care or moderate intensity exercise and HIIT (mean difference (MD) 0.83, 95% CI-0.51 to 2.17 kg/ml/min, p=0.12), similarly no significant effect of HIIT was noted on VO_{2peak} in PRE-HIIT (MD 1.16 95% CI -3.8 to 1.4 kg/ml/min, p=0.368).

There are factors across the two chapters which may have influenced the results and interpretation. In Chapter 2 there was significant variation in exercise protocols, therefore exercise dose completed. Two of the studies, although falling within the definition of HIIT, are on the lower end of the high intensity scale (80-85% of WRp or heart rate max) (Sebio García et al., 2017, Banerjee et al., 2017). Only one of these studies carried out a cardiopulmonary exercise test (CPET) and did not report significant improvement in VO_{2peak} or oxygen consumption at anaerobic threshold ($VO2_{AT}$) post-intervention (Banerjee et al., 2017). Additionally, Minnella et al. (2020) compared HIIT to moderate intensity exercise and reported no significant difference in VO_{2peak}. However, a significant increase in VO_{2peak} from baseline was reported (Minnella et al., 2020). Importantly, while the mean difference (MD) in VO_{2peak} between groups was not statistically significant, the within-group change in the HIIT arm was both statistically and clinically significant. This suggests that both approaches have an impact on VO_{2peak}, however, higher intensity programmes may be required to elicit a clinically relevant change in the short time-frames available. It is noteworthy that the two shortest duration interventions (median duration 26 and 30 days) also had two of the highest intensity protocols and both reported a significant increase in VO_{2peak} and peak power output (Licker et al., 2017, Karenovics et al., 2017, Bhatia and Kayser, 2019, Blackwell et al., 2020). Conversely, the longest intervention (mean duration 54 days) had one of the lowest intensity programmes. This study did report a significant increase in physical fitness (measured by time to completion); however, notably the time period available to achieve this change was longer. Additionally, VO_{2peak} was not measured so direct comparison is not possible (Sebio García et al., 2017). Blackwell and colleagues compared the effect of HIIT versus usual care on VO_{2peak} in less than eight weeks in a recent meta-analysis (Blackwell et al., 2018b). Nine of the 13 studies included prescribed peak intensities of >90% of WRp or VO_{2peak}, and all reported a significant improvement VO_{2peak} (Blackwell et al., 2018b). However, these time frames are not available preoperatively for many cancer patients and optimal training intensity over time-periods <31 days remains to be elucidated.

Consequently, PRE-HIIT prescribed a higher-intensity HIIT programme with the goal of eliciting a significant change within two weeks. However, similar to Minnella et al. (2020), the preliminary analysis of PRE-HIIT presented in this thesis found no significant difference between moderate

intensity exercise and HIIT in VO_{2peak} but did report a significant within-group change in PPO. This increase from baseline in PPO following HIIT was similarly noted in four of the six studies included in the meta-analysis. All four of these studies additionally reported a significant within-group change in VO_{2peak} while PRE-HIIT did not. There are several potential reasons for observing similar changes in PPO but not in VO_{2peak} these include: equipment malfunction, the physiological impact of COVID-19 and underpowered results.

Recruitment for PRE-HIIT is ongoing to reach an accrual target of 78. The results for VO_{2peak} presented in this thesis are a preliminary analysis and therefore were underpowered for this outcome. This was exacerbated by attrition, missing T1 assessment, equipment failure and the physiological impact of COVID-19. VO_{2peak} was measured by indirect calorimetry using the portable COSMED $K4b^2$ and COSMED Quark CPET devices. These devices are state of the art equipment and are calibrated routinely. However, they are sensitive to use, and equipment malfunction can occur despite standardised operating procedures and, in PRE-HIIT, use limited to two assessors to prevent equipment damage. Of the 32 CPETs completed at T1, breath-by-breath analysis is available for 31. Furthermore, due to equipment malfunction the validity of five is uncertain. As VO_{2peak} was a secondary measure for this thesis, these data points were included despite this concern, however it is important to consider the impact that they may have had on the results presented. VO_{2peak} describes the volume of oxygen consumed at peak exercise, therefore malfunction in the O_2 analyser or interference with the mask may lead to inaccurate results being generated. One participant in the HIIT arm interfered with his mask throughout the last 35 seconds of his CPET, disrupting O_2 measurements and possibly diluting the volume of exhaled O_2 with room air. This resulted in a significant drop from 10.1 ml/kg/min (average of the 30 seconds before interference with mask) to an average of 6.9 ml/kg/min in the last 30 seconds. Three participants (6.3%) had an abnormally low VO_{2peak} results (between 5-8kl/kg/min), despite achieving approximately eight minutes of a maximal exercise test and a peak power output of 75-90 watts. While the PPO and the time to completion achieved were the lowest reported, aligning with a lower VO_{2peak} result, the level did not suggest an accurate reflection of the participants' cardiopulmonary fitness. Furthermore, there were issues with the accuracy of measurements obtained using the $K4b^2$ indirect calorimeter and therefore it had to be replaced with the COSMED Quark. This will impact the interpretation of oxygen consumption readings, which were captured using the $K4b^2$ and also the comparability of measurements taken by both indirect calorimeters.

Two participants on the HIIT arm (none in the control arm) were affected by COVID-19 during the intervention. Data on the impact of COVID-19 on functional capacity and cardiopulmonary fitness is emerging and studies have reported significant impact on functional capacity following COVID-

19 infection (O'Brien et al., 2022, Raman et al., 2021), which is comparable in mild, moderate, severe and critical infections. The acute impact of COVID-19 on response to exercise fitness is unknown, however it is reasonable to assume that the effect of HIIT on cardiopulmonary fitness may have been attenuated by the COVID-19 infection. As COVID-19 was first described in January 2020, this was not an influencing factor in any of the previously described HIIT studies, therefore the physiological impact of COVID-19 on a person's ability to respond to a HIIT programme is not established.

Furthermore, there was data contamination due to additional exercise completed in the control arm. In fact, one participant in the control arm reported completing six to seven sessions of HIIT per week for five weeks in the lead-up to surgery. Controlling for additional exercise outside an exercise protocol is very difficult, and while subjective measurement of this data gives insight to exercise levels, the nature of it introduces potential recall bias and makes inference about the impact on cardiopulmonary fitness challenging. Nevertheless, it is important to consider the impact it can have and the implications on interpretation of results. These cumulative factors make interpretation of the effect of HIIT on preoperative cancer patients' cardiopulmonary fitness difficult. The increase in PPO suggests a positive trend, however a larger participant pool is required to adequately power PRE-HIIT and compensate for potential inaccuracies as a result of COVID-19, attrition and equipment failure. Therefore, the accuracy of VO_{2peak} results for these seven participants (14.5%) will be considered when the full trial analysis is completed. As described above, recruitment to PRE-HIIT is ongoing and it is powered to 64 participants, with a target accrual of 78 to allow for 20% attrition.

The role of HIIT prior to oncological resection has a strong rationale, indicating potential for this intervention. However, to date there is insufficient evidence to clarify its role and effect on preoperative fitness and postoperative complications. Results presented in this thesis indicate that studies to date are small, with varying cohorts, heterogeneous outcome measures and reporting deficits. These findings lead to inconclusive results on the impact of preoperative HIIT on VO_{2peak} and postoperative complications. However, the significant within group change in PPO identified in all studies included in the systematic review and in Study I, suggest a potential positive effect of HIIT on cardiopulmonary fitness. There are a growing number of studies investigating the role of HIIT in these complex cohorts, including the PRE-HIIT trial. However, to comprehensively understand the future of HIIT in this population, there is a need for multiple high quality, large-scale, multi-centre studies. These studies would significantly contribute to the existing body of evidence, providing crucial data for robust meta-analyses. Such analyses are vital for pooling results and determining the definitive role of preoperative HIIT in these complex cohorts.

The benefits of exercise prehabilitation go beyond the impact on physical functional status. The preoperative phase is associated with significant anxiety and stress and the psychological benefits of exercise are well established. Exercise is associated with reduction in anxiety, depression and improved mood (Mikkelsen et al., 2017). Research in exercise prehabilitation primarily focuses on the impact of exercise on physical outcomes and health-related quality of life (HR-QL), however the psychological benefits of exercise during the preoperative phase must not be underestimated (Durrand et al., 2019, Waterland et al., 2021, Heger et al., 2020). Participants in Study III identified exercise as an important stress management tool, which is well placed in the preoperative phase. This was mirrored by participants in PRE-HIIT, who were motivated to take part in the prehabilitation programme with the goal of preparing both physically and mentally for surgery. Preoperative anxiety, stress and depression are independently predictive of postoperative complications (Rosenberger et al., 2006); therefore, interventions to improve anxiety and depression management in the preoperative phase are crucial.

Psychological interventions focusing on stress management and anxiety are a key pillar of prehabilitation (Durrand et al., 2019). However, exercise prehabilitation offers a complementary tool that has the potential to enhance patient psychological outcomes even further (Durrand et al., 2019). Participants in PRE-HIIT felt the direct benefits of exercise on their mental health with improvements in stress levels and mood. These findings are similar to experiences of patients following vigorous intensity exercise prehabilitation, who reported enhanced mental preparedness (Banerjee et al., 2021). Therefore, the benefits of exercise prehabilitation extends beyond that of physical outcomes and these benefits should be promoted to enhance both engagement and referrals.

Participation in exercise prehabilitation offers multiple psychological advantages. One of these advantages is the increased sense of control experienced by patients when they actively participate in their own healthcare. Individuals facing a cancer diagnosis often perceive a loss of control and participants in both Study II and Study III valued the opportunity that exercise prehabilitation presents to regain some control (Ranchor et al., 2010). Perceived control is an important healthcare variable, with higher levels associated with enhanced physical health status and quality of life, and reduction in psychological distress, anxiety and depression (Calfee et al., 2006, Milte et al., 2015, Lin et al., 2020, Moser et al., 2009, McKinley et al., 2012). As previously discussed, preoperative anxiety and depression directly affects postoperative recovery and therefore any tool which has potential to impact in this way is vital. In surgical cardiac patients, a higher perceived control over recovery was associated with a shorter length of hospital stay (Rosenberger et al., 2006). Regaining a sense of control consistently emerges as a motivator for participating in exercise prehabilitation

in this thesis and is supported by the existing literature (Beck et al., 2021, Matthew et al., 2022, Gillis et al., 2021, Van der Velde et al., 2023, Brahmbhatt et al., 2020). The positive effect this has on patients' psychological well-being and preparedness for surgery is evident in both Study II and Study III. Participants felt empowered by prehabilitation, and the higher perceived control was acknowledged as a powerful asset to the programme. Whether this impact comes from the psychological benefits of exercise, or as an independent factor associated with regaining control, is unclear. Regardless, exercise prehabilitation may serve as a tool to enhance perceived control in patients, leading to improved psychological well-being and potentially facilitating their recovery process.

7.2.4 Implications of Research

Preoperative HIIT is feasible and acceptable to patients prior to surgery and may represent a more enjoyable approach to preoperative exercise compared to moderate intensity exercise, even in the context of delivering the intervention at a time of considerable uncertainty and strain on the health service due to an unprecedented pandemic. This may have practical applications in the design and implementation of exercise prehabilitation programmes for patients scheduled for surgery. However, recruitment onto HIIT trials may represent a challenge and consideration should be given to expansion of the trial to support satellite offices, allowing patients to attend assessments and intervention locally, thereby reducing the burden. While this may reduce the burden for patients and enhance recruitment, implementation of CPETs for assessment requires highly trained personnel and expensive equipment, therefore the feasibility of this approach should be appropriately assessed to determine if it is an option.

Additionally, education should be provided to surgical teams regarding how best to approach and educate patients on HIIT. Acceptability levels are comparable across groups, with highest levels evident in patients in the preoperative phase. This suggests that the preoperative phase represents an opportune time to educate and motivate patients to participate in exercise. Furthermore, the disparity between perceived burden and actual burden suggests that all patients should have the opportunity to discuss exercise prehabilitation with their healthcare provider, regardless of preconceptions regarding experience with exercise or perceived burden. The benefits associated with exercise prehabilitation extend beyond purely physical and may be of particular help to patients who are experiencing high levels of stress or anxiety in the preoperative phase. Therefore, future trials should consider assessing the impact of exercise on mental status. Finally, the goal of research is to advance care, and reporting deficits in trials act as a barrier to replication of effective strategies. Therefore, enhanced reporting, focusing on recruitment strategies, adherence and

adverse events would enable replication of effective approaches and may enhance the standard of evidence produced.

7.3 Critical Analysis of Work

7.3.1 Study Design and Methods

Rigorous methodological approaches have been applied to each component of this thesis. However, there are some limitations which must be addressed. The methodological quality of studies included in the meta-analysis effects the interpretation of results, therefore these results should be considered preliminary. Results of GRADEpro which impacted the quality score included imprecision, risk of bias and inconsistency of results. Of these three, two are directly related to the nature of exercise. The exercise interventions prescribed in each study vary significantly, leading to a high risk of imprecision due to the heterogeneity. Considering exercise is dose-respondent, the variation in dose prescribed effects the impact on cardiopulmonary fitness, therefore contributing to the inconsistencies in the results generated. However, it is not feasible for numerous exercise trials to have identical exercise prescription and it is common to conduct systematic reviews and meta-analyses in the exercise field. Furthermore, the risk of bias was predominantly attributed to reporting deficits and not significant methodological concerns. Therefore, despite this low grade assigned, there were valid reasons to proceed with the analysis. Future research in this area should emphasise the importance of improved reporting to reduce potential bias and aim to refine the definition of HIIT for more standardised and reliable comparisons. By addressing these challenges, future systematic reviews and meta-analyses in the exercise field can yield more robust and informative findings.

In Study I, the RCT methodology aims to achieve a random and unbiased representation of the target population, enhancing the internal validity of the study. This approach is considered the gold standard for trials. However, the strict inclusion and exclusion criteria excludes those with significant co-morbidities. While this was necessary to ensure the safety of participants on the trial, this ultimately excludes those who may benefit most from prehabilitation therefore limiting representation.

7.3.2 Sampling and Recruitment

A thorough search strategy, including forward and backwards citation was employed in the systematic review and meta-analysis, in addition to comprehensive recruitment strategies used in Study I and III. However, despite this, there is a limited and imbalanced sample size in this thesis. The small sample size in the systematic review, and the imbalance of cancer types and number in stakeholder groups may limit the generalisability of results across the population. PRE-HIIT was a

single centre trial, and as discussed there was unique barriers associated with the trial in this centre. Therefore, this may limit the impact of feasibility results in other centres, which may face different challenges. Additionally, while the rigorous RCT methodology limits the impact of sampling bias, it must be considered that participants in all studies may represent a more willing cohort, who actively engage in research and are more likely to engage in exercise prehabilitation. Finally, convenience sampling was employed in all studies, leading to the potential of sampling bias. Data was collected in Study I regarding decisions to decline, however due to the study design this was not possible in Study III.

7.3.3 Outcome Measures

Across this thesis, valid and reliable outcome measures were utilised to assesses change in fitness, levels of acceptability and number of postoperative complications. However, despite selecting the most appropriate outcome measure, some limitations must be considered. Cardiopulmonary exercise testing is the gold standard in exercise testing; therefore, it is the most appropriate form of measuring cardiopulmonary fitness. However, there were many limitations encountered with CPET throughout the trial. Despite using COSMED equipment, which is described on the company's website as high quality equipment with 'unsurpassed accuracy, reliability and real breath-by-breath analysis of pulmonary gas exchange', there were significant challenges encountered with reliable output and at times the machine failed to function (COSMED). Therefore, only 31 of the 32 CPETs included breath-by-breath analysis. Additionally, the first 10 patients' CPETs were completed using the K4b^2 and the remainder were completed using the Quark CPET. While the equipment should be comparable, there is the potential for error to be introduced and in combination with the missing data, may limit the interpretation of results regarding impact of HIIT on oxygen consumption at peak and anaerobic threshold.

As discussed in Chapter 6, there are no cut points for mild, moderate and high levels of acceptability using the Theoretical Framework of Acceptability. While this limitation is discussed in Study III, it also has applicability on acceptability outcomes in Study I. The mixed-methods approach to analysis of acceptability employed in this thesis allowed for corroboration from the qualitative component. However, qualitative research is open to bias which must be considered. Results can be influenced by the researchers' opinions and are difficult to replicate. Therefore, to eliminate potential bias, a standardised approach to grading acceptability levels should be produced to allow easy interpretation of acceptability levels, without relying on qualitative components to corroborate results.

7.4 Implications for Future Research

Given the sparsity of previous literature investigating prehabilitation strategies in lung and oesophageal cancer, there is considerable scope for future research in this complex cohort. Although no significant improvement in VO_{2peak} following HIIT was observed in the systematic review and PRE-HIIT, additional robust research is required. These studies should be appropriately powered to identify the optimal preoperative dose of exercise to elicit significant changes within the short timeframes available. The PRE-HIIT trial is powered to 63 and is actively recruiting and consideration will be given to the interpretation of VO_{2peak} readings. However, the robust design and appropriately powered group will give important insight into the effect of HIIT preoperatively in lung and oesophageal cancer. Additionally, future research should focus on high-risk patients, such as those with significant co-morbidities who may benefit even more from a preoperative intervention. It is also important to acknowledge that lung and oesophageal cancer are just one example of a complex cancer cohort where prehabilitation may play an important role. Little is known regarding the effect and need for prehabilitation in head and neck cancers and pancreatic cancers. Furthermore, consideration should be given to the psychological impact of participating in prehabilitation in relation to preparedness for surgery. A master's student in our Exercise Oncology Research Group will be following on from these findings and looking at this area examining patients' psychological preparedness following PRE-HIIT.

7.5 Conclusion

In conclusion, results of this systematic review and meta-analysis, and PRE-HIIT demonstrate there is insufficient evidence to support HIIT as a method of improving preoperative fitness prior to oncologic resection. Importantly, the quality of evidence to date is low and underpowered, therefore results should be interpreted with caution and further research is required for clarity. While recruitment onto PRE-HIIT may represent a challenge, preoperative HIIT completed face-to-face or via telehealth is feasible, safe and acceptable for participants and comparable between groups for patients scheduled for lung and oesophageal cancer resection. While the prehabilitation was challenging, participants valued and enjoyed the physical and psychological benefits of participating in the PRE-HIIT trial, particularly in the HIIT arm.

Key factors identified to facilitate participation in prehabilitation are recommendations from the surgical team, support from the physiotherapy team and accessibility through multiple mediums. Exercise prehabilitation is highly acceptable to key stakeholders. Although prehabilitation may be associated with some burden, stakeholders involved in delivering and receiving prehabilitation are positive about its role. They understand its goal and support the provision of the service. However,

consideration should be given to execution of the service to enhance implementation. Three recommendations have been generated from Study III in this thesis:

- **Introduction of the service should be comprehensively designed and clearly presented.** The discussion should be approached in a supportive and accessible manner, discussing potential barriers and empowering patients to participate. The information should include a concise outline of the components of prehabilitation and potential benefits.
- **Prehabilitation programmes should be patient-centred and prioritise accessibility for all.** Programmes should be designed in collaboration with patients, addressing specific needs and goals and enabling them to overcome barriers. Therefore, programmes should be flexible, accommodating of other commitments and accessible through multiple mediums.
- **Service must be appropriately resourced with a clear referral process** to ensure the longevity of the prehabilitation programme.

Results from this thesis indicate that that the effect of preoperative HIIT is unclear, nevertheless it demonstrates a feasible, acceptable and enjoyable approach to exercise prehabilitation. Furthermore, stakeholders acknowledge and value the role of prehabilitation and believe it to be an acceptable approach to enhancing fitness preoperatively. These findings enrich our understanding of the role and effectiveness of exercise prehabilitation within the scope of oncological resection.

Chapter 8 References

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Appendix I Publication of Preoperative High Intensity Interval Training for Oncological Resections: A Systematic Review and Meta-Analysis

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Preoperative high intensity interval training for oncological resections: A systematic review and meta-analysis

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ABSTRACT

Exercise prehabilitation prior to major surgery targets a reduction in postoperative complications through improved conditioning and respiratory function. However its effectiveness in cancer surgery is unclear. The objective of this review was to determine if preoperative high-intensity interval training (HIIT) improves preoperative fitness in patients scheduled for oncologic resection, and whether postoperative complications are impacted.

Methods: CINAHL, AMED, PEDro, EMBASE, The Cochrane Library and PubMed/MEDLINE were searched until April 2021 using predefined search strategy and accompanied by manual forward and backwards citation review. Screening of titles, abstracts, full-texts, data extraction, risk of bias assessment and methodologic quality was performed independently by two reviewers. Mean difference (MD) with 95% confidence intervals (CI) was compared and heterogeneity assessed using Chi Squared Test and I^2 statistic. Six randomised controlled trials (RCTs) were included in the systematic review. Interventions prescribed bouts of high-intensity exercise [80–115% peak work rate (WRp)] interspaced with low-intensity (rest-50% WRp) exercise. The meta-analysis included five RCTs reporting peak oxygen consumption (VO_{2peak}). Preoperative HIIT did not result in significantly higher VO_{2peak} in comparison to usual care or moderate intensity exercise (MD 0.83, 95%CI-0.51–2.17) kg/ml/min, p = 0.12). Studies were insufficiently powered with respect to postoperative complications, but there is no evidence of significant impact. No adverse events occurred and high adherence rates were reported. Results of this systematic review and meta-analysis demonstrate there is insufficient evidence to support HIIT as a method of improving preoperative fitness prior to oncologic resection. Further work is needed to determine if specific HIIT parameters can be adapted to improve efficacy over short time-frames.

1. Introduction

Prehabilitation represents a defined multidisciplinary process of enhancing physical, nutritional and physiological resilience to better tolerate the stresses associated with surgery [1,2]. The principal goal is to reduce surgical complications, length of stay, and the burden of cost on the health system, and to enhance recovery of health related quality of life (HR-QL) [3]. Exercise is a key component and may include aerobic, inspiratory muscle and resistance training [4–6].

Aerobic exercise is a key element of prehabilitation and targets an increase in aerobic capacity before surgery, with an anticipated reduction in postoperative pulmonary complications (PPCs) and improved HR-QL [4,7,8]. Peak oxygen consumption (VO_{2peak}) is the principal metric. Patients with VO_{2peak} of <15 ml/kg/min are high risk for PPCs and cardiac morbidity following lung resection [9–11]. In colonic surgery, a multivariate analysis reported that an increase of 1 ml/kg/min in oxygen consumption at lactate threshold was associated with an approximate 20% reduction in complications (odds ratio (OR) 0.77, 95% confidence interval (CI) 0.66, 0.89), and an increase of 2 ml/kg/min was associated with a roughly 40% reduction (OR 0.6, 95% CI 0.45–0.80) [12]. Intuitively it is logical that such a programme may have therapeutic impact in reducing complications. However, a barrier

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may exist where the time-frame to effect change is limited, and this is particularly applicable to time-sensitive cancer surgery.

The time-frame for preoperative interventions may also be limited by national policies. For instance, the NHS mandates a maximum of 31 days from diagnosis of cancer to initiation of treatment [13]. The Irish Department of Health advises that patients should have a surgical date within 30 days of the decision to operate [14]. These limited time-frames may restrict the effect that moderate-intensity exercise can have on the cardiorespiratory system and has led to increasing interest in alternative methods. Accordingly, administration of high-intensity aerobic training in a concentrated period may have a pragmatic rationale. High intensity interval training (HIIT) is defined as 'repeated short-to-long bouts of rather high-intensity exercise interspersed with recovery periods' [15] or 'intense work periods, may range from 5 s to 8 min long, and are performed at 80%–95% of a person's estimated maximal heart rate' [16]. This low volume of high-intensity work is an effective method of training in healthy individuals [15,17]. It can elicit physiological changes similar or superior to moderate-intensity continuous training [18,19]. It has also been shown to improve aerobic capacity in cancer patients undergoing treatment or in survivorship [20]. A 2018 meta-analysis by Blackwell and colleagues, reported mean difference (MD) of 3.38 (95% CI 2.7–4.05) ml/kg/min between HIIT and control groups, in less than eight weeks in a population with diverse disease [21]. Metabolic adaptations on oxidative capacity and peripheral insulin sensitivity, along with improvements in cardiac and respiratory function, are achieved by the higher intensities reached in each exercise session [19,22]. This principle of HIIT achieving physiological benefits fits well into treatment pathways for patients requiring major cancer surgery, either alone or after preoperative chemotherapy or combination chemotherapy and radiotherapy [19,22].

This systematic review and meta-analysis explores whether HIIT improved preoperative fitness in patients scheduled for oncologic resection, and whether this impacted on postoperative complications. The primary aim of this review was to assess change in preoperative fitness in patients scheduled for oncological resection. Secondary aims were to analyse the impact on postoperative complications and report on measures of feasibility.

2. Methods

In order to identify the most robust evidence, randomised controlled trials (RCTs) which examined the effects of HIIT versus usual care in patients scheduled for oncological resection were included. HIIT was defined as exercise sessions which involved 'repeated short-to-long bouts of rather high-intensity exercise interspersed with recovery periods'. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines were followed [23]. The review protocol has been registered with the International Prospective Register for Systematic Reviews (PROSPERO) (CRD42020178959).

The intervention arms of the studies consisted of patients who participated in preoperative HIIT and the control arm consisted of usual care provided in each centre or moderate intensity exercise programme. Non-English language publications were excluded, as were studies with participants under the age of 18. All interventions meeting the criteria were included regardless of sample size. The primary outcome examined was aerobic fitness, primarily VO_{2peak}, peak power output (PPO) and anaerobic threshold (AT) preoperatively. Secondary outcomes were postoperative complication outcomes prior to hospital discharge including Clavien Dindo Classification System; Melbourne Group Scale; Thoracic Morbidity and Mortality scale; length of stay in hospital, intensive care unit and or high dependency unit and 30 day mortality.

A search strategy was defined using keywords and key surgeries in consultation with the subject librarian. The databases CINAHL, AMED, PEDro, EMBASE, The Cochrane Library and PubMed/MEDLINE were searched until April 20, 2021. Search terms included 'high-intensity intermittent exercise' OR 'high-intensity intermittent training' OR 'high-intensity interval exercis*' OR 'high-intensity interval training' OR HIIT OR HIIE' and 'cancer surgery', 'lung resection' Pneumonectom × OR lobectom × OR segmentectom × OR pneumoresection × OR pulmonectom × were used (see Appendix A for full search strategy). Forward citing (forward searching of all studies which cited articles identified in the database search), backwards citing (backward searching through all references in articles identified in the database search) were also performed manually. Clinicaltrials.gov was searched for titles of completed and published articles, ongoing trials were not considered for inclusion.

Data was extracted onto a preformatted Excel sheet. Data extracted included age, sex, cancer type, surgery type, intervention characteristics, results of outcomes used for aerobic capacity, feasibility outcomes, sources of funding and postoperative complications. Data extraction was carried out independently by two reviewers (ES and LOC) and any differences were discussed and resolved with a third author (EG). Three authors were contacted by email to retrieve data to allow for meta-analysis of VO_{2peak}, AT and PPO; however data was not available from two of these papers.

Risk of bias was assessed independently by ES and LOC using the Cochrane Collaboration's 'Risk of Bias' tool [24]. Discrepancies and concerns were considered discussed with EG. Methodologic quality was evaluated using GRADEpro GDT software.

Data available for meta-analysis was assessed using RevMan 5 (version 5.3). Fixed effects method was used to examine post-intervention VO^2_{peak} data (expressed by mean difference). Heterogeneity was assessed using chi square test and I^2 statistic.

3. Results

In March 2020 a total of 94 titles were identified by electronic database search, 4 were removed due to duplication leaving 90. After screening of abstracts, 18 full-texts were read to assess for eligibility. 11 papers were excluded due to non-RCT design [6], abstract only [2] and HIIT not prescribed [3]. Seven studies remained for inclusion in the review. An additional 428 papers were identified through manual forward and backward citation chasing and trial registry search. After screening of abstracts and full texts, no additional studies were identified for inclusion. The search was updated in April 2021. Twenty-four papers were screened, two full texts were read for eligibility and one was included (Fig. 1). Of the eight full-texts identified for inclusion, three related to The Lung Cancer Rehabilitation Study (LCRS) [25–27]. Therefore, six unique exercise interventions were identified for inclusion. In total 384 participants were included in the systematic review. Types of oncologic resections included lung resection by thoracotomy and VATS [25–28], liver resection [29] radical cystectomy, robot assisted or open prostatectomy, laparoscopic nephrectomy [30,31] and laparoscopic colorectal surgery [32]. Five interventions reported sources of funding [25–29,31,32] and one did not [30]. The mean age of participants in each study ranged from 61 to 72 years. The combined ratio of males to females was 255:97. Mean baseline body mass index of participants ranged from 24.4 to 29.7 kg m^{-2}.

3.1. Risk of bias

3.1.1. Randomisation

All studies used a valid randomisation technique of either computer-generated lists or random permuted block randomisation, held by an independent person.

All studies were therefore deemed to have low risk of bias regarding randomisation.

3.1.2. Deviations from intended interventions

All studies described exercise protocols in terms of planned intensity, number of sessions and session duration, and recorded adherence as achieving these parameters. Additional details describing adherence to

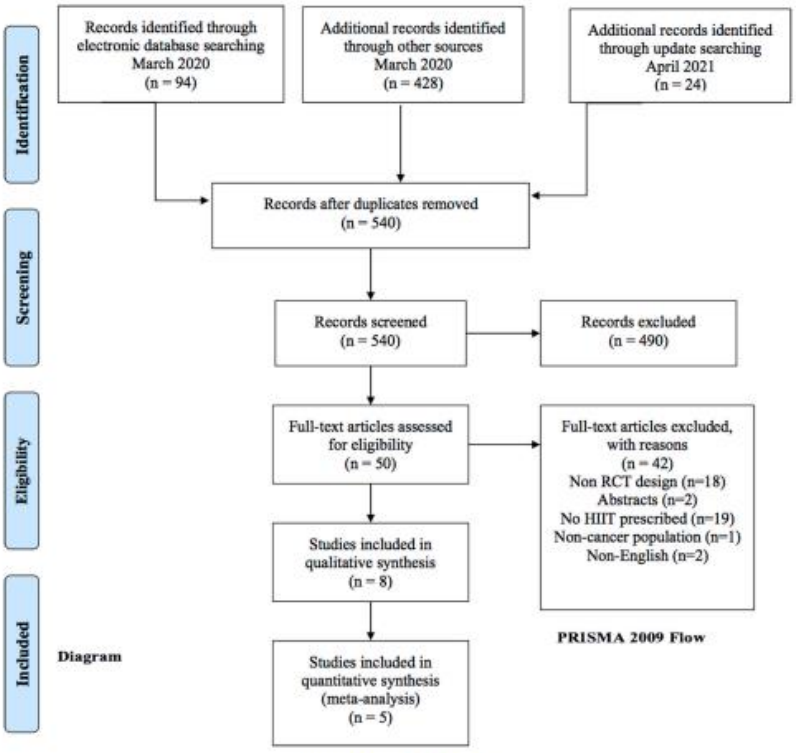

Fig. 1. PRISMA flow diagram.

each intervention session i.e. actual intensity achieved by participants was described by only one study [32]. Dose modifications and early session termination were not reported in any. Due to the nature of the interventions, all participants and those delivering the intervention were aware of study allocation. The intervention arms in five of the six studies were considered high risk of deviation from intended interventions, largely due to lack of reporting rather than intervention design [25–31]. One study was deemed low risk in both the HIIT and moderate intensity arms due to the reporting of both session attendance and adherence to prescribed intensities [32]. The usual care group were deemed low risk for deviation from the intended intervention. Even if participants assigned to control arms had increased habitual physical activity levels, they were unlikely to have achieved the high-intensity training loads prescribed to the intervention arms. Furthermore, in three of the studies, patients in both groups were advised to maintain habitual levels of exercise and/or encouraged to partake in 30 min of mobilisation four times weekly allowing for a potential increase or maintenance of aerobic capacity amongst control participants.

3.1.3. Measurement of the outcome

All six interventions used appropriate outcome measures and measurement time-frames. In five of the papers, assessors were blinded to participant allocation and therefore deemed low risk of bias [28–32]. Blinding of assessor was not stated in the LCRS trial and therefore deemed high risk of bias due to the lack of reporting [25–27].

3.1.4. Missing outcome data

One study, which analysed 55% of randomised participants post-intervention and 48% at the three month follow-up, was considered high risk of bias due to missing outcome data [28]. Furthermore, reported attrition was due to factors which may have had a direct impact on the true value, for example addition of neoadjuvant therapy to treatment plan after randomisation (n = 1), abandonment of intervention (n = 2) and rescheduling of surgery (n = 2). One study reported significant drop-out in the HIIT arm (80.95% completing follow-up assessment in the HIIT arm versus 95% in the moderate intensity arm) [32]. The study employed an analysis models to adjust for missing data and was considered low risk [32]. Of the remaining four interventions, while all analysed <95% of randomised participants [25–27,29–31], three analysed >92% of participants [25–27,29,30], one analysed >85% of participants [31] and attrition rates were comparable between all arms, and therefore they were considered low risk of bias.

3.1.5. Selection of the reported results

Three of the six interventions had trial protocols registered with clinicaltrials.gov [25–29]. Of these three, two were scored low risk while one [28,29], the LCRS, was deemed to have some concerns due to the secondary outcomes planned in the protocol differing from the final reported study results [25–27]. This criteria was difficult to assess in the other three studies as no published protocols could be found and were therefore considered of some concern [30–32] (Fig. 2).

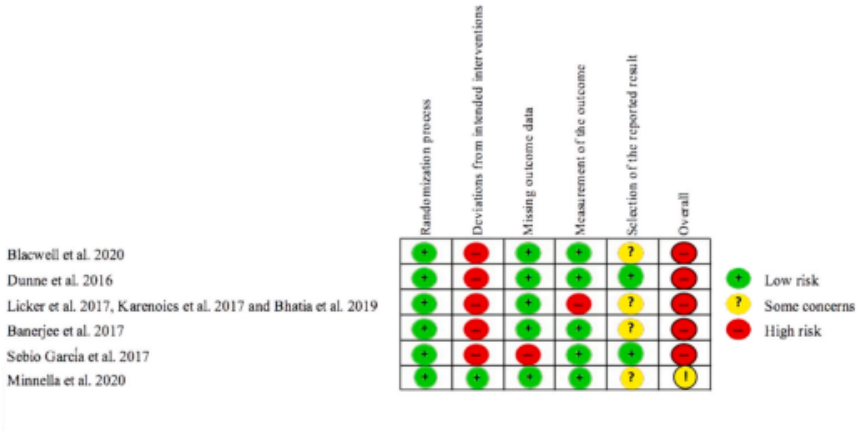

Fig. 2. Risk of bias assesment.

3.2. Feasibility

Feasibility was the primary outcome in one trial and was assessed by 'recruitment and attrition, willingness to be randomised, acceptability of the outcome measures, adherence to the intervention, safety and suitability of the exercise dose and adverse events' [30]. Of 112 potentially eligible participants, 53.5% agreed to participate [30]. All included participants were willing to be randomised and no objections to the outcome measures were reported [30]. Attrition rates were comparable between study arms and median number of sessions attended was eight (range 1–10) [30]. No adverse events were reported [30]. The other five interventions reported feasibility in terms of recruitment, intervention adherence and adverse events [25–29,31,32]. The LCRS assessed 189 patients for eligibility, of which 164 were randomised [25–27]. Dunne and colleagues assessed 193 for eligibility of which 115 were eligible and 38 randomised [29]. 76 were deemed eligible for inclusion in a recent study by Blackwell et al. and 40 were randomised [31]. García et al. assessed 319 for eligibility, excluding 279 and including 40 [28]. Seventy six were assessed for eligibility by Minnella et al. and 42 were randomised [32]. Two participants in the HIIT arm refused to complete preoperative Cardiopulmonary Exercise Testing (CPET) [32]. The LCRS reported an adherence rate of 87 (standard deviation (SD)18%) with a median of eight (inter quartile range (IQR) 7–10) sessions attended [25–27]. Of the 19 participants randomised to the HIIT intervention by Dunne and colleagues, 18 completed 100% of the exercise sessions [29]. Blackwell and colleagues defined adherence as attending >10 exercise sessions and reported an 84% adherence rate with a median of 11(IQR 10–12) sessions attended [31]. García et al. reported a median of 16 (range 8–25) sessions attended [28]. Minnella et al. defined adherence as weekly attendance and percentage of time spent at prescribed work rate [32]. An attendance of 88.5 (standard deviation (SD 19.9)% was reported in the HIIT arm and 92.7(SD12.1)% in the moderate intensity arm, adherence to intensity in the HIIT arm was 89.3 (SD25%) in the HIIT arm and 97(SD7)% in the comparator ($p = 0.282$) [32]. No serious adverse events were reported in any of the interventions [25–32]. Blackwell and colleges reported two mild adverse events (discomfort with the cycle ergometer seat and mild leg pain post-intervention) [31].

3.3. Interventions

Five trials compared HIIT to usual care provided [25–31] and one compared HIIT to moderate intensity exercise [32]. The moderate intensity arm completed 40 min of exercise three times a week at 80–85% of power achieved at [32]. Usual care provided was not defined in any of the five studies, however two studies instructed the usual care group to maintain habitual levels of exercise [30,31], two advised following clinical recommendations for exercise prior to surgery [25–27,29] and one did not report on any recommendations given [28]. HIIT interventions varied by intensity prescribed, duration and number of intervals and the number of sessions per week. Intensity was prescribed from baseline CPET using VO_{2peak} or work rate peak (WRp) in five interventions [25–27,29–32]. Three of these four prescribed >90% of WRp or VO_{2peak} [25–27,29,31], one prescribed 85–90% of WRp [32] and one prescribed >80% of WRp during periods of high-intensity [28]. The sixth intervention prescribed intensity of 13–15 on the Borg Scale of Perceived Exertion reportedly equating to 70–85% of predicted heart rate max (HR_{max}) [30]. Two interventions incorporated HIIT as the aerobic component of a larger multi-component prehabilitation programme [28,32]. In addition to HIIT, the LCRS trial included resistance training exercises, prescribed at an individual level; however details are not provided [25–27]. Minnella et al. prescribed individualised resistance training, nutritional interventions and relaxation techniques in both the HIIT and moderate intensity arms of the trial [32]. The number of sessions prescribed ranged from two to five per week and number of intervals ranged from six repetitions of 5 min to 30 min' worth of 15 s alternating repetitions. The duration of high-intensity intervals ranged from 15 s to 5 min. The rest intervals were only described in five of the six studies and consisted of a low-intensity active rest or a 15 s pause (Table 1). Four interventions were carried out in a university exercise lab [28–31], one in an outpatient department [25–27] and one in a hospital [32]. The duration of planned interventions ranged from 31 days to six weeks. In the intervention arm between baseline assessment and surgery: one study reported median of 30 (IQR 27–29,31) days [31]; another reported a median of 26 (IQR 21–33) days [25–27] the third study reported a mean of 54.5 (SD15.4) [28] and the final study reported a mean of 23 (SD 6.5) days [30]. Two did not report the mean time from baseline assessment to surgery [29,32]. None of the studies reported a significant difference in duration from baseline to surgery between arms [25–32].

3.4. Impact of preoperative HIIT on preoperative cardiopulmonary fitness

3.4.1. VO_{2peak}

A CPET, which has long been established as the gold standard for

Table 1
Intervention characteristics table.

Study	Country	Participants (number and surgery)	Randomisation	Duration	HIIT frequency	HIIT Session duration	High intensity interval	Low intensity interval	Progression	Adherence
Minnella et al (2020)	Canada	n = 42 laparoscopic colorectal surgery	HIIT or moderate intensity training	4 weeks	3×/week	30min	85–90% of peak power output	80–85% power at anaerobic threshold	Not reported	Attendance: 88.5 ± 19.9% Adherence to intensity: 89.3 ± 25%
Blackwell et al (2020)	U·K.	n = 40 radical robotic-assisted laparoscopic prostatectomy, open prostatectomy, radical cystectomy, laparoscopic nephrectomy	HIIT or UC provided at centre and instructions to maintain habitual physical activity and dietary regimes for the duration of the study.	31 days	3–4x/week	Not reported	5 × 1min @ 100–115% of max load	Not reported	10% after 6 sessions	84%
Banerjee et al (2017)	U·K.	n = 60 radical cystectomy	HIIT or UC provided at centre. UC group advised to carry on lifestyles in usual way.	3–6 weeks	2×/week	approx. 45min	@ 6 × 5 min perceived exertion of 13–15 on borg scale	2.5 min with light resistance	Not reported	8†sessions (1–10)
Dunne et al (2016)	U·K.	n = 38 liver resection	HIIT or UC provided at centre. No restrictions were placed on either arm of intervention and they were encouraged to follow clinical advice on exercise before surgery.	4 weeks	10 HIIT in total +2 recovery sessions	30min	>90% per cent VO_{2peak}	<60% of VO_{2peak}	Not reported	18 completed all sessions
Licker et al (2017) Karenovics et al (2017) Bhatia and Kayser, (2019)	Switzerland	n = 164 lung resection	randomised to HIIT or UC provided at centre. Both groups were given advice on walking 30min 4×/week	3–4 weeks	2–3x/week	2 × 10min interspaced by 4min rest period.	15 s @ 80%–100% of WRp	15 s pauses.	Adjusted during each session to target near-maximal heart rates toward the end of each series of sprints on the basis of the individual's exercise response.	87% ± 18% 8‡ sessions (IQR 7–10)
García et al (2017)	Spain	n = 40 video-assisted thoracoscopic surgery	HIIT or UC provided at centre. No further information reported.	4 weeks	3–5x/week	30min	1min @ 80% of WRp	4 min @50% of WRp f	Not reported	16‡ sessions (8–25)

Abbreviations: ± = standard deviation, @ = at, x/week = times per week,† = median, ‡ = mean, ( ) = range, (IQR) = interquartile range, approx. = approximately, min = minutes, n = number of participants, WRp = work rate peak, VO_{2peak} = peak oxygen consumption.

measuring exercise capacity, was used to evaluate physiological variables and establish VO_{2peak} in five out of the six interventions [25–27,29–32]. VO_{2peak} was defined as the highest VO_2 recorded during the last 30 s of the CPET in three of the studies [25–27,29,30], the last 20 s of the CPET in one [31] and the averaged values recorded in the last 20 s in one [32]. Data from these five interventions were included in the meta-analysis of VO_{2peak} post intervention [26,29–32]. Data was analysed using a fixed effect method and presented as MD. Heterogeneity was considered not significant ($I^2 = 0\%$). There was no significant difference in post-intervention VO_{2peak} in the HIIT group (n = 155) compared to usual care or moderate intensity exercise (n = 154) (MD 0.83, 95% CI-0.51 to 2.17) kg/ml/min, p = 0.12) (Fig. 3). The certainty of evidence was deemed low using the GRADEpro. García and colleagues measured submaximal aerobic capacity using Constant-load Cycle Endurance Test and therefore could not be included in the meta-analysis [28]. This study used time until exhaustion as the primary outcome of aerobic capacity and reported a significant increase of 396.6 s (SD 197.9, p < 0.001) from baseline in the prehabilitation group. No post-intervention Constant-load Cycle Endurance Test was carried out in the control group.

3.4.2. Power

Power output was expressed as WRp in five interventions [25–27,29,30,32] and wattage at CPET failure in one [31]; all reported a significant improvement in power with HIIT. Dunne and colleagues reported a significant MD between group post-intervention (MD 13 (95% CI 4 to 22) watts, p = 0.005) [29]. Banerjee and colleagues reported a significant adjusted mean difference between groups post-intervention (MD 19 (95% CI 10 to 27) watts = 0.000) [30]. The LCRS reported a significantly greater increase (p = 0.021) from baseline in the HIIT group (MC +8 (95%CI 1 to 15) watts in comparison to the usual care (MC -4 (95% CI -9 to +1) watts [25–27]. Blackwell et al. described a significant increase in preoperative wattage at failure (MD 12.86 (95% CI 5.52 to 20.19) watts [31]. Minnella et al. reported no significant between group differences for peak work rate following HIIT or moderate intensity interventions (MD = 4.74, 95% CI 6.56 to 16.04, p = 0.402)watts [32].

3.4.3. Anaerobic threshold

Five interventions measured and reported AT. Three of these five evaluated AT using the v-slope and analysed ventilatory equivalents [25–27,29,30] and two used the modified v-slope and ventilatory equivalents method [31,32]. Dunne and colleagues reported a significant MD between groups post-intervention (MD 1.5, 95% CI (0.2–2.9) kg/ml/min, p = 0.023) [29]. Blackwell and colleagues reported a significant increase in AT from baseline in the HIIT group (MD 2.26, (95% CI 1.25 to 3.26)ml/kg/min p < 0.0) and no significant change in the usual care group (data not reported) (p > 0.05) [31]. No numerical data was reported for the usual care group in this trial [31]. In contrast, two interventions reported no significant effect of HIIT on preoperative AT [25 27,30]. Minnella et al. reported a mean change from baseline of 1.97 (95% CI 0.75 to 3.19, p = 0.001)kg/ml/min in the HIIT group vs. 1.71 (95% CI 0.56 to 2.85, p = 0.002) kg/ml/min in the moderate intensity group with no significant difference between groups (MD 0.26 95%CI 1.41 to 1.94 p = 0.753)kg/ml/min [32].

3.5. Impact of preoperative HIIT on postoperative outcomes

Postoperative complications (Table 2): Only the LCRS utilised postoperative complications as its primary outcome [25–27]. The LCRS study assessed 'composite end point of postoperative morbidity' which was described as a combination of 30-day mortality and any complications which scored >2 on the Thoracic Morbidity and Mortality System [25–27]. Postoperative morbidity did not differ between groups (p = 0.018) [25–27]. However, the power calculated requirement of 400 was not reached, due to a higher than anticipated postoperative complication level, resulting in recruitment cessation. The LCRS did however report a difference in the incidence in PPCs (23% in the control arm versus 44% in the usual care group p = 0.018) [25–27]. Garcia et al. examined postoperative outcomes as a secondary measure and reported no differences in PPCs (HIIT group 50%, usual care group 66%, p = 0.361) [28].

3.5.1. Length of stay

Hospital length of stay was described but underpowered for statistical analysis in five interventions [25–30,32] (Table 2).

4. Discussion

There is a logical and scientific rationale suggesting that preoperative HIIT may improve conditioning, pulmonary physiology and impact on outcomes after cancer surgery. Notwithstanding, the results of this systematic review and meta-analysis demonstrate that there is a paucity of research in this area with little evidence currently exists to support this hypothesis. Encouragingly, the evidence in this area is still emerging, with all included trials herein published in the past four years. Moreover, the existing data supports the feasibility and safety of this approach, with low reported numbers of adverse events.

VO_{2peak} defines a metric that is associated with risk in surgery, in particular thoracic surgery and consequently represents a modifiable factor for HIIT. Two recent meta-analysis reported HIIT to be effective across the cancer care continuum and in other clinical populations (endocrine, cardiovascular, respiratory and psychiatry) [20,21]. After results pooling and analysis of the five papers, there was no significant MD between HIIT versus usual care or moderate intensity exercise. There are factors across the five interventions such as variation in protocols, which may have influenced the results and interpretation of the meta-analysis. Two of the studies, although falling within the definition of HIIT, are on the lower end of the high-intensity scale (80–85% of WRp or heart rate max) [28,30]. Only one of these studies carried out a CPET and did not report significant improvement in VO_{2peak} or AT post-intervention [30]. One study prescribed 85–90% of PPO and reported a significant increase in VO_{2peak} from baseline [32]. However, they did not report a significant difference when compared to moderate intensity exercise. Importantly, while the mean difference between groups was not statistically significant, the HIIT group reported a statistically and clinically significant increase in VO_{2peak} while the moderate intensity group did not. This suggests that while both methods are effective at increasing VO_{2peak}, higher intensity programmes are required to elicit a clinically relevant change in the short time-frames

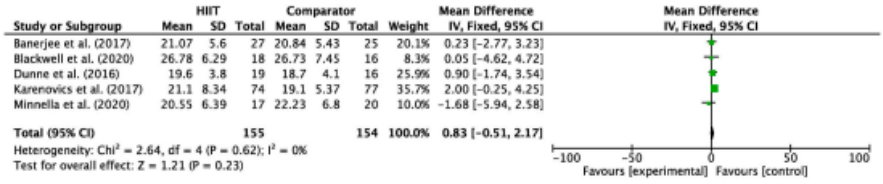

Fig. 3. HIIT versus usual care or moderate intensity.

Table 2
Postoperative outcomes.

Study	Postoperative Complications				Length of Stay (Days)		
	Outcome Measure	HIIT	Usual care/MIE	*P*-value	HIIT	Usual Care/MIE	*P*-Value
Minnella et al (2020)	Clavien Dindo Classification System (grade (n))	I (3 ± 23) II (2 ± 15)	I (6 ± 43) II (2 ± 14)	Descriptive analysis	3.5 (3–6)	4 (3–5)	0.626
Blackwell et al (2020)	Clavien Dindo Classification System (grade (n))	I (2) II (1) IIIb (1) IVb (1)	I (1) II (2) IIIb (0) IVb (0)	Descriptive analysis	Not reported	Not reported	Not reported
Banerjee et al (2017)	Clavien Dindo Classification System (grade (n))	I (4) ≥ III (1)	I (10) ≥ III(4)	Descriptive analysis	7 (4–78)	7 (5–107)	Descriptive analysis
Dunne et al (2016)	Clavien Dindo Classification System (grade (n))	I (0) II (8) III (4) IV (0)	I (4) II (7) III (0) IV (1)	Descriptive analysis	5 (4–6)	5 (4.5–7)	Descriptive analysis
García et al (2016)	Melbourne Group Scale (n (%))	5 (50%)	8 (66%)	p = 0.361	2	3	p = 0.539
Licker et al (2017) Karenovics et al (2017) Bhatia and Kayser, (2019)	30-day mortality or any complications with TMM grades of >2 (n (%))	27 (36.5%)	39 (50.6%)	p = 0.08	10 (8–12)	9 (7–13)	p = 0.223

MIE = Moderate intensity exercise. Values are median (IQR), n = number of participants, ± = standard deviation, grade = grade scored on Clavien Dindo Classification System, descriptive analysis = no statistical analysis carried out, High Intensity Interval Training = HIIT, TMM = Thoracic Morbidity and Mortality System.

available [32]. It is noteworthy that the two shortest duration interventions (median duration 26 and 30 days) also had the highest intensity protocols and both reported a significant increase in VO_{2peak} and power output [25–27,31]. The longest intervention (mean duration 54 days) had one of the lowest intensity interventions and reported a significant increase in preoperative fitness [28]. Blackwell and colleagues compared the effect HIIT versus usual care on VO_{2peak} in less than eight weeks in a recent meta-analysis [21]. Nine of the 13 studies included prescribed peak intensities of >90% of WRp or VO_{2peak} and all reported a significant improvement VO_{2peak} [21]. However, the time frames reported are not available to many cancer patients and optimal training intensity over time-periods <31 days remains to be elucidated. Therefore, there is sound theoretical basis for additional studies to clarify appropriate protocols within short time-frames.

The application of HIIT in cancer cohorts highlights specific challenges such as the magnitude of surgery, administration of chemotherapy, co-morbidities, sarcopenia, and fatigue. Due to the short bouts of intervention, HIIT may provide a more acceptable approach in patients with fatigue compared with longer low-intensity sessions [33]. Accurate reporting of participants' mild adverse events and adherence is important in the context of the clinical applicability of HIIT. Reporting deficits feature in five of the six interventions and are reflected in the risk of bias assessment. Deviation from the intended intervention was considered high risk of bias due to issues with how adherence was reported in these trials. Although overall intervention adherence was defined and reported in each study, a recent paper suggests that when considering adherence to an exercise programme, planned and achieved components should be reported individually [34]. This method advocates documenting intensities achieved in each session, dose modifications in sessions, early termination of sessions and any interruption to treatment or termination of treatment. This gives a clear indication if the planned protocols were achieved by each participant and clearly captures adherence and all adverse events. In all interventions, no serious adverse events were reported. However, only one of the six studies addressed mild adverse events and captured perceived acceptability of the programme [31]. This absence of reporting is similar to findings in 2020 meta-analysis by Wallen and colleagues [20], which reported HIIT to be a feasible and safe method of improving VO_{2peak} across the cancer care pathway [20]. However, only two of the 12 papers in this review explicitly reported mild adverse events [20]. Furthermore, measurement of outcomes in the LCRS was considered high risk of bias due a lack of information on assessor blinding. Considering there is a well-established awareness on the impact of blinding on CPET performance, it is likely that this was due to a reporting oversight opposed to a protocol error [35]. Further trials should pay careful attention to reporting factors to ensure the clinical applicability of the intervention and enable integration into clinical pathways.

The impact of preoperative HIIT on postoperative outcome was difficult to determine in the trials reviewed, largely due to small sample sizes; however no significant benefit was observed. Trials such as the PREPARE-ABC trial, which is powered to examine the impact of exercise prehabilitation on postoperative outcome, cite accrual targets of up to 1146 in contrast to the sample sizes of the studies reviewed (n = 38–164) [36]. The LCRS was the only intervention which evaluated postoperative outcome as its primary outcome and was powered for 400 participants. However, due to higher than anticipated incidence of complications, at a pre-planned interim analysis, recruitment was stopped after 164 participants were enrolled. While insufficiently powered, it is worth noting that there was a reduction of 45% in occurrence of PPCs in the HIIT group. This is similar to the findings of García et al. who reported 50% of participants had at least one PPCs in the exercise group and 65% in the usual care [28]. While these findings are preliminary, they do highlight the need for further analysis given PPCs occur in between 15 and 40% of patients after thoracic surgery for oesophageal or lung cancer [37–39].

This review albeit comprehensive has some limitations. The sample size analysed in the meta-analyses and the number of studies included in both the meta-analysis and narrative synthesis were small. Despite a thorough search strategy, only a small number of papers were identified. To supplement this, a comprehensive manual search which included prospective and retrospective review was carried out. Only five of the six studies were appropriate for inclusion in the meta-analysis of $VO_{2\ peak}$ and due to the variation in outcome measures and requests for further data on AT and PPO was not met. It is also important to consider that a due to the heterogeneity in protocols prescribed it may not be possible to generalize these results [40]. Furthermore in two studies, despite a statistically homogenous baseline VO_{2peak}, the usual care group and the moderate intensity exercise group had a slightly higher baseline VO_{2peak} [31,32]. This between group difference was not of statistical significance. However, when data was collected for meta-analysis, despite both HIIT groups reporting a significant increase in VO_{2peak} while the comparator did not, the within group differences post intervention were not well reflected in the meta-analysis [31,32]. Furthermore, while the intervention carried out by García et al. satisfied the inclusion criteria, no post-intervention CCPT on the control group was undertaken, limiting its interpretation of the outcomes [28]. In our view, the limited studies with variable quality highlights the need to develop a core

outcome set for exercise prehabilitation, which would provide a standard battery of outcomes and time-points to make published results more comparable. Finally, considering the varied types of cancer included in this review, it is important to consider that physiological adaptations to HIIT may vary by diagnosis. There is a paucity of evidence in this area, however considering the physiological implications of different cancer diagnosis and treatments (e.g. direct tumour burden and reduced oxygen diffusion reported in lung cancer or systemic effects of chemotherapy on cardiac function and respiratory muscle strength in breast cancer) response to exercise may be effected [41,42].

In conclusion, HIIT is an intense intervention, and its feasibility must be strongly considered prior to integration into clinical pathways in cancer patients. This systematic review and meta-analysis revealed no significant benefit compared with usual care however a significant benefit was found when compared to usual care and moderate intensity programme. Clearly further work is required to fully analyse the acceptability and feasibility of HIIT programmes and to determine the intensity required to see significant changes over the short preoperative periods. In this context, thee Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus (PRE-HIIT) from this centre is a novel study protocol with the goal of establishing if HIIT can produce a significant improvement in preoperative fitness [43]. This RCT will carry out an in-depth analysis of participant's adherence and the effects of HIIT on VO_{2peak} and will advance knowledge in this area.

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Data sharing

The data that support the findings of this study are available from Emily Smyth (Smythe3@tcd.ie) upon reasonable request.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2021.101620.

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1 Search Strategy for Systematic Review

EMBASE

1. 'cancer surgery'/exp 'colon resection'/exp OR 'cystectomy'/exp OR 'liver resection'/exp OR 'hysterectomy'/exp OR 'lung resection'/exp OR 'nephrectomy'/exp OR 'esophagus resection'/exp OR 'pancreaticoduodenectomy'/exp OR 'thyroidectomy'/exp OR 'transurethral resection'/exp OR 'mastectomy'/exp OR 'laryngectomy'/exp
2. (Oncological NEAR/2 resection*):ti,ab
3. ((Cancer OR neoplas*) NEAR/2 surger*):ti,ab
4. ((cancer OR neoplasm*) NEAR/2 (excision OR extirpation OR resection*)):ti,ab
5. (tumo?r* NEAR/2 (excision OR exeresis OR resection*)):ti,ab
6. (Tumo?rectom*):ti,ab
7. ((lung* OR colon OR breast OR prostat* OR colorectal OR abdominoperineal) NEAR/3 resection*):ti,ab
8. ((bladder OR stomach OR liver OR gastric OR Liver) NEAR/3 resection*):ti,ab
9. ((lung* OR kidney* OR esopha?g* OR oesopha?g* OR pancreato-duodenal OR pancreatoduodenal) NEAR/3 resection*):ti,ab
10. (Colectom* OR proctocolectom* OR proctosigmoidectom* OR ileocolectom*):ti,ab
11. (Cystectom* OR prostatocystectom*):ti,ab
12. (Gastrectom* OR gastroresection* OR hemigastrectom* OR ‘stomach extirpation’):ti,ab
13. (Hepatectom* OR ‘hepatic lobectom*’ OR trisegmentectom* OR segmentectom*):ti,ab
14. (Hysterectom* OR ‘salpingo-oophorectom*’ OR salpingectom* OR vaginectom* OR vulvectom* OR ‘Pelvic exenteration’ OR colpohysterectom* OR hysterocolpectom* OR panhysterectomy OR ‘uterus extirpation’):ti,ab
15. (Pneumonectom* OR lobectom* OR segmentectom* OR pneumoresection* OR pulmonectom*):ti,ab
16. (Oesopha?gectom* OR esopha?gectom*):ti,ab
17. (Pancreaticoduodenectom* OR ‘Whipples procedure’ OR ‘brunschwig operation*’ OR duodenopancreatectom* OR ‘pancreatico duodenectom*’ OR ‘pancreato duodenectom*’ OR pancreatoduodenectom* OR ‘Whipple operation’):ti,ab
18. (Thyroidectom* OR strumectom* OR Hemithyroidectom* OR Isthmectom*):ti,ab
19. Prostatectom*:ti,ab
20. (Mastectom* OR Lumpectom* OR mammectom*):ti,ab
21. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #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

22. 'high intensity interval training'/exp
23. (‘high-intensity intermittent exercise’ OR ‘high-intensity intermittent training’ OR ‘high-intensity interval exercis*’ OR ‘high-intensity interval training’ OR HIIT OR HIIE):ti,ab
24. (Interval NEAR/2 (training OR exercise)):ti,ab
25. (Intermittent NEAR/2 (training OR exercise)):ti,ab
26. (‘repeated sprint training’ OR ‘intensive exercise*’ OR ‘intensity intermittent exercise*’ OR ‘anaerobic interval’ OR ‘repeated sprint’ OR ‘sprint interval*’ OR ‘high aerobic intensity training’ OR ‘intensity training’ OR ‘intensi* exercis*’ OR ‘circuit training’ OR ‘repeated sprint training’ OR ‘high intensity intermittent exercis*’):ti,ab
27. #22 OR #23 OR #24 OR #25 OR #26
28. #21 AND #27

OVID Medline

1. Cystectomy/ or Hepatectomy/ or Hysterectomy/ or exp Nephrectomy/ OR pancreaticoduodenectomy/ or Thyroidectomy/ or exp Mastectomy/ OR Laryngectomy/ OR exp Colectomy/ or exp Prostatectomy/ or exp Gastrectomy/ or exp Proctectomy/ or exp Pneumonectomy/ or Esophagectomy/
2. (Oncological adj2 resection*).ti,ab.
3. ((Cancer OR neoplas*) adj2 surger*).ti,ab.
4. (cancer adj2 (excision OR extirpation OR resection*)).ti,ab.
5. (tumo?r* adj2 (excision OR exeresis OR resection*)).ti,ab.
6. (Tumo?rectom*).ti,ab.
7. ((lung* OR colon OR breast OR prostat* OR colorectal OR abdominoperineal) ADJ3 resection*).ti,ab.
8. ((bladder OR stomach OR liver OR gastric OR Liver) ADJ3 resection*).ti,ab.
9. ((lung* OR kidney* OR esopha?g* OR oesopha?g* OR pancreato-duodenal OR pancreatoduodenal) ADJ3 resection*).ti,ab.
10. (Colectom* OR proctocolectom* OR proctosigmoidectom* OR ileocolectom*).ti,ab.
11. (Cystectom* OR prostatocystectom*).ti,ab.
12. (Gastrectom* OR gastroresection* OR hemigastrectom* OR stomach extirpation).ti,ab.
13. (Hepatectom* OR hepatic lobectom* OR trisegmentectom* OR segmentectom*).ti,ab.
14. (Hysterectom* OR salpingo-oophorectom* OR salpingectom* OR vaginectom* OR vulvectom* OR Pelvic exenteration OR colpohysterectom* OR hysterocolpectom* OR panhysterectomy OR uterus extirpation).ti,ab.
15. (Pneumonectom* OR lobectom* OR segmentectom* OR pneumoresection* OR pulmonectom*).ti,ab.
16. (Oesopha?gectom* OR esopha?gectom*).ti,ab.
17. (Pancreaticoduodenectom* OR Whipples procedure OR brunschwig operation* OR duodenopancreatectom* OR pancreatico duodenectom* OR pancreato duodenectom* OR pancreatoduodenectom* OR Whipple operation).ti,ab.
18. (Thyroidectom* OR strumectom* OR Hemithyroidectom* OR Isthmectom*).ti,ab.
19. Prostatectom*.ti,ab.
20. (Mastectom* OR Lumpectom* OR mammectom*).ti,ab.
21. or/1-20
22. High-Intensity Interval Training/

23. (high-intensity intermittent exercise OR high-intensity intermittent training OR high-intensity interval exercis* OR high-intensity interval training OR HIIT OR HIIE).ti,ab.
24. (Interval adj2 (training OR exercise)).ti,ab.
25. (Intermittent adj2 (training OR exercise)).ti,ab.
26. (repeated sprint training OR intensive exercise* OR intensity intermittent exercise* OR anaerobic interval OR repeated sprint OR sprint interval* OR high aerobic intensity training OR intensity training OR intensi* exercis* OR circuit training OR repeated sprint training OR high intensity intermittent exercis*).ti,ab.
27. or/22-26
28. and/21,27

CINAHL

1. (MH "Colonic Neoplasms+/SU") OR (MH "Cystectomy") OR (MH "Pancreatic Neoplasms+") OR (MH "Liver Neoplasms+/SU") OR (MH "Peritoneal Neoplasms/SU") OR (MH "Hysterectomy") OR (MH "Salpingectomy") OR (MH "Lung Neoplasms+/SU") OR (MH "Nephrectomy") OR (MH "Esophageal Neoplasms/SU") OR (MH "Otorhinolaryngologic Neoplasms/SU") OR (MH "Thyroid Neoplasms/SU") OR (MH "Gastrointestinal Neoplasms+/SU") OR (MH "Digestive System Neoplasms+") OR (MH "Intestinal Neoplasms+/SU") OR (MH "Pancreaticoduodenectomy") OR (MH "Thyroidectomy") OR (MH "Transurethral Resection of Prostate") OR (MH "Mastectomy") OR (MH "Lumpectomy") OR (MH "Prophylactic Mastectomy") OR (MH "Laryngectomy")
2. TI (Oncological N2 resection*) OR AB (Oncological N2 resection*)
3. TI ((Cancer OR neoplas*) N2 surger*) OR AB ((Cancer OR neoplas*) N2 surger*)
4. TI (cancer N2 (excision OR extirpation OR resection*)) OR AB (cancer N2 (excision OR extirpation OR resection*))
5. TI (tumo#r* N2 (excision OR exeresis OR resection*)) OR AB (tumo#r* N2 (excision OR exeresis OR resection*))
6. TI (Tumo#rectom*) OR AB (Tumo#rectom*)
7. TI ((lung* OR colon OR breast OR prostat* OR colorectal OR abdominoperineal) N3 resection*) OR AB ((lung* OR colon OR breast OR prostat* OR colorectal OR abdominoperineal) N3 resection*)
8. TI ((bladder OR stomach OR liver OR gastric OR Liver) N3 resection*) OR AB ((bladder OR stomach OR liver OR gastric OR Liver) N3 resection*)
9. TI ((lung* OR kidney* OR esopha#g* OR oesopha#g* OR pancreato-duodenal OR pancreatoduodenal) N3 resection*) OR AB ((lung* OR kidney* OR esopha#g* OR oesopha#g* OR pancreato-duodenal OR pancreatoduodenal) N3 resection*)
10. TI (Colectom* OR proctocolectom* OR proctosigmoidectom* OR ileocolectom*) OR AB (Colectom* OR proctocolectom* OR proctosigmoidectom* OR ileocolectom*)
11. TI (Cystectom* OR prostatocystectom*) OR AB (Cystectom* OR prostatocystectom*)
12. TI (Gastrectom* OR gastroresection* OR hemigastrectom* OR “stomach extirpation”) OR AB (Gastrectom* OR gastroresection* OR hemigastrectom* OR “stomach extirpation”)
13. TI (Hepatectom* OR “hepatic lobectom*” OR trisegmentectom* OR segmentectom*) OR AB (Hepatectom* OR “hepatic lobectom*” OR trisegmentectom* OR segmentectom*)

14. TI (Hysterectom* OR “salpingo-oophorectom*” OR salpingectom* OR vaginectom* OR vulvectom* OR “Pelvic exenteration” OR colpohysterectom* OR hysterocolpectom* OR panhysterectomy OR “uterus extirpation”) OR AB (Hysterectom* OR “salpingo-oophorectom*” OR salpingectom* OR vaginectom* OR vulvectom* OR “Pelvic exenteration” OR colpohysterectom* OR hysterocolpectom* OR panhysterectomy OR “uterus extirpation”)
15. TI (Pneumonectom* OR lobectom* OR segmentectom* OR pneumoresection* OR pulmonectom*) OR AB (Pneumonectom* OR lobectom* OR segmentectom* OR pneumoresection* OR pulmonectom*)
16. TI (Oesopha#gectom* OR esopha#gectom*) OR AB (Oesopha#gectom* OR esopha#gectom*)
17. TI (Pancreaticoduodenectom* OR “Whipples procedure” OR “brunschwig operation*” OR duodenopancreatectom* OR “pancreatico duodenectom*” OR “pancreato duodenectom*” OR pancreatoduodenectom* OR “Whipple operation”) OR AB (Pancreaticoduodenectom* OR “Whipples procedure” OR “brunschwig operation*” OR duodenopancreatectom* OR “pancreatico duodenectom*” OR “pancreato duodenectom*” OR pancreatoduodenectom* OR “Whipple operation”)
18. TI (Thyroidectom* OR strumectom* OR Hemithyroidectom* OR Isthmectom*) OR AB (Thyroidectom* OR strumectom* OR Hemithyroidectom* OR Isthmectom*)
19. TI (Prostatectom*) OR AB (Prostatectom*)
20. TI (Mastectom* OR Lumpectom* OR mammectom*) OR AB (Mastectom* OR Lumpectom* OR mammectom*)
21. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR 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
22. (MH "High-Intensity Interval Training")
23. TI (“high-intensity intermittent exercise” OR “high-intensity intermittent training” OR “high-intensity interval exercis*” OR “high-intensity interval training” OR HIIT OR HIIE) OR AB (“high-intensity intermittent exercise” OR “high-intensity intermittent training” OR “high-intensity interval exercis*” OR “high-intensity interval training” OR HIIT OR HIIE)
24. TI (Interval N2 (training OR exercise)) OR AB (Interval N2 (training OR exercise))
25. TI (Intermittent N2 (training OR exercise)) OR AB (Intermittent N2 (training OR exercise))
26. TI (“repeated sprint training” OR “intensive exercise*” OR “intensity intermittent exercise*” OR “anaerobic interval” OR “repeated sprint” OR “sprint interval*” OR “high aerobic intensity training” OR “intensity training” OR “intensi* exercis*” OR “circuit training” OR “repeated sprint training” OR “high intensity intermittent exercis*”) OR AB

(“repeated sprint training” OR “intensive exercise*” OR “intensity intermittent exercise*” OR “anaerobic interval” OR “repeated sprint” OR “sprint interval*” OR “high aerobic intensity training” OR “intensity training” OR “intensi* exercis*” OR “circuit training” OR “repeated sprint training” OR “high intensity intermittent exercis*”)

27. S22 OR S23 OR S24 OR S25 OR S26
28. S21 AND S27

Web of Science

1. TI =((Oncological NEAR/2 resection*) OR ((Cancer OR neoplas*) NEAR/2 surger*) OR (cancer NEAR/2 (excision OR extirpation OR resection*)) OR (tumo$r* NEAR/2 (excision OR exeresis OR resection*)) OR (Tumo$rectom*) OR ((lung* OR colon OR breast OR prostat* OR colorectal OR abdominoperineal) NEAR/3 resection*) OR ((bladder OR stomach OR liver OR gastric OR Liver) NEAR/3 resection*) OR ((lung* OR kidney* OR esopha$g* OR oesopha$g* OR pancreato-duodenal OR pancreatoduodenal) NEAR/3 resection*) OR (Colectom* OR proctocolectom* OR proctosigmoidectom* OR ileocolectom*) OR (Cystectom* OR prostatocystectom*) OR (Gastrectom* OR gastroresection* OR hemigastrectom* OR "stomach extirpation") OR (Hepatectom* OR "hepatic lobectom*" OR trisegmentectom* OR segmentectom*) OR (Hysterectom* OR "salpingo-oophorectom*" OR salpingectom* OR vaginectom* OR vulvectom* OR "Pelvic exenteration" OR colpohysterectom* OR hysterocolpectom* OR panhysterectomy OR "uterus extirpation") OR (Pneumonectom* OR lobectom* OR segmentectom* OR pneumoresection* OR pulmonectom*) OR (Oesopha$gectom* OR esopha$gectom*) OR (Pancreaticoduodenectom* OR "Whipples procedure" OR "brunschwig operation*" OR duodenopancreatectom* OR "pancreatico duodenectom*" OR "pancreato duodenectom*" OR pancreatoduodenectom* OR "Whipple operation") OR (Thyroidectom* OR strumectom* OR Hemithyroidectom* OR Isthmectom*) OR Prostatectom* OR (Mastectom* OR Lumpectom* OR mammectom*)) OR AB =((Oncological NEAR/2 resection*) OR ((Cancer OR neoplas*) NEAR/2 surger*) OR (cancer NEAR/2 (excision OR extirpation OR resection*)) OR (tumo$r* NEAR/2 (excision OR exeresis OR resection*)) OR (Tumo$rectom*) OR ((lung* OR colon OR breast OR prostat* OR colorectal OR abdominoperineal) NEAR/3 resection*) OR ((bladder OR stomach OR liver OR gastric OR Liver) NEAR/3 resection*) OR ((lung* OR kidney* OR esopha$g* OR oesopha$g* OR pancreato-duodenal OR pancreatoduodenal) NEAR/3 resection*) OR (Colectom* OR proctocolectom* OR proctosigmoidectom* OR ileocolectom*) OR (Cystectom* OR prostatocystectom*) OR (Gastrectom* OR gastroresection* OR hemigastrectom* OR "stomach extirpation") OR (Hepatectom* OR "hepatic lobectom*" OR trisegmentectom* OR segmentectom*) OR (Hysterectom* OR "salpingo-oophorectom*" OR salpingectom* OR vaginectom* OR vulvectom* OR "Pelvic exenteration" OR colpohysterectom* OR hysterocolpectom* OR panhysterectomy OR "uterus extirpation") OR (Pneumonectom* OR lobectom* OR segmentectom* OR pneumoresection* OR pulmonectom*) OR (Oesopha$gectom* OR esopha$gectom*) OR (Pancreaticoduodenectom* OR "Whipples

procedure” OR “brunschwig operation*” OR duodenopancreatectom* OR “pancreatico duodenectom*” OR “pancreato duodenectom*” OR pancreatoduodenectom* OR “Whipple operation”) OR (Thyroidectom* OR strumectom* OR Hemithyroidectom* OR Isthmectom*) OR Prostatectom* OR (Mastectom* OR Lumpectom* OR mammectom*))

2. TI =((“high-intensity intermittent exercise” OR “high-intensity intermittent training” OR “high-intensity interval exercis*” OR “high-intensity interval training” OR HIIT OR HIIE) OR (Interval NEAR/2 (training OR exercise)) OR (Intermittent NEAR/2 (training OR exercise)) OR (“repeated sprint training” OR “intensive exercise*” OR “intensity intermittent exercise*” OR “anaerobic interval” OR “repeated sprint” OR “sprint interval*” OR “high aerobic intensity training” OR “intensity training” OR “intensi* exercis*” OR “circuit training” OR “repeated sprint training” OR “high intensity intermittent exercis*”)) OR AB =((“high-intensity intermittent exercise” OR “high-intensity intermittent training” OR “high-intensity interval exercis*” OR “high-intensity interval training” OR HIIT OR HIIE) OR (Interval NEAR/2 (training OR exercise)) OR (Intermittent NEAR/2 (training OR exercise)) OR (“repeated sprint training” OR “intensive exercise*” OR “intensity intermittent exercise*” OR “anaerobic interval” OR “repeated sprint” OR “sprint interval*” OR “high aerobic intensity training” OR “intensity training” OR “intensi* exercis*” OR “circuit training” OR “repeated sprint training” OR “high intensity intermittent exercis*”))
3. #1 AND #2

2 Calibration SOP for COSMED K4b^2 and Quark

COSMED K4b^2 Calibration SOP

Warm-up & Setup

1. Plug receiver unit in
2. Press power button – screen should come on
3. "Optimum warm up" will come up on screen, press enter
4. Ideally, leave it to warm up for 45 minutes
    a. The pump needs to be on for at least 10 mins before calibration
    b. You can calibrate after 10 mins
    c. The buzzing sound indicates the pump is on
5. Plug turbine and sampling line into unit
6. Insert USB cable into USB port on desktop

Fig. 1

7. Open K4b^2 program on desktop

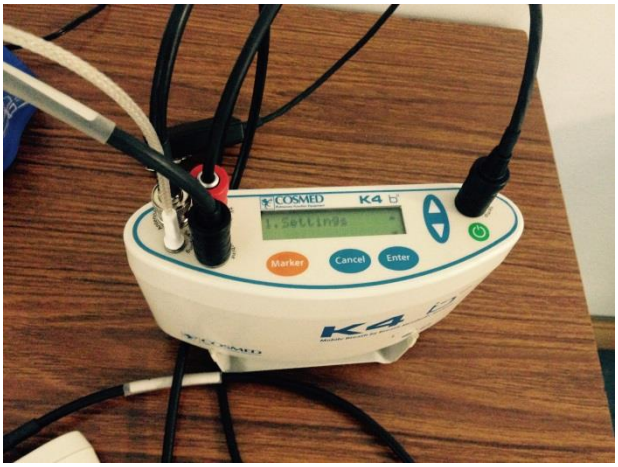


Figure 2.1 - Attachments

Calibration:

Using the laptop, go to 'Test' > 'Calibration'

1. Room Air…… (Room Air Calibration)
    - Press 'Room Air' and 'ok'
    - Room air calibration will take place. (DO NOT BREATHE NEAR SAMPLING LINE)
    - Press 'Close' when complete

2. Gas.... (Reference Gas Calibration)
    - Press ‘Gas’
    - Plug O_2 tank line into reference gas calibration box
    - Open valves (one on side of O_2 tank with wrench (anticlockwise to open, clockwise to close); one in front of dial)
    - Note: valves are perpendicular to O^2 line when closed, parallel to line when open) See Fig. 2 – valves are open

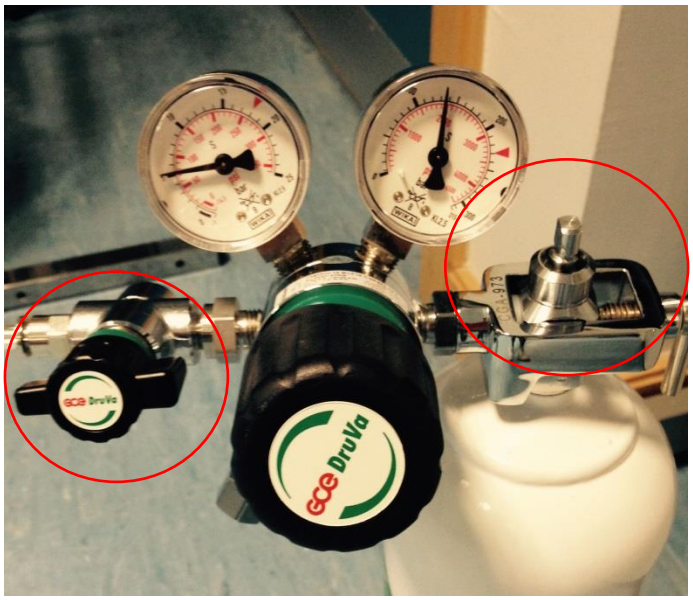


Figure 2.2 - Valves

    - Press Ok
    - Room air calibration will take place
        - DO NOT BREATHE NEAR SAMPLING LINE
    - When prompted, insert sampling line into reference gas calibration box
    - When calibration is done, press ok
    - Close all three valves, take care when removing O_2 line from box
3. Turbine calibration
    - Attach turbine connectors
    - Insert sampling line into turbine
    - Click ‘Calibration’ and ‘Turbine Calibration’ and press enter
    - Fit turbine to calibration syringe and operate syringe by smoothly pulling handle fully out and pushing it fully in

- When calibration is done, press ok and return syringe

4. O_2/CO_2 Delay Calibration
    - Unplug sampling line from turbine
    - Click ‘Calibration’, click ‘Delay’ and ‘ok’
    - Room air calibration will take place as above
    - When prompted, insert sampling line into turbine
    - Inhale, then place turbine in mouth and press enter
    - Inhale and exhale in sync with the beeps
    - When calibration is done, press ok
    - Failed – error warning may come up on screen if breaths not synced properly
    - Repeat calibration in this case from number 4. above

<u>Post-test</u>

- All equipment must be washed and left ready for next user
- Wash turbine, facemask and plastic attachment by soaking for 15 minutes in a jug with one tablet of disinfectant (ensure it is fully dissolved before putting turbine in)
- DO NOT LET SAMPLING LINE GET WET
- Leave to dry on the draining board
- Put K4b^2 and all attachments back in the case, and place back in mobile computer unit(Fig. 3)

COSMED Quark SOP

- **Assembling the mask**

1. Do not disconnect the valves of the turbine
2. Use the mask adapter to connect the turbine to the mask
3. Make sure the mask size fits the participant´s face

- **Calibration and pre-testing steps**

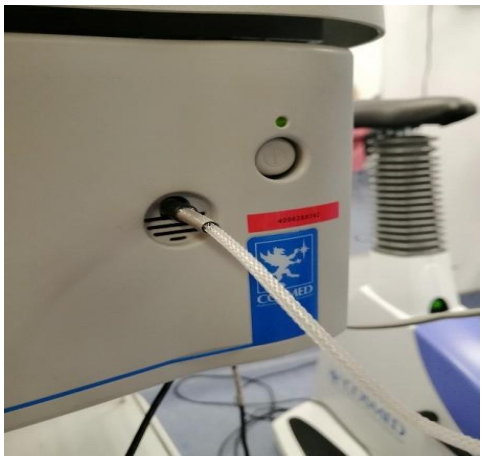
Preparing the Cosmed Quark:

- Turn on the computer
- Turn on the Cosmed Quark
- Insert password: Mr. D´Arcy+Cara
- Wait 5 minutes (Cosmed Quark)

Start Calibration:

- Select test
- Connect the turbine to the syringe

- Select turbine
- Press OK (some values will appear)
- Move the syringe until the program tells you to stop
- Click OK (calibration results will appear)
- Disconnect the turbine and sampling line off the syringe.
- Check the calibration gas bottle
- Insert the sampling line into the Quark



- Select calibration
- Select Ergo-RMR
- Press OK , Do not breath near the calibration valve
- Press OK (after the Ergo-RMR calibration is done)

Pre-testing steps:

- Select Patient in Archive
- Go to test
- Insert weight and height
- Ensure Ergometer is selected as ‘Cosmed Bike’
- Select protocol (e.g. EXCONC10, EXCONC15 etc) (or programme manually on bike if required)
- Ensure Workspace is VO2max
- Ensure Mode is ‘Gas BxB’
- Press ‘start’ to start the test
- When the test is complete select ‘stop’ to end the test.
- Click export to excel and save the test.

3 Short Performance Battery Test Standard Operating Procedure

Equipment required:

- Chair with arms 18-19” in height
- Stopwatch
- Tape measure
- 2 cones to mark 4 metres

i) Balance Test

Balance testing consisted of three balance tests; side-by-side, semi-tandem and tandem standing test.

Side-by-Side Stand

- Participants were provided with upper limb support to gain balance
- Participants were advised to stand with their arms by their side and feet together
- Timing with a stopwatch began when participant had feet together and had no upper limb support
- Participants scored as below in Figure 3.1

Figure 3.1 Scoring for side-by-side stand

A. Side-by-Side Stand

Held for 10 sec	○ 1 point	***If participant did not attempt test or failed, circle why:***
Not held for 10 sec	○ 0 points	Tried but unable
Not attempted	○ 0 points	Participant could not hold position unassisted
If 0 points, end Balance Tests		Not attempted, you felt unsafe
		Not attempted, participant felt unsafe
Number of seconds held if less than 10 sec:		Participant unable to understand instructions
____.____ Sec		Other (specify)
		Participant refused

If participants were able to complete 10 second side-by-side standing, participants were progressed to semi-tandem stand.

Semi-tandem stand

- Participants were provided with upper limb support to gain balance
- Participants were advised to stand with the heel of their right foot placed by the big toe of the other foot

- Timing with a stopwatch began when participant had the heel of their right foot placed by the big toe of the left foot and had no upper limb support
- Participants scored as below in Figure 3.2.

Figure 3.2 Scoring for semi-tandem stand.

A. Semi-Tandem Stand

Held for 10 sec	○ 1 point	***If participant did not attempt test or failed, circle why:***
Not held for 10 sec	○ 0 points	Tried but unable
Not attempted	○ 0 points	Participant could not hold position unassisted
If 0 points, end Balance Tests		Not attempted, you felt unsafe
		Not attempted, participant felt unsafe
Number of seconds held if less than 10 sec:		Participant unable to understand instructions
		Other (specify)
____.____ Sec		Participant refused

If participants were able to complete 10 second semi-tandem standing participants were progressed to tandem stand.

Tandem Stand

- Participants were provided with upper limb support to gain balance
- Participants were advised to stand with the heel of their right foot touching the toes of the other foot
- Timing with a stopwatch began when participant had the heel of their right foot touching the toe of the left foot and had no upper limb support
- Participants were scored according to Figure 3.3

Figure 3.3 Scoring of tandem stand

A. Tandem Stand

Held for 10 sec	○ 2 points	***If participant did not attempt test or failed, circle why:***	
Held for 3 to 9.99 sec	○ 1 point	Tried but unable	1
Not held for < than 3sec	○ 0 points	Participant could not hold position unassisted	2
Not attempted	○ 0 points	Not attempted, you felt unsafe	3
		Not attempted, participant felt unsafe	4
		Participant unable to understand instructions	5
Number of seconds held if less than 10 sec:		Other (specify)	6
		Participant refused	7
____.____ Sec			

ii) Gait Speed Test

4m was measured with a tape measure and a cone was placed at either end. Participants completed this test twice and the shorter of the two times was used to score. If participants mobilised with a walking aid outside of the home, the test was completed using the walking aid.

- Participant was advised to walk at their usual pace
- Participants began walking before the cone and stopped once they had passed the cone
- Timing with the stopwatch began when the participant passed the first cone and stopped when the participant passed the second cone
- Time to completion was recoded for both tests
- If the participant did not complete the test, the reason was recoded
- Participants were scored based on their shortest time according to Figure 3.4

Figure 3.4 Scoring of gait speed

If the participant was unable to do the walk: ○ 0 points

For 4 metre walk:

If time > 8.70 sec	○ 1 point
If time is 6.21-8.70 sec	○ 2 points
If time is 4.82-6.20 sec	○ 3 points
If time is < 4.82 sec	○ 4 points

iii) Repeated Chair Stands

The repeated chair stand consisted of five timed sit to stands from a chair. Participants were not permitted to use upper limb support, if participants were unable to go from sitting to standing safely or without upper limb support the test was terminated and the participant was scored zero out of four.

- Participant were advised to stand up and sit down as quickly as possible five times without stopping
- Timer began when participant began movement
- Timer stopped when the participant sat down the fifth time

4 Cardiopulmonary Exercise Testing Standard Operating Procedure

Pre-test Screening

Prior to CEPT, participants were screened for any absolute contraindications to maximal exercise testing as per the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) Medicine (Ross, 2003).

- Acute myocardial infarction
- Unstable angina
- Uncontrolled arrhythmias causing symptoms or hemodynamic compromise
- Syncope
- Active endocarditis
- Symptomatic severe aortic stenosis
- Uncontrolled heart failure
- Acute pulmonary embolous or pulmonary infarction
- Thrombosis of lower extremities
- Suspected dissecting aneurysm
- Uncontrolled asthma
- Pulmonary edema
- Room air desaturation at rest ≤ 85%
- Respiratory failure
- Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)
- Cognitive impairment leading to inability to cooperate
- Left main coronary stenosis or equivalent
- Moderate stenotic valvular heart disease
- Severe untreated arterial hypertension at rest (>200 mmHg systolic, >120 mmHg diastolic)
- Tachyarrhythmias or bradyarrhythmias
- High degree atrioventricular block
- Hypertrophic cardiomyopathy
- Significant pulmonary hypertension
- Pregnancy
- Electrolyte abnormalities
- Orthopaedic impairment that compromises exercise performance

Resting Measures

All resting measures were completed prior to commencing exercise testing cardiopulmonary exercise testing.

Blood pressure measurement

- Blood pressure was measured using a recently calibrated automated device with the participant sitting quietly in a chair, back supported, feet on the ground and arm supported at heart level.
- The cuff was wrapped firmly around the left upper arm at heart level; aligned with brachial artery.
- The bladder within the cuff should encircle at least 80% of the upper arm.
- Blood pressure was measured twice.

Resting ECG

- 12-lead ECG was performed

The participant positioned on the plinth in a semi-recumbent position. Electrodes were applied as follows;

- V1 – Fourth intercostal space just to the right of the sternal border
- V2- Fourth intercostal space just to the left of the sternal border
- V3 - At the midpoint of a straight line between V2 and V4
- V4 – On the midclavicular line in the fifth intercostal space
- V5 – On the anterior axillary line on a horizontal plane through V4
- V6 – On the midaxillary line and on a horizontal plane through V4 and V5
- Limb leads are positioned over the left and right superior clavicular region for the arm leads, and over the left and right lower quadrants of the abdomen for the leg leads.

ECG strip was printed for interpretation and clearance to proceed by the medical physician.

Preparation of Patient

- The face mask was fitted to the face, ensuring there were no air leaks
- The saddle of the ergometer was adjusted to participants height
- Place blood pressure cuff on arm

- Attach turbine to face mask

Monitoring during test

Heart Rate: Heart Rate was recorded during the last 5 seconds of each minute by ECG/pulse oximeter

SPO_2: SPO_2 was recorded during the last 5 seconds of each minute by pulse oximetry

Perceived rate of exertion: was recorded during the last 10 seconds of each minute.

ECG was monitored continuously by a physician during each stage of the test.

Blood pressure: measures were recorded after warming up, every three minutes through the test, and at work rate max.

- The cuff was secured on the upper arm for the duration of the test, at heart level, aligned with brachial artery.
- The stethoscope bell was placed below the antecubital space over the brachial artery
- The cuff was inflated to 20mmHg above first Korotkoff
- The pressure was slowly released at a rate equal to 2 to 5mmHg per second
- Systolic and diastolic BP was identified and recorded

CEPT Test Standard Operating Procedure

Warm-Up

- Duration: Three minutes
- Resistance: 0Watts

Cycling with load

- Duration: until exhaustion
- Resistance: increased each minute

Stopping the test

- The following criteria was applied to indicate that the test should be terminated:
- The pedal frequency dropped below 40 rotations per minute (RPM)
- Extreme hypertension (e.g. > 115 diastolic and >250 systolic).
- Abnormal exercise ECG with symptoms
- Severe cardiac arrhythmias.

- If the patient feels unwell or indicates having non-test specific pain

Cool down

- Duration: Three minutes
- Resistance: 0Watts

Recovery

- Duration: Three minutes
- Position: semi-recumbent position on plinth
- Measure: heart rate, SPO_2, perceived rate of exertion, and Blood Pressure after the 1st and 3rd minute
- Post ECG strip was provided for the supervising medical physician to sign off post-exercise ECG

5 One Repetition Maximum Standard Operating Procedure

Starting Position

- Participant sat in machine with lower back firmly supported against back rest
- Feet were positioned on metal plate
- Knees positioned at 90^0 shoulder width apart

Warm-Up

- Participants completed 2 warm-up rounds
- 6 repetitions at estimated 60% of 1RM with 2 minutes rest
- 3 repetitions at estimated 80% of 1RM with 2 minutes rest

1RM Test Trials

- Participants were given a rest period of two minutes between each trial
- Appropriate level of motivation should be consistent between all clients and time points
- All attempts recorded, highest score was recorded

Criteria for 1RM test

- No compensatory movement
- No change in speed
- No changes in movement range

6 Anthropometry Measures

Anthropometry measures were taken following a standard protocols.

Height and Weight

Standing height and weight were measured using a stadiometer and SECA digital medical scale.

- Participants stood barefoot, with their back against the stadiometer, with legs together, arms by their sides and mid-axillary line in parallel to the stadiometer. Participants head was placed in the Frankfort horizontal plane. This established by passing a line through the tragion (front of the ear) and the lowest point of the eye socket.
- The headboard was lowered until it touched the crown of the head, compressing the hair.

Measurements were recorded to the nearest 0.1cm and 0.1kg respectively.

Body Mass Index

Body mass index will be calculated by dividing the participants weight in kilograms by their height in metres squared.

Bioimpedance analysis (BIA) was measured using the SECA mBCA 515.

- Participants were screened for contraindication to BIA
- Electronic implants (pacemaker/ implantable cardioverter defibrillator)
- Metallic joint replacements e.g. total hip replacement, total knee replacement.
- Participants removed outer layers of clothing, shoes and large pieces of jewellery.
- Participants stood bare-foot, on the SECA mBCA515, ensuring their heels and balls of their feet are in contact with the metal electrodes on the base of the machine.
- Participants height was input to the SECA mBCA515.
- During analysis participants stood still, keeping both hands and feet in contact with the electrodes.

Once completed, estimated daily expenditure, date of birth, sex and ethnicity were input to the SECA mBCA515.

Body weight, body mass index (BMI), fat mass, fat free mass, % fat mass were recorded.

7 Ethical Approval for PRE-HIIT and Feedback Interview Patient's Perspectives of their Participation on the PRE-HIIT Trial

SJH/TUH Research Ethics Committee Secretariat
email: researchethics@tuh.ie

JREC Reference: 2020-02 List 7 – Response to Comments (09)

Dr Linda O'Neill,
St James's Hospital,
James' Street,
Dublin 8

10th February 2020

REF: Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus: The PRE_HIIT Trial

REC: 2020-02 List 7 – Response to Comments (09)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 29.11.2019
Date of Ethical Review: 07.02.2020

Dear Dr O'Neill,

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the Response to the Committees comments you submitted to the SJH/TUH JREC and has given **FULL** approval for this study to proceed in **St James's Hospital.** However, please update the following:

- Add response point 9 to the Patient information leaflet.

The following documents were reviewed:

- Response to Comments letter, dated 29.11.2019.
- Patient Information leaflet A, V2.
- Patient Information leaflet B, V2.
- GP Letter for Anxiety/depression V1.

Please note that ethical approval for this study is only active under the following conditions:

- ✓ *Applicants must submit an annual report for ongoing projects.*
- ✓ *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
- ✓ *All adverse events must be reported to the JREC.*
- ✓ *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Seamus O'Neill

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

SJH/TUH Research Ethics Committee Secretariat
email: researchethics@tuh.ie

Dr Linda O'Neill,
St James's Hospital,
James' Street,
Dublin 8

09th March 2020

REF: Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus: The PRE-HIIT Trial

REC: 2020-02 List 7 – Response to Comments (18)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 12.02.2020
Date of Ethical Review: 21.02.2020

Dear Dr O'Neill

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the Response to the Committees comments you submitted to the SJH/TUH JREC and has given **FULL** approval for this study to proceed in **St James's Hospital.**

The following documents were reviewed:

- Response to Comments, dated 12.02.2020
- PIL A, V3
- PIL B, V3

Please note that ethical approval for this study is only active under the following conditions:

- ✓ *Applicants must submit an annual report for ongoing projects.*
- ✓ *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
- ✓ *All adverse events must be reported to the JREC.*
- ✓ *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Sadhbh O'Neill

_____
REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

Dr Linda O'Neill,
St James's Hospital,
James' Street,
Dublin 8

20th August 2020

REF: Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus: The PRE-HIIT Trial

REC: 2020-07 List 25 – Amendment (22)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 16.07.2020
Date of Ethical Review: 31.07.2020

Dear Dr O'Neill,

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the amendment you submitted to the SJH/TUH JREC for the above named study and has given **FULL** approval for this amendment.

The following documents were reviewed:

- 200706 Pre-HIIT_PIL_B_Version 4.docx
- 200706 PRE-HIIT_PIL_C_Version 2.docx
- 200707 PRE-HIIT Protocol Version 2 Clean.docx
- 200707 TUH-SJH_REC_Standard_Application_V5-6_GDPRUpdate-Nov18-11 Version 3.doc
- 200708 Pre-HIIT_PIL_A_Version 4.docx
- 200715 Amendment I, Cover Letter.docx
- 200715 PRE-HIIT Exercising at Home Advice Sheet.docx
- 200715 PRE-HIIT Interview Guide Version 2.docx
- 200715 PRE-HIIT Telehealth Usability Questionnaire V1.docx

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Sadhbh O'Neill

REC Officer – Dr Sadhbh O'Neill

Tallaght University Hospital | Ospidéal Ollscoile Thamhlachta

An Academic Partner of Trinity College Dublin

Ospidéal San Séamas – Seirbhís Dé agus A Phobail

Research Office

Project ID: 0059

Approval Date: 25 May 2021

Submission Number: 41:
Submission Date: 11/03/2021 10:00

Dear Ms Smyth,

On behalf of the Chair and members of the SJH/TUH Joint Research Ethics Committee I wish to inform you that your study amendment has received **FULL APPROVAL.** Your study can now proceed.

The following documents were reviewed and approved:

Document Type	File Name	Date	Version
Default	Amendment II, Cover Letter	09/03/2021	1
Default	210225 Ethics Edits TUH-SJH_REC_Standard_Application_V5-6 Version 3	09/03/2021	3
Default	190329 APPENDIX XIII PRE-HIIT Acceptability Questionnaire Version 1.0	09/03/2021	1
Default	190329 APPENDIX IV PRE-HIIT Interview Guide Version 2.0	09/03/2021	2

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Ms Chita Murray

Research Ethics & Clinical Trials Manager,

8 PRE-HIIT Participant Information Leaflet

ST. JAMES'S HOSPITAL
James's Street, Dublin 8
Telephone (+353 1) 410 3000
www.stjames.ie

PARTICIPANT INFORMATION LEAFLET

Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus: The PRE-HIIT trial

Co-Principal Investigators:	Prof Juliette Hussey	Professor in Physiotherapy
	Dr Emer Guinan	Assistant Professor
Co-investigators:	Prof John Reynolds	Professor of Surgery
	Mr Ronan Ryan	Consultant Cardiothoracic Surgeon
	Dr Grainne McDermott	Consultant Anaesthetist
	Dr Suzanne Doyle	Assistant Professor
	Dr Linda O'Neill	Project Manager
	Dr Louise Brennan	Postdoctoral Researcher
	Ms Emily Smyth	Research Physiotherapist
	Ms Fatemeh Sadeghi	Research Dietitian

You are being invited to take part in a research study. Before you decide whether or not you wish to take part, you should carefully read the information provided below. Please take your time to make your decision. You may wish to discuss this with your family, friends, or healthcare team. If you have any questions, you can ask a member of the research team. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you. This process is known as Informed Consent.

PART 1 – THE STUDY

Why is this study being done?

Treatment for cancer of the lung or the oesophagus (food-pipe) often involves surgery. Current research informs us that physical fitness before surgery is beneficial to recovery after surgery. People with a certain level of aerobic fitness have a shorter hospital stay and have less risk of serious complications after surgery.

While physical fitness can be improved by exercise, the lead-in time to surgery following a cancer diagnosis is often very short. High Intensity Interval Training is a specific form of exercise that has been shown to lead to improvements in physical fitness in a small timeframe. We are aiming to determine if this short-term high intensity exercise programme can lead to greater improvements in physical fitness in the two weeks leading to surgery compared to conventional care.

Why am I being asked to take part?

You are being asked to participate in this study as you are scheduled for surgery of the lung or oesophagus at St James's Hospital.

Do I have to take part? What happens if I say no? Can I withdraw?

No, it is up to you whether or not you take part.

If you decide to take part, you will be asked to give initial consent verbally over the telephone. We will then perform a screening assessment with you over the telephone, if you meet the criteria to take part in the study we will then schedule an appointment with you in the Clinical Research Facility in St James's Hospital during which we will take written informed consent and ask you to complete some assessments.

If you decide not to take part it won't affect your current or future medical care. You can change your mind about taking part in the study and opt out at any time even if the study has started. If you decide to opt out,

it won't affect your current or future medical care. You don't have to give a reason for not taking part or for opting out.

If you wish to opt out, please contact Dr Linda O'Neill/ Ms Emily Smyth (email: exercise oncology @tcd.ie, telephone: 01 8964809/ 087 6577927), who will be able to organise this for you.

How will the study be carried out?

This study began in Summer 2021 and will continue for 32 months. A total of 78 participants will be recruited. The study will take place at St James's Hospital, Dublin. This study is a **randomized controlled trial**, a very high quality form of research where participants who share a particular characteristic (i.e. scheduled for surgery for oesophageal or lung cancer) are randomly assigned to receive either a new treatment or the standard of care. In this way researchers can compare the outcomes between the two groups and decide if the new treatment had any effect.

In this project participants will be randomly assigned to participate in either the **intervention group** or the **control group**. The **intervention group** will undertake the new treatment, the **high intensity interval exercise programme**. The **control group** will receive **usual pre-operative care** at St James's Hospital, including a moderate intensity exercise programme.

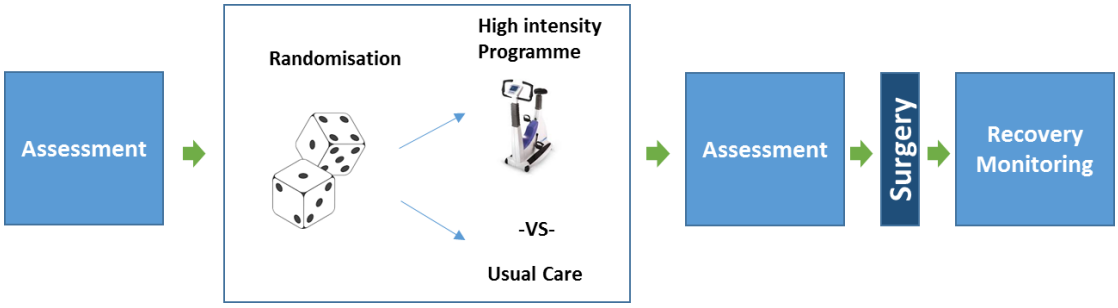


Figure 1. Overview of Study

What will happen to me if I agree to take part?

If you decide to join the study you will be asked to attend the Wellcome Trust-HRB Clinical Research Facility at St James's Hospital, Dublin for a screening assessment. To minimise face-to-face contact time, the first part of this screening assessment will be carried out with a member of the research team via telephone. During this telephone assessment, the researcher will ask you questions about your medical history and your diet and they will schedule the second part of the assessment in the Clinical Research Facility at St. James's Hospital for you. You may also be posted some questionnaires about your quality of life, diet, energy levels, and physical activity levels to complete before the second part of your assessment.

A member of the research team will call you the day before your assessment at the Clinical Research Facility at St. James's Hospital to ask you some questions to check that you are not displaying any symptoms of COVID-19. You will be asked these questions again on the day of your assessment when you arrive at the Clinical Research Facility to reconfirm that you are not displaying symptoms of Covid-19. During your assessment visit you will be required to wear a facemask and the researcher will wear personal protective equipment in line with health and safety standards and will maintain physical distancing as much as possible during the assessment. The assessment components are detailed below.

Physical Performance

- You will perform an **exercise test** to calculate your physical fitness. This test will be performed on a stationary bike. The test will require you to exercise on a stationary bike until exhaustion. You will wear a face mask and have a pin prick blood test taken during the test. The test will last approximately 6-10 minutes. During the test you will be monitored by a physiotherapist/exercise physiologist and a doctor.
- We will measure your **leg strength** using a leg press machine.
- You will perform a **short battery of physical tests**, including a balance test, walking speed test, and repeated stands from a chair.
- We will assess your **physical activity levels** with a questionnaire.

Body Composition

- We will measure your **height** and **weight,** and **muscle mass**.

Dietary intake

- You will **discuss** your **diet** with the study dietitian to highlight specific issues

Quality of Life

- You will be required to complete a **questionnaire** about your quality of life.

As part of the screening assessment, we will also collect information about your medical history. The total time needed to complete this assessment is approximately 1 hour.

Randomisation

If you successfully complete the screening assessment you will be officially enrolled on to the study and will be randomly assigned to one of the two study groups.

High Intensity Interval Exercise Programme

If you are randomised to take part in the high intensity interval exercise programme you will be asked to participate in ten exercise sessions. You will have the option to complete the exercise programme either at home or face-to-face in St James Hospital. The sessions will be performed 5 days a week, Monday to Friday for two weeks before your surgery. The programme is suitable for all fitness levels and will be tailored to your abilities.

If you choose to complete the programme at home, an exercise bike will be provided to you in your home to carry out the programme. A member of the research team will visit you in your home for the first session to insure you are set-up right with the bike. The researcher will be wearing appropriate protective equipment and will maintain physical distancing as much as possible. Subsequent sessions will be monitored by the

research team remotely using a heart rate monitor and video/telephone call. If you select to choose to complete the programme in St James Hospital, sessions will be completed face-to-face in the Clinical Research Facility. The researcher will be wearing appropriate protective equipment and will maintain physical distancing as much as possible.

Each session will consist of having your heart rate, and rate of exertion monitored. You will then perform a warm-up by cycling on a stationary bike. Following the warm-up you will follow a high intensity interval programme on the bike. You will perform maximal exercise for 15 seconds and then for rest for 15 seconds. This pattern will be repeated for up to 30 minutes or until you are tired. Each session should last approx. 45 minutes.

If for any reason your surgery is delayed, you will continue with the exercise programme. If your surgery is delayed by one week or less, you will continue performing 5 sessions a week until the scheduled surgery date. In the unlikely event surgery is delayed by 1-2 week is you will perform three sessions a week. In the unlikely event surgery is delayed by more than 2 weeks you will perform 2 sessions a week. During the intervention period you will also receive a dietary counselling session with our study dietitian, this will be conducted over video/ telephone call.

Usual Care at St James's Hospital
If you are randomized to the usual care group, you will receive standard pre-operative care at St James's Hospital. This standard care involves routine pre-operative advice and a pre-operative moderate exercise programme which is currently delivered either face-to-face or via video call.

After the programme
Before you proceed to surgery, you will be required to repeat the series of assessments.

Following surgery a member of the research team will follow you up. This member of the team will take notes on your recovery including number of complications and length of stay.

We will also continue to monitor your recovery and quality of life for up to 3 months post-surgery. This will assist us in calculating the cost-effectiveness of the programme.

Are there any benefits to me or others if I take part in the study?

If you take part in the study and share your medical information, you may help scientists and doctors understand the importance of exercise before surgery. This may improve treatment for patients with cancer in the future. By participating in the exercise programme, you may benefit from the experience of taking regular exercise.

Are there any risks to me or others if I take part in the study?

We do not anticipate adverse effects during the assessments or exercise sessions. You will only be invited to join the study if your doctors feel that you are well enough to participate in this programme. The exercise test involves exercising you to your maximum, which carries a risk of cardiac event. To guarantee safety, the research team will carry out screening of your heart and lungs before your exercise test. A medical doctor will then review your screening results and will decide if it is safe for you to proceed with the exercise test.

Occasionally people can feel dizzy or breathless when doing an exercise test. However because the exercise test is carefully graded and monitored by a physiotherapist/exercise physiologist and doctor, the risk of this happening are minimal. You may also feel a little tired after the exercise test, but this should pass quickly.

What will happen if something goes wrong when I'm taking part in the study?

Your safety while taking part in the study is most important. All study assessments and intervention sessions will be carried out by Professionals with expertise in this area. The Clinical Research Facility where assessments will be performed have trained medical professionals on site and is covered by the hospital emergency team. In the event of you becoming unwell during an assessment you will be evaluated and referred for appropriate treatment. During the assessment, your exercise test will be reviewed by a doctor and, if you are to proceed with the study, you will receive medical clearance to exercise at a high intensity in your own home. We require that someone else is home with you during all exercise sessions so that if you do feel unwell they can assist you, with guidance from the study physiotherapist. If you experience any adverse effects as a result of the study assessments or exercise programme it is important that you inform a member of the research team immediately.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

When the results of the study are known, we will be able to provide you with an individual summary of your personal results on request. When the study is complete participants and their families will be invited to an information evening in which the overall results of the study will be presented.

Results will also be shared with healthcare professionals at an education day hosted by the research team. Overall findings will also be presented at relevant conferences and published in relevant peer-reviewed journals.

PART 2 – DATA PROTECTION

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

The following **clinical data** will be recorded at your first assessment.

- **Age**
- **Gender**
- **Height and weight**
- **Information related to cancer diagnosis**
- **Past Medical History**
- **Medications**
- **Smoking status**
- **Education**
- **Alcohol intake**
- **Dietary intake**

Access to your healthcare records at St James's Hospital will be required to gather this information. In addition, your healthcare records will be accessed to record information on your length of stay in hospital, your recovery post-operatively, and to calculate the hospital costs relating to your surgery.

Study data also includes information collected during your assessments; exercise test results, physical performance measures, body composition, and quality of life. We will also record how participants adhere to the exercise programme (e.g. number of sessions completed etc.).

What will happen my personal data?

If you consent to take part in this study, your personal details and your responses to questionnaires will remain strictly confidential at all times. Personal data will be processed **only as is necessary** to achieve the objectives of the health research.

You will be allocated a study number, which will be used as a code to identify you on all documentation. Your name and contact details will not be passed to anyone other than members of the research team. Your information will be kept filed securely for up to 10 years after which it will be destroyed. Your data will not be transferred outside the EU. An anonymous version of the study data set will be made available on a secure online data repository post study completion in line with open access publication requirements.

Who will access and use my personal data as part of this study?

Members of the PRE-HIIT research team will access and use your personal data as part of the study. Research team members will only be granted access to your data when they have completed training in data protection.

Will my personal data be kept confidential? How will my data be kept safe?

Your personal data will be kept confidential. We will keep it in a secured file. Your study data will be identified with a code number which will not include your name or other information that directly identifies you. Your data will not be identifiable in any future presentations/publications on the study.

To protect the security of data collected for this study a Data Protection Impact Statement has been completed. A Data Management Plan is also in place and will be reviewed on a monthly basis throughout the study.

What is the lawful basis to use my personal data?

The lawful basis for processing of your personal data is covered by Article 6(1)(e) and Article 9(2)(j) of GDPR.

Article 6(1)(e) states processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller.

Article 9(2)j) states that processing is necessary for scientific research purposes in accordance with Article 89(1) based on Union or Member State law which shall be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject.

What are my rights?

You have the following rights regarding your **data**.

- Right to access data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability

PART 3 – COSTS, FUNDING & APPROVAL

Will it cost me anything if I agree to take part?

You will not be charged for participation in this study. The research team will cover any parking costs incurred at St James's Hospital during the study.

Who is funding this study?

This study is funded by the Health Research Board (HRB) and the Medical Research Charities Group (MRCG).

Has this study been approved by a research ethics committee?

Ethical approval has been granted by the Tallaght University Hospital/ St James's Hospital Research Ethics Committee (researchethics@tuh.ie).

PART 4 – FUTURE RESEARCH

Will my personal data and/or biological material be used in future studies?

When consenting to this study you will only give permission for your data to be used for this current study. In the final section of the consent form you will be asked if you are happy for your data to be used in possible future studies to help answer future research questions.

PART 5 – FURTHER INFORMATION

Where can I get further information?

Co-Principal Investigators:		
Professor Juliette Hussey		Email: jmhussey@tcd.ie
Dr Emer Guinan	+353 1 8964125	Email: guinane1@tcd.ie
Data Controller: Trinity College Dublin/ St James's Hospital Dublin		
Data Processors: Trinity College Dublin/ St James's Hospital Dublin Pre-HIIT Research Team Email: exerciseoncology@tcd.ie		
Data Protection Officer, Trinity College Dublin Email: dataprotection@tcd.ie		

If you have any questions or would like more information about the study please contact a ***member of the research team*** *(Dr Linda O'Neill/ Ms Emily Smyth)*, Monday – Friday from 8.00 am to 5.00pm (telephone: +353 1 8964809/ 087 6577927, email: exerciseoncology@tcd.ie).

What happens if I wish to make a complaint?

Complaints regarding this study should be directed to the Co-Principal Investigators Professor Juliette Hussey and Dr Emer Guinan (contact details above). Complaints regarding data protection should be directed to the Data Protection Officer (email address above).

Will I be contacted again?

The research team may wish to contact you in the future. In particular, they may wish to contact you with regards participation in future studies. In the consent form you will be explicitly asked to consent to receiving information about future research studies.

9 Informed Consent Form for Study I

CONSENT FORM

Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus: The PRE-HIIT Trial

To be completed by the **PARTICIPANT**:

I have read and understood the information leaflet.	YES ☐	NO ☐
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.	YES ☐	NO ☐
I have received enough information about this study.	YES ☐	NO ☐
I understand that I am free to withdraw from the study at any time without giving a reason and this will not affect my future medical care.	YES ☐	NO ☐
I agree to allow the researchers use my information (personal data) as part of this study as outlined in the information leaflet.	YES ☐	NO ☐
I agree to allow the researchers access my medical records as part of this study.	YES ☐	NO ☐
I agree to be contacted by researchers as part of this study	YES ☐	NO ☐
I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study	YES ☐	NO ☐
I understand and agree to allow my data to be used for future research. Before any future research is carried out the ethics committee must agree with the research.	YES ☐	NO ☐
I am happy to be contacted in the future about future research projects by the research team.	YES ☐	NO ☐

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES □	NO □
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES □	NO □

Researcher's Name (Block Capitals):	
Researcher's Title & Qualifications:	
Researcher's Signature:	
Date:	

10 Adapted Generic Theoretical Framework of Acceptability Questionnaire

Intervention Acceptability Questionnaire

We are interested in your experience completing the PRE-HIIT intervention and would like to understand how acceptable you found the programme. The term ***acceptability*** refers to how tolerable (manageable, bearable, reasonable) you found PRE-HIIT to be. Please read each of the statements below carefully and pick your response to each by circling the number that best applies to you.

There are no right or wrong answers. The information that you provide will be strictly confidential.

1. Did you like or dislike PRE-HIIT?				
Strongly dislike	Dislike	No opinion	Like	Completely Like
2. How much effort did it take to complete PRE-HIIT?				
No effort at all	A little effort	No opinion	A lot of effort	Huge effort
3. There are moral or ethical concerns regarding the PRE-HITT programme:				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
4. PRE-HIIT is likely to improve patient's physical fitness:				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
5. It is clear to me how PRE-HIIT would help improve physical fitness in cancer patients:				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
6. How confident did you feel about completing PRE-HIIT?				
Very unconfident	Unconfident	No opinion	Confident	Very confident
7. PRE-HIIT interfered with my other priorities:				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
8. Overall, how acceptable did you find PRE-HIIT?				
Completely unacceptable	Unacceptable	No opinion	Acceptable	Completely acceptable

11 Telehealth Usability Questionnaire

Telehealth Usability Questionnaire

We are interested in your experience of completing your prehabilitation exercise programme via telehealth. Please read each of the statements below carefully and pick your response to each **by circling the number** that best applies to you.

There are no right or wrong answers. *The information that you provide will be strictly confidential.*

Usefulness						
		Fully agree	**Somewhat agree**	**Neither agree or disagree**	**Somewhat disagree**	**Completely disagree**
Q1	Telehealth improved my access to prehabilitation services	5	4	3	2	1
Q2	Completing my prehabilitation by telehealth saved me time traveling to a hospital or specialist clinic	5	4	3	2	1
Q3	My prehabilitation needs were met by the telehealth prehabilitation programme	5	4	3	2	1
Ease of Use and Learnability						
		Fully agree	**Somewhat agree**	**Neither agree or disagree**	**Somewhat disagree**	**Completely disagree**
Q1	It was simple to use the system	5	4	3	2	1
Q2	It was easy to learn to use the system	5	4	3	2	1
Q3	I believe I was productive quickly using this system	5	4	3	2	1
Interface Quality						

		Fully agree	Somewhat agree	Neither agree or disagree	Somewhat disagree	Completely disagree
Q1	The way I interact with this system is pleasant	5	4	3	2	1
Q2	I like using the system	5	4	3	2	1
Q3	The system is simple and easy to understand	5	4	3	2	1
Q4	This system is able to do everything I would want it to be able to do	5	4	3	2	1
Interaction Quality						
		Fully agree	**Somewhat agree**	**Neither agree or disagree**	**Somewhat disagree**	**Completely disagree**
Q1	I could easily talk to the clinician using the telehealth system	5	4	3	2	1
Q2	I could hear the clinician clearly using the telehealth system	5	4	3	2	1
Q3	I felt I was able to express myself effectively	5	4	3	2	1
Q4	Using the telehealth system, I can see the clinician as well as if we met in person	5	4	3	2	1
Reliability						
		Fully agree	**Somewhat agree**	**Neither agree or disagree**	**Somewhat disagree**	**Completely disagree**

Q1	I think the visits provided over the telehealth system are the same as in-person visits	5	4	3	2	1
Q2	Whenever I made a mistake using the system, I could recover easily and quickly	5	4	3	2	1
Q3	If there was an error or problem with the system, a member of the clinical/research team was able to help me solve the problem easily.	5	4	3	2	1
Satisfaction and Future Use						
		Fully agree	**Somewhat agree**	**Neither agree or disagree**	**Somewhat disagree**	**Completely disagree**
Q1	I feel comfortable communicating with the clinician using telehealth system	5	4	3	2	1
Q2	Telehealth is an acceptable way to receive prehabilitation services	5	4	3	2	1
Q3	I would use telehealth services again	5	4	3	2	1
Q4	Overall, I am satisfied with the prehabilitation programme I received via telehealth.	5	4	3	2	1

Adapted from the Telehealth Usability Questionnaire (TUQ) (Parmanto et al. Int J Telerehabil 2016;8(1): 3-10) designed to evaluate the usability and user's satisfaction of telehealth Implementation and services.

12 PRE-HIIT Control Home Exercise Diary

Study_ID	Week One	Week 2	Week 3	Week 4	Week 5
PRE001					
PRE002	45 min walk	40 min walk			
PRE005	Pre-recorded classes	Pre-recorded prehab class	Pre-recorded class online		
PRE009					
PRE011					
PRE012					
PRE015					
PRE017					
PRE018	1 extra class recording per week. Daily for 30 mins (1 walk per day)	1 extra class recording per week. Daily for 30 mins (1 walk per day)	1 extra class recording per week. Daily for 30 mins (1 walk per day)		
PRE021					
PRE023					
PRE027	15min walk	15min walk	15min walk		
PRE029	20 min walk	20 min walk			

PRE032	1 walk x30 mins	1 walk x30 mins	1 walk x 30 mins	1 walk x30 mins	
PRE034	3x5km run	3x5km run	Cross trainer x20 mins & cross trainer x15mins moderate intensity both		
PRE036	X3 Brisk walk ~40 mins, 3 long leisurely walks X2 hours, x10 stairs climb non consecutively	X3 Brisk walks ~40 mins, X3 days commuting face paced walks, >10 daily stairs climbs, general stretches for LL			
PRE040	3 walks light to moderate pace	4 walks 30 mins moderate intensity 30 mins each and stretches at home	5 walks 30-40 mins. x5 strengthening class in Island Bridge once roughly 45 minutes in length	1 resistance class, 5XS 30 mins 3xs a week	Strength class in Island Bridge, x3 times 30-40 mins per week

PRE041	no additional exercise reported on call	Surgery on 9.2.23; no additional follow up call completed			

PRE042	Attended gym 5 times in past week. Daily programme included: Assault bike 20 sec resistance on, 10 sec resistance off for 8x5 sets. 30 mins treadmill fast walk. UL and LL weights at 15kg including: chest press, seated row, shoulder press, knee extension, hamstring curl. Cross trainer for 15mins light-	Attended gym x6 times in past week. Daily programme included: Assault bike 20 sec resistance on, 10 sec resistance off for 8x5 sets. 35 mins treadmill fast walk with incline. UL and LL weights at 15kg. Swimming pool 6 lengths light leisurely (pool about 30m).	Attended gym x7 times in past week. Daily programme Treadmill 5minutes fast walk/slow jog, Assault bike 20seconds hard 10 seconds rest sets of 8 x 3 sets. Strengthening work in gym - shoulder press 15kg 3x 12, Bench press 10kg 3x12, Seated row 15kg 3 x 12, leg extension 15kg 3x12, leg curl 15kg 3x12. Followed by 30-	Attended gym x5 times in past week. Daily programme Treadmill 5minutes fast walk/slow jog, Bike x 5minutes, Assault bike 20seconds hard 10 seconds rest sets of 8 x 3 sets. Strengthening work in gym - shoulder press 15kg 3x 12, Bench press 10kg 3x12, Seated row 15kg 3 x 12, leg extension 15kg 3x12, leg cyrl 15kg 3x12. Followed by 30-	Attended gym x5 times in past week. Daily programme Treadmill 5minutes fast walk/slow jog, Bike x 5minutes, Cross trainer level 8 x 5minutes Strengthening work in gym - shoulder press 15kg 3x 12, Bench press 10kg 3x12, Seated row 15kg 3 x 12, leg extension 15kg 3x12, leg curl 15kg 3x12. Followed by 30 minutes swimming in pool.

	mod intensity. Swimming pool 4-5 lengths light leisurely.		40minute swimming in pool. Total 1hr 30 per day	40minute swimming in pool. Total 1hr 30 per day. Completed one hour spin class on two days that did not attend the gym.	Total 1hr 30 per day.

PRE045	30 mins x2 on bike at moderate resistance, exercise bike, stretching with resistance bands	Half an hour cycling each day, 7 days, 15km 30 mins each day, 40 min walk Monday, stretching with resistance band and for lower back x3 times, 3x10 press-ups, 3x10 sit ups x2 days			
PRE050					
PRE052					

13 Participant Information Leaflet for Feedback Interview Patient's Perspectives of their Participation on the PRE-HIIT Trial

PARTICIPANT INFORMATION LEAFLET

Feedback Interview

Patient's Perspectives of their Participation on the PRE-HIIT Trial

Co-Principal Investigators:	Prof Juliette Hussey	Professor in Physiotherapy
	Dr Emer Guinan	Assistant Professor
Co-investigators:	Prof John Reynolds	Professor of Surgery
	Mr Ronan Ryan	Consultant Cardiothoracic Surgeon
	Dr Grainne McDermott	Consultant Anaesthetist
	Dr Suzanne Doyle	Assistant Professor
	Dr Linda O'Neill	Project Manager
	Ms Emily Smyth	Research Physiotherapist

You are being invited to take part in an interview study. Before you decide whether or not you wish to take part, you should carefully read the information provided below.

PART 1 – THE STUDY

Why is this study being done?

Thank you for participating in the Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the lung or Oesophagus (PRE-HIIT) study. PRE-HIIT was designed to help improve physical fitness in preparation for surgery. We will measure your physical fitness using fitness tests however we are also keen to talk to you about your experience with the study. This information will be used to improve how we prepare patients for surgery in the future. We will gather this information through a one to one semi-structured interview.

What is a Semi-Structured Interview and what will we discuss?

During the semi-structured interview you will meet with a member of our research team. The researcher will ask you a series of open questions regarding your experience of the PRE-HIIT trial. The researcher may explore your answers to some questions in more detail and may enquire about how your participation in the PRE-HIIT trial has prepared you for your surgery.

The researcher will make an **audio-recording** of your interview. You will have access to the transcripts of the interview if you wish and you can request change to be made to your personal comments if you are unhappy with the content. The interview will take place following your pre-surgical assessment for the PRE-HIIT study in a quiet private room at St James's Hospital. If you wish a family member or friend may accompany you for your interview. The interview will last approximately 15 minutes. Please note, due to the COVID-19 pandemic the research team may decide to hold your interview via telephone or video call to minimise face to face contact time during your assessment.

Do I have to take part? What happens if I say no? Can I withdraw?

No, participation is voluntary. It is up to you whether or not you take part.

If you decide not to take part it won't affect your current or future medical care. You can change your mind about taking part in the study and opt out at any time even if the study has started. If you decide to opt out, it won't affect your current or future medical care. You don't have to give a reason for not taking part or for opting out. If you wish to opt out, please contact Dr Linda O'Neill/ Ms Emily Smyth (Telephone: 01 8964809/ 087 6577927, Email: exerciseoncology@tcd.ie), who will be able to organise this for you.

Are there any benefits to me or others if I take part in the study?

There are no direct benefits to you for taking part in this study. However, the results may help us understand how to better prepare people for surgery in the future.

Are there any risks to me or others if I take part in the study?

We do not anticipate any harms from taking part in the interview.

PART 2 – DATA PROTECTION

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

For this study we will use the audio recording and transcript of your interview.

What will happen my personal data?

If you decide to take part in this study, you give the researcher permission to collect an audio of your discussion during your individual interview. Your data will be identified with a code number which will not include your name or other information that directly identifies you. Your personal details will be kept confidential. All data will be filed and stored securely. At any time, you may ask to see your personal information. Your data will be processed **only as is necessary** to achieve the objectives of this research. Your information will be kept filed securely for up to 10 years, after which it will be destroyed. The results of the study may be used in presentations or published in scientific reports. You will not be identified in any presentation or publication.

Who will access and use my personal data as part of this study?

Authorised members of the research team will have access to and use your personal data for analysis as part of this study.

Will my personal data be kept confidential? How will my data be kept safe?

Your personal data will be kept confidential. We will keep it in a secured file. Your study data will be identified with a code number which will not include your name or other information that directly identifies you. Your data will not be identifiable in any future presentations/publications on the study. To protect the security of data collected for this study a Data Protection Impact Statement has been completed. A Data Management Plan is also in place and will be reviewed on a monthly basis throughout the study.

What is the lawful basis to use my personal data?

The lawful basis for processing of your personal data is covered by Article 6(1)(e) and Article 9(2)(j) of GDPR.

Article 6(1)(e) states processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller.

Article 9(2)j) states that processing is necessary for scientific research purposes in accordance with Article 89(1) based on Union or Member State law which shall be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject.

What are my rights?

You have the following rights regarding your **data**.

- Right to access data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability

PART 3 – COSTS, FUNDING & APPROVAL

Will it cost me anything if I agree to take part?

No, it will not cost you anything if you agree to take part. The research team will cover any parking costs incurred at St James's Hospital during the study.

Who is funding this study?

This study is funded by the Health Research Board and Medical Research Charities Group.

Has this study been approved by a research ethics committee?

Ethical approval has been granted by the Tallaght University Hospital/ St James's Hospital Research Ethics Committee (researchethics@tuh.ie).

PART 4 – FUTURE RESEARCH

Will my personal data and/or biological material be used in future studies?

No your personal data will not be used in future studies.

PART 5 – FURTHER INFORMATION

Where can I get further information?

Co-Principal Investigators:		
Professor Juliette Hussey		Email: jmhussey@tcd.ie
Dr Emer Guinan	+353 1 8964125	Email: guinane1@tcd.ie
Data Controller: Trinity College Dublin/ St James's Hospital Dublin		
Data Processors: Trinity College Dublin/ St James's Hospital Dublin		
Pre-HIIT Research Team Members		Email: exerciseoncology@tcd.ie
Data Protection Officer, Trinity College Dublin		Email: dataprotection@tcd.ie

If you have any questions or would like more information about the study please contact a ***member of the research team*** *(Dr Linda O'Neill/Ms Emily Smyth)*, Monday – Friday from 8.00 am to 5.00pm (telephone: +353 1 8964809/ 087 6577927, email: exerciseoncology@tcd.ie).

What happens if I wish to make a complaint?

Complaints regarding this study should be directed to the Co-Principal Investigators Professor Juliette Hussey and Dr Emer Guinan (contact details above). Complaints regarding data protection should be directed to the Data Protection Officer (email address above).

Will I be contacted again?

The research team may wish to contact you in the future. In particular they may wish to contact you with regards participation in future Public and Patient Involvement (PPI) activities. In the consent form you will be explicitly asked to consent to receiving information about future PPI activities.

14 Informed Consent for Study II: Feedback Interview Patient's Perspectives of their Participation on the PRE-HIIT Trial

CONSENT FORM

Feedback Interview

Patient's Perspectives of their Participation on the PRE-HIIT Trial

To be completed by the **PARTICIPANT**:

I have read and understood the information leaflet.	YES ☐	NO ☐
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.	YES ☐	NO ☐
I have received enough information about this study.	YES ☐	NO ☐
I understand that I am free to withdraw from the study at any time without giving a reason and this will not affect my future medical care.	YES ☐	NO ☐
I agree to allow the researchers use my information (personal data) as part of this study as outlined in the information leaflet.	YES ☐	NO ☐
I agree to be contacted by researchers as part of this study.	YES ☐	NO ☐
I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study.	YES ☐	NO ☐
I give my explicit consent to have my data processed as part of this research study.	YES ☐	NO ☐
I agree to have the interview recorded so that it can be transcribed.	YES ☐	NO ☐
I agree to be contacted by the researchers about other research activities in the future.	YES ☐	NO ☐

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES □	NO □
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES □	NO □

Researcher's Name (Block Capitals):	
Researcher's Title & Qualifications:	
Researcher's Signature:	
Date:	

15 Semi-structured Interview Guide for Study II

PRE_HIIT Interview Guide

1. How would you describe your level of physical activity before this programme started?
2. Before starting the programme, what did you think you would get out of it?
    a. PROMPT what did you think was the purpose of it
3. How confident did you feel in your ability to fully take part/participate the programme?
4. Did you have any concerns about exercising before your surgery?
5. Can you talk me through your overall experience of completing /participating in the PRE-HITT programme?
6. What impact has this preoperative exercise programme had on you? Please tell me about both the positive and any negative effects.
    a. Earlier you mentioned…….and the programme, do you think it's helped you improve?
    b. Can you please tell me how you think the programme may or may not have helped improve your outcome?
    c. Do you feel that PRE-HIIT will influence your postoperative recovery? In what way?
7. What aspect of the programme did you most enjoy? Ok tell me about that, was that surprising to you, did you expect that.
8. What aspect of the programme did you find most challenging?
9. Did completing the PRE-HITT programme interfere with any other priorities? If so, can you tell me how?
10. What changes, if any, would you make to the programme?

16 Ethical Approval for Study III

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Emily Smyth,
Physiotherapy Post Graduate Room,
Physiotherapy Department,
Trinity Health Centre,
St James Hospital,
James Street,
Dublin 8

1st June 2021

Ref: 210202

Title of Study: The Acceptability of Exercise Prehabilitation Before Cancer Surgery

Dear Emily,

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in February 2021. We are pleased to inform you that the above project has ethical approval to proceed.

This study has been ethically approved. We would advise you to seek review and comments on your DPIA from the DPO if required prior to study commencement'

As a researcher you must ensure that you comply with other relevant regulations, including DATA PROTECTION and HEALTH AND SAFETY.

Yours sincerely,

Prof. Jacintha O'Sullivan
Chairperson
Faculty Research Ethics Committee

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Emily Smyth,
Physiotherapy Post Graduate Room,
Physiotherapy Department,
Trinity Health Centre,
St James Hospital,
James Street,
Dublin 8

8th February 2022

Ref: 210202
Title of Study: The Acceptability of Exercise Prehabilitation before Cancer Surgery

Dear Emily,

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in February 2022, we are pleased to inform you that the above project (as amended with the following changes) has ethical approval to proceed.

We would advise you to seek review and comments on your DPIA from the DPO if required prior to study commencement.

Please give specific details of the requested amendment(s):
A hard copy of the Acceptability of Exercise Prehabilitation will be distributed to patients at oncological surgical clinics in St James Hospital. Changes to current protocol include

1. Recruitment of patients and family members group will be carried out from surgical clinics in St James Hospital.
2. There will be no named gatekeeper for clinic recruitment. A member of each administrative team will be identified prior to recruitment and asked to distribute the questionnaire packs in clinic.
3. Oncological surgical clinics approached will include
    a. Gastrointestinal
    b. Breast
    c. Gynaecological
    d. Maxillofacial
    e. Urology
    f. Colorectal
    g. Cardiothoracic
4. Questionnaire packs will include
    a. Patient Information Leaflet (appendix k)
    b. Exercise Prehabilitation Information Leaflet (appendix o)
    c. A hard copy version of the Acceptability of Exercise Prehabilitation Questionnaire (appendix n)
    d. Stamped and addressed return envelope

5. No healthcare workers will be recruited during this recruitment.
6. Participants will not be invited to participate in a semi structured interview as they are with the online version.

An additional question has been added to the questionnaire (appendix c and n). This question will enhance understanding of participants perception of the effectiveness of exercise prehabilitation.

As a researcher you must ensure that you comply with other relevant regulations, including DATA PROTECTION
and HEALTH AND SAFETY.

Yours sincerely,

Jacintha O'Sullivan

Prof. Jacintha O'Sullivan
Chairperson Faculty Research Ethics Committee

Dámh na nEolaíochtaí Sláinte
Foirgneamh na Ceimice,
Coláiste na Tríonóide,
Ollscoil Átha Cliath,
Baile Átha Cliath 2, Éire.

Faculty of Health Sciences
Chemistry Building,
Trinity College Dublin,
The University of Dublin,
Dublin 2, Ireland.

www.healthsciences.tcd.ie

Beacon Hospital
Sandyford, Dublin 18, Ireland, D18 AK68
T: +353 1 293 6600 | www.beaconhospital.ie

Ms. Emily Smyth
PhD Student
Trinity Centre for Health Sciences
St. James Hospital
Dublin

Date: 4th November 2022

BHREC Ref: BEA0197

Study Title: The acceptability of exercise prehabilitation prior to oncological resection.

Dear Ms. Emily Smyth,

Following review of your application, BHREC has given your study *Full Approval* to proceed.

The documents submitted, reviewed and approved are listed as follows:

Initial submission:

- ST-FORM 1- RECSAF
- ST-FORM 3-DPIA
- ST-FORM 2-PILICF
- ST-FORM-4-Checklist_Signatory_Page
- Appendix_A_Questionnaire
- Appendix_B_Educational_infographics
- Appendix_C_Protocol
- Appendix_D_Semi_Structured_Interviews
- Appendix_E_PIL
- Appendix_F_Consent
- Appendix_G_InterviewPIL
- Appendix_H_Contact_form
- Appendix_I_OR_code
- Appendix_J_TCD_ethical_approval
- Cover_letter
- PI_cv_2022

1st Amendments:

- Video_link

The submission has been reviewed from an ethical perspective only. It is the responsibility of the PI/sponsor/data controller to ensure and monitor compliance with any relevant data protection legislation in the country where the study is due to take place and or with any local policy in the site where the study is being conducted.

Beacon Hospital
Sandyford, Dublin 18, Ireland, D18 AK68
T: +353 1 293 6600 | www.beaconhospital.ie

The application was reviewed by the Beacon Hospital Data Protection Committee and the Data Protection Officer, Ms. Ailish Daly.

Approval will be rescinded if the following terms are also not adhered to:

- **Annual Progress Reports** must be submitted to the REC for the duration of the project, with the first report due within a period of no later than 12 months from the date of this letter
- A **Final Report** must be submitted to the REC following completion of the project
- All application/protocol amendments must be submitted for review and approval to the REC **prior to implementation**
- The REC must be notified of all/any **Serious Adverse Events (SAEs) or new issues/events likely to affect the conduct or safety of the study and/or participants**

Name	Position	Signature	Date
Prof Ray McDermott	Chair, REC, Beacon Hospital		
Ms. Ailish Daly	Data Protection Officer		

*Please inform the BHREC of **any dissemination outputs** arising from conducting your research study concerning Beacon Hospital patients.*

Please acknowledge receipt of this letter and if you have any queries relating to the terms and conditions outlined in this letter, please do not hesitate to contact me.

Kind regards,

Beacon Hospital Research Ethics Committee Administrator
Beacon Hospital
Suite 13
Sandyford
Dublin 18
Email: ethics@beaconhospital.ie

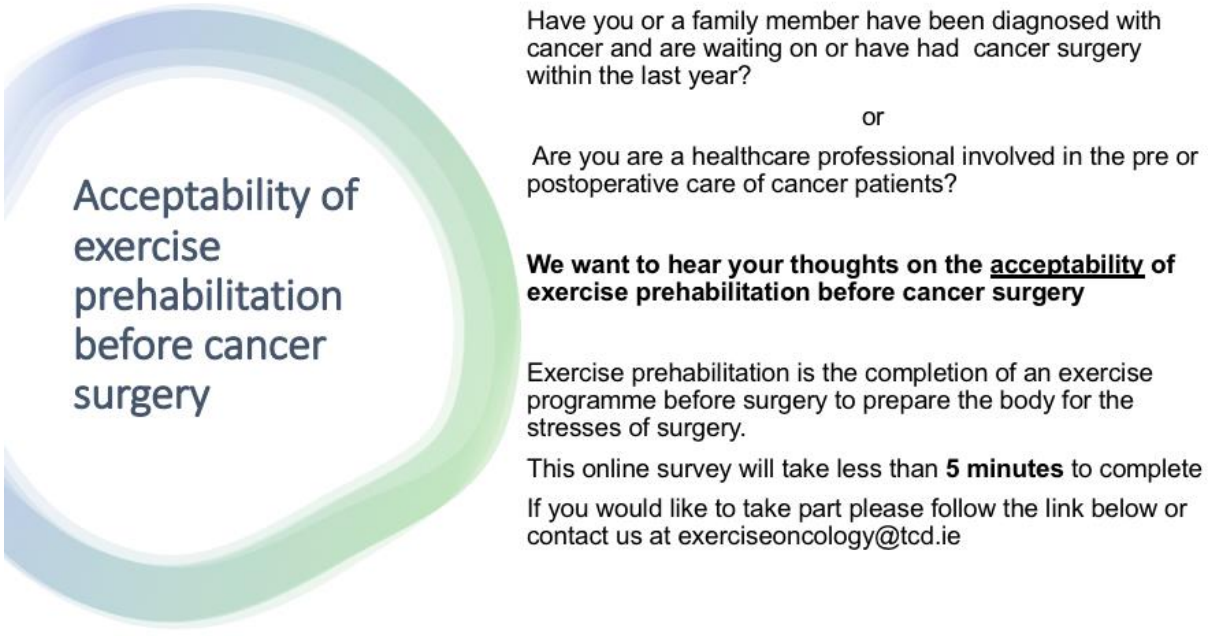
17 Recruitment Posters for Study III

Sample twitter post:

If you or a family member have #cancer or you are involved in the surgical care of someone with #cancer we want to hear from you. Follow this link: https://nursingandmidwifery.fra1.qualtrics.com/jfe/form/SV_6ygskjNpGBaR0Eu

Or please email me or DM to find out more: exerciseoncology@tcd.ie

reposts appreciated!



18 Recruitment Emails for Professional Bodies

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Trinity Exercise Oncology Research Group,
Discipline of Physiotherapy
Trinity Centre for Health Sciences,
St James Street,
Dublin 8, Ireland.

Exercise prehabilitation is an exercise intervention which carried out before surgery. The goal is to improve preoperative fitness, prepare the body for surgery and potentially reduce postoperative complications. However, exercise prehabilitation is challenging in a clinical context and therefore the acceptability must be considered prior to integration into a clinical pathway.

For this reason, Emily Smyth a researcher with the Trinity Exercise Oncology Research group at Trinity College Dublin is completing a study to understand how acceptable patients, their family members and healthcare providers consider exercise prehabilitation. Acceptability refers to the extent to which people receiving or delivering prehabilitation consider it to be appropriate based on experienced or expected responses to prehabilitation. This will allow for identification of any obstacles in the process and guide intervention design.

Participants will be asked to watch a short clip explaining the concept of prehabilitation and then complete an anonymised online survey. This process should take no longer than 10 minutes. After the questionnaire participants will be invited to partake in a short interview where concepts can be discussed in greater detail.

We would greatly appreciate if you would consider forwarding this onto members of the ISCP. Furthermore, please feel free to distribute the link to family, friends and any patient groups you feel appropriate.

http://bit.ly/acceptability

Best wishes,

Professor Juilette Hussey,

Trinity Exercise Oncology Research Group,

Department of Physiotherapy,

Trinity College Dublin, Ireland.

Email: exerciseoncology@tcd.ie

19 Recruitment Emails for Charities

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Trinity Exercise Oncology Research Group,
Discipline of Physiotherapy
Trinity Centre for Health Sciences,
St James Street,
Dublin 8, Ireland.

Exercise prehabilitation is an exercise intervention which carried out before surgery. The goal is to improve preoperative fitness, prepare the body for surgery and potentially reduce postoperative complications. However, exercise prehabilitation is a challenge for patients and requires a high level of patient engagement. For cancer patients this may be difficult and may be limited by symptom burden and restricted timeframes.

For this reason, Emily Smyth a researcher with the Trinity Exercise Oncology Research group at Trinity College Dublin is completing a study to understand how acceptable patients, their family members and healthcare providers consider exercise prehabilitation. Acceptability refers to how tolerable people consider an intervention to be. This will allow for identification of any obstacles in the process and guide intervention design.

Participants will be asked to watch a short clip explaining the concept of prehabilitation and then complete an anonymised online survey. This process should take no longer than 10 minutes. After the questionnaire participants will be invited to partake in a short interview where concepts can be discussed in greater detail.

Please feel free to distribute the link to patients, family, friends and any groups you feel appropriate.

http://bit.ly/acceptability

Best wishes,

Professor Juilette Hussey,

Trinity Exercise Oncology Research Group,

Department of Physiotherapy,

Trinity College Dublin, Ireland.

Email: exerciseoncology@tcd.ie

20 The SJH and Online Acceptability Questionnaire Pack

Exercise Prehabilitation Before Cancer Surgery

1

What is exercise prehabilitation before cancer surgery?

Exercise prehabilitation is the participation in an exercise programme before surgery. This occurs after a cancer diagnosis and before surgery. For some people, this may mean after their chemotherapy or radiation therapy and before their surgery.

2

What is the goal of exercise prehabilitation?

To prepare the body for the stresses associated with surgery.
Prehab is associated with

- Fewer post-operative complications
- Reduced length of stay in hospital
- Faster return to normal function
- Improved health-related quality of life

3

Exercise prehabilitation programmes may include

- Cycling
- Resistance Training
- Flexibility
- Walking
- Exercise Classes

4

Exercise prehabilitation programmes may be

•**Mild intensity**: Meaning you could sing while exercising

•**Moderate intensity**: Meaning you could talk but not sing while exercising

•**High intensity**: Meaning you would be unable to speak more than a few words during exercise

5

Exercise prehabilitation programmes may

•Last from 30-90 minutes.
•Take place as often as 3-7 times a week.

The Acceptability of Exercise Prehabilitation Before Cancer Surgery

Thank you for taking the time to ready this questionnaire. Full details about this questionnaire can be found in the participant information leaflet you received with this questionnaire.

Exercise prehabilitation is an exercise programme which carried out before a surgery. The goal is to improve preoperative fitness, prepare the body for surgery and potentially reduce postoperative complications. However, exercise prehabilitation is a challenge for patients and requires a high level of patient engagement. For cancer patients this may be difficult and may be limited by symptom burden and restricted timeframes. Therefore, in order to establish an effective programme, it is important to understand the view of how acceptable exercise prehabilitation is to patients, family members and health professionals. The term ***acceptability*** refers to how tolerable you consider prehabilitation to be. In order to establish this, we have created an information leaflet which will help with your understanding of exercise prehabilitation. Thank you for your participation.

For the purpose of this questionnaire, you will be asked to identify as a member of one of three stakeholder groups. Please read the definitions below to assist your selection.

Patient group: A person who is waiting on a cancer surgery or has had cancer surgery within the last 12 months.

Family member group: A family member of a person who is waiting on a cancer surgery or has had cancer surgery within the last 12 months.

Please tick the appropriate box

Question 1:

I confirm I have read and understood the Information Leaflet for the above study and I consent to participate in this questionnaire.

Yes ☐

No ☐

Question 2:

Which stakeholder group do you belong to?

Patient group ☐

Family member group ☐

Question 3:

What age are you?

_____

Question 4:

What sort of cancer surgery will/did you (or your family member) have?

- Breast Surgery ☐
- Oesophageal Surgery (surgery of the food pipe) ☐
- Lung Surgery ☐
- Stomach Surgery ☐
- Ovarian Surgery (surgery of the ovaries) ☐
- Womb Surgery ☐
- Bladder Surgery ☐
- Prostate Surgery ☐
- Thyroid Surgery ☐
- Bowel Surgery ☐
- Other (Please specify below) ☐

Question 5:

When was/ is your (or your family member) surgery?

- Currently waiting on surgery ☐
- Surgery within the last 6 months ☐
- Surgery within the last 6 months -12 months ☐

Question 6:

Did you (or your family member) have

- Chemotherapy ☐
- Radiotherapy ☐
- Chemoradiotherapy ☐
- No chemotherapy or radiotherapy ☐

Question 7:

Reflecting on your or your family members physical activity levels before surgery, how many minutes of aerobic exercise such as brisk walking, cycling, jogging, tennis etc. were achieved per week?

- None ☐
- <60 minutes ☐
- 60-150 minutes ☐

Question 8:

Reflecting on your own current physical activity levels, how many minutes of aerobic exercise such as brisk walking, cycling, jogging, tennis etc. do you complete per week?

- None ☐
- <60 minutes ☐
- 60-150 minutes ☐

Question 9:

Prehabilitation is the participation in a programme with the goal of enhancing physical, nutritional and the bodies resilience before surgery. This may involve education on diet, assistance with stopping smoking, exercise or psychological support. Do you/did you (or your family member) take part in any form of prehabilitation before surgery?

- Yes ☐
- No ☐

Question 10:

Exercise prehabilitation is the participation in an exercise programme prior to surgery in order to improve fitness before surgery. Do you/did you (or your family member) take part in form of exercise prehabilitation before surgery?

- Yes ☐
- No ☐

Please circle the appropriate box below

Question 11:

How would you rate the acceptability of exercise prehabilitation before cancer surgery?				
Completely unacceptable	Unacceptable	No opinion	Acceptable	Completely acceptable
Do you like or dislike the idea of exercise prehabilitation prior to cancer surgery?				
Strongly dislike	Dislike	No opinion	Like	Completely Like
How much effort from yourself do you feel exercise prehabilitation would require?				
No effort at all	A little effort	No opinion	A lot of effort	Huge effort
How important do you feel it is for patients to have access to exercise prehabilitation as part of their cancer care service?				
Very unimportant	unimportant	No opinion	Important	Very important
Exercise prehabilitation is likely to improve patient engagement with cancer care services				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
It is clear to me how exercise prehabilitation would help cancer patients before surgery				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
How confident do you feel about patients being able to complete exercise prehabilitation before cancer surgery?				
Very unconfident	Unconfident	No opinion	Confident	Very confident

Please rate your level of agreement/disagreement with the following statement. Exercise prehabilitation may interfere with other priorities before cancer surgery?				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
Please rate your level of agreement/disagreement with the following statement. Exercise prehabilitation is likely to improve physical fitness?				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree

Many thanks for taking the time to complete this questionnaire.

The Acceptability of Exercise Prehabilitation before Cancer Surgery: Questionnaire

You are being invited to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. If you have any questions you can contact the research team at exerciseoncology@tcd.ie. Take time to decide whether or not to take part.

PART 1- THE STUDY

Why is this study being done?

Exercise prehabilitation is a growing area of interest in cancer care. The aim of exercise prehabilitation prior to surgery is to prepare the body for the physical stresses of surgery. There is a growing body of evidence to support prehabilitation, however exercise prehabilitation requires significant patient engagement. Therefore, in order to establish an intervention which is applicable in practice, we must first consider how acceptable the intervention is perceived to be. Acceptability refer to how tolerable you consider an intervention to be. Understanding your opinions on the acceptability of prehabilitation will enable us to implement a preoperative exercise intervention which can be implemented in a care pathway.

Why am I being asked to take part?

You are being asked to participant as you fall within the category of 'Key Stakeholder' in the area of cancer surgery. This means you may be: currently waiting for or have had cancer surgery within the past 12 months; a family member of someone awaiting cancer surgery; or a healthcare provider/hospital manager working in this clinical area.

Do I have to take part? What happens if I say no? Can I withdraw?

No, you do not have to take part. You do not have to give any reason for not taking part.

What will happen to me if I agree to take part?

First you will be asked to watch a short animation or given a leaflet which will explain what exercise prehabilitation is and what it entails. You will then complete a short questionnaire.

Once you have completed the questionnaire you will be invited to participate in an interview with the research team. You do **not** have to take part in the interview if you complete the questionnaire. If you would like to receive further information about the interview you will be asked to provide contact details at the end of the questionnaire. These contacts details will be collected independently, stored securely and will not be linked to your initial responses.

Are there any benefits to me or others if I take part in the study?

There are no direct benefits to you. The results of this study will help to inform the future design of exercise prehabilitation interventions.

How do I provide consent?

Consent is given in question one of the questionnaire.

PART 2- DATA PROTECTION

What data about me will be collected

All data collected will be anonymised.

Data	Patient/ Family Member	Healthcare Provider
Age	**X**	
Cancer and Surgery Type	**X**	
Neoadjuvant Chemotherapy and/or Radiotherapy	**X**	

Time point in treatment i.e before surgery or after surgery	**X**	
Preoperative Activity Levels	**X**	
Current Activity Levels	**X**	**X**
Years of Clinical Experience		**X**
Occupation		**X**
Experience with Prehabilitation	**X**	**X**
Experience with Exercise Prehabilitation	**X**	**X**

At the end of the questionnaire you may be invited to take part in an interview. If you wish to take part personal data (see table below) will be collected to allow the research team to contact you for participation in the interview. Importantly any personal information provided will be collected through a separate online form which will not be matched to your questionnaire responses.

Data to be Collected	Name
	Address
	Contact Number
	Email Address

What will happen to my personal data?

If you decide to take part in the questionnaire your responses will be anonymous. These will be kept securely for up to 7 years after which they will be destroyed.

Personal data will only be collected and processed if you think you may be interested in taking part and wish to hear more information about the interview. Only personal data necessary to achieve the objectives of this research project will be collected. You will be allocated a study number, which

will be used as a code to identify you on all documentation. Your name and contact details will not be passed to anyone other than members of the research team. Your personal data will be kept securely for up to 7 years after which it will be destroyed. Your data will not be transferred outside the EU. An anonymous version of the study data set will be made available on a secure online data repository post study completion in line with open access publication requirements.

Who will access and use my personal data?

Members of the research team will access and use your personal data as part of the study only if you elect to take part in the interview. Research team members will only be granted access to your data when they have completed training in data protection.

Will my personal data be kept confidential?

If you decide to take part in the questionnaire, responses to the questionnaire will be anonymous and therefor confidential.

If you elect to take part in the interview your personal data will be kept confidential. We will keep it in a password protected file. Your study data will be identified with a code number which will not include your name or other information that directly identifies you. Your data will not be identifiable in any future presentations/publications on the study.

To protect the security of data collected for this study a Data Protection Impact Assessment has been completed.

What are my rights?

Questionnaire will be anonymous and therefore once submitted cannot be identified. For this reason, once your responses have been submitted we will be unable to access, restrict, correct, delete or transfer data.

If you provide personal data for participation in the interview you have the following rights regarding your personal data.

- Right to access data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability

Will my data be used in future research?

Your data will not be used in future research without your consent.

PART 2- FUNDING & APPROVAL

Who is funding this study?

This study is funded by the Health Research Board (HRB) and the Medical Research Charities Group (MRCG).

Has this study been approved by an Ethics Committee?

Ethical approval has been granted by the Faculty of Health Science, Research Ethics Committee, Trinity College Dublin (approval number to be included).

PART 3- FURURE INFORMATION

Where can I get further information?

Research Team: Emily Smyth Email: exerciseoncology@tcd.ie

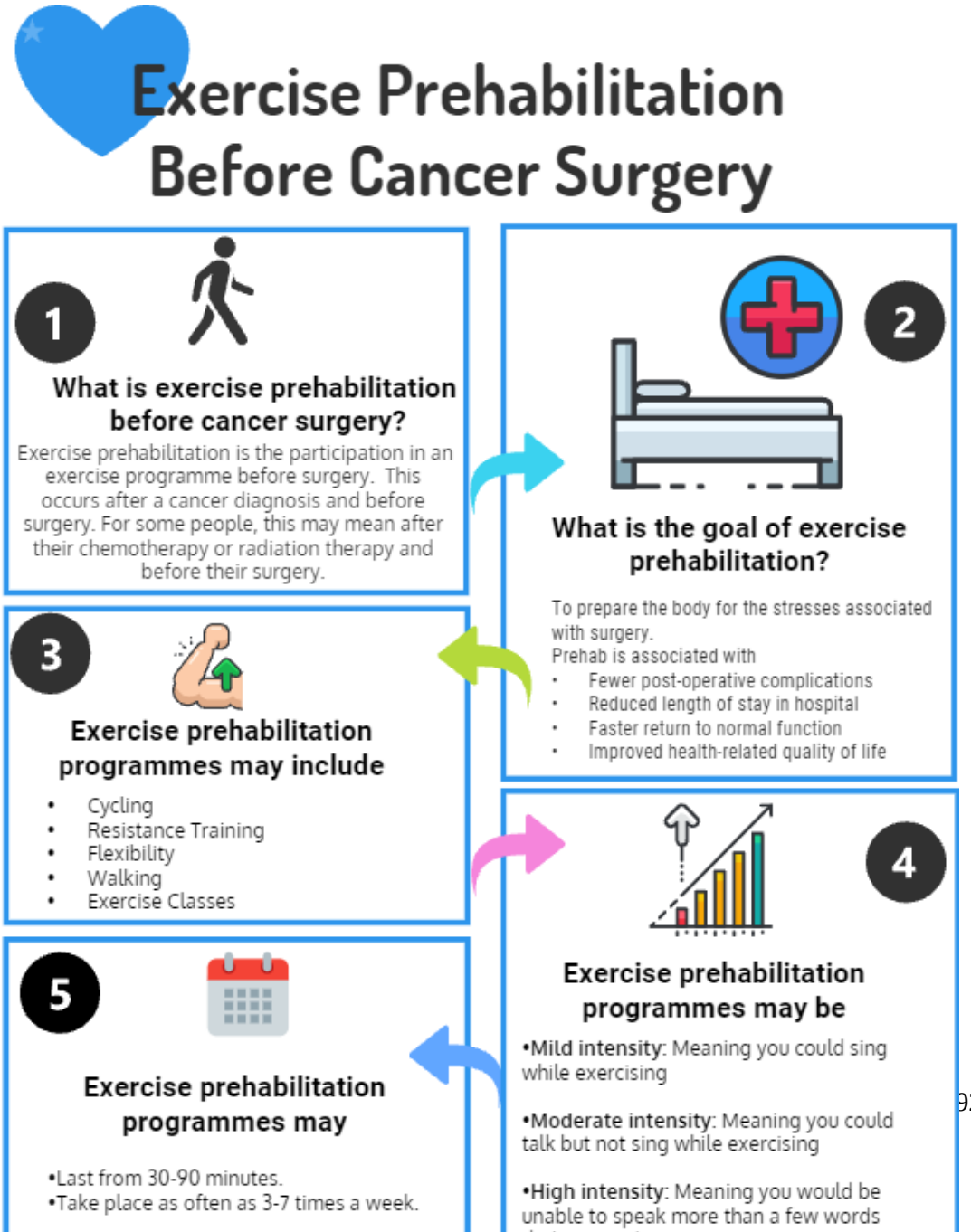
Data Protection Officer, Trinity College Dublin Email: dataprotection@tcd.ie

Data Controller: Trinity College Dublin/ St James's Hospital Dublin

Data Processors: Trinity College Dublin/ St James's Hospital Dublin

Prehabilitation Research Study

Part 1: Questionnaire



Please see page 9 for Participant Information Leaflet

The Acceptability of Exercise Prehabilitation before Cancer Surgery: Questionnaire

You are being invited to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. If you have any questions, you can contact the research team at exerciseoncology@tcd.ie. Take time to decide whether or not to take part.

If you would like to complete this questionnaire online, please scan the QR code below. To do this

1) **Open the camera app on your phone**
2) **Focus the camera on the QR code below by gentle taping the QR code on your screen**
3) **A box with a link to a website will appear at the top of the page**
4) **Press the link**

The Acceptability of Exercise Prehabilitation Before Cancer Surgery

For the purpose of this questionnaire, you will be asked to identify as a member of one of three stakeholder groups. Please read the definitions below to assist your selection.

Patient group: A person who is waiting on a cancer surgery or has had cancer surgery within the last 12 months.

Family member group: A family member of a person who is waiting on a cancer surgery or has had cancer surgery within the last 12 months.

Please tick the appropriate box

Question 1:

I confirm I have read and understood the Information Leaflet for the above study and I consent to participate in this questionnaire.

Yes ☐
No ☐

Question 2:

Which stakeholder group do you belong to?

Patient group ☐

Family member group ☐

Question 3:

What age are you? _____

Question 4:

What sort of cancer surgery will/did you (or your family member) have?

- Breast Surgery ☐
- Oesophageal Surgery (surgery of the food pipe) ☐
- Lung Surgery ☐
- Stomach Surgery ☐
- Ovarian Surgery (surgery of the ovaries) ☐
- Womb Surgery ☐
- Bladder Surgery ☐
- Prostate Surgery ☐
- Thyroid Surgery ☐
- Bowel Surgery ☐
- Other (Please specify below) ☐

Question 5:

When was/ is your (or your family member) surgery?

- Currently waiting on surgery ☐
- Surgery within the last 6 months ☐
- Surgery within the last 6 months -12 months ☐

Question 6:

Did you (or your family member) have

- Chemotherapy ☐
- Radiotherapy ☐
- Chemoradiotherapy ☐
- No chemotherapy or radiotherapy ☐

Question 7:

Reflecting on your or your family members physical activity levels before surgery, how many minutes of aerobic exercise such as brisk walking, cycling, jogging, tennis etc. were achieved per week?

- None ☐
- <60 minutes ☐
- 60-150 minutes ☐

Question 8:

Reflecting on your own current physical activity levels, how many minutes of aerobic exercise such as brisk walking, cycling, jogging, tennis etc. do you complete per week?

- None ☐
- <60 minutes ☐
- 60-150 minutes ☐

Question 9:

Prehabilitation is the participation in a programme with the goal of enhancing physical, nutritional and the bodies resilience before surgery. This may involve education on diet, assistance with stopping smoking, exercise or psychological support.

Do you/did you (or your family member) take part in any form of prehabilitation before surgery?

- Yes ☐
- No ☐

Question 10:

Exercise prehabilitation is the participation in an exercise programme prior to surgery in order to improve fitness before surgery.

Do you/did you (or your family member) take part in form of exercise prehabilitation before surgery?

- Yes ☐
- No ☐

Question 11: Please turn over the page

Please circle the appropriate box below

How would you rate the acceptability of exercise prehabilitation before cancer surgery?				
Completely unacceptable	Unacceptable	No opinion	Acceptable	Completely acceptable
Do you like or dislike the idea of exercise prehabilitation prior to cancer surgery?				
Strongly dislike	Dislike	No opinion	Like	Completely Like
How much effort from yourself do you feel exercise prehabilitation would require?				
No effort at all	A little effort	No opinion	A lot of effort	Huge effort
How important do you feel it is for patients to have access to exercise prehabilitation as part of their cancer care service?				
Very unimportant	Unimportant	No opinion	Important	Very important
Exercise prehabilitation is likely to improve patient engagement with cancer care services				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
It is clear to me how exercise prehabilitation would help cancer patients before surgery				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
How confident do you feel about patients being able to complete exercise prehabilitation before cancer surgery?				
Very unconfident	Unconfident	No opinion	Confident	Very confident

Please rate your level of agreement/disagreement with the following statement. Exercise prehabilitation may interfere with other priorities before cancer surgery?				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree
Please rate your level of agreement/disagreement with the following statement. Exercise prehabilitation is likely to improve physical fitness?				
Strongly disagree	Disagree	No opinion	Agree	Strongly agree

Many thanks for taking the time to complete this questionnaire.

PARTICIPANT INFORMATION LEAFLET

PART 1- THE STUDY

Why is this study being done?

Exercise prehabilitation is a growing area of interest in cancer care. The aim of exercise prehabilitation prior to surgery is to prepare the body for the physical stresses of surgery. There is a growing body of evidence to support prehabilitation, however exercise prehabilitation requires significant patient engagement. Therefore, in order to establish an

intervention which is applicable in practice, we must first consider how acceptable the intervention is perceived to be. Acceptability refers to how tolerable you consider an intervention to be. Understanding your opinions on the acceptability of prehabilitation will enable us to implement a preoperative exercise intervention which can be implemented in a care pathway.

Why am I being asked to take part?

You are being asked to participant as you fall within the category of 'Key Stakeholder' in the area of cancer surgery. This means you may be: currently waiting for or have had cancer surgery within the past 12 months; a family member of someone awaiting cancer surgery; or a healthcare provider/hospital manager working in this clinical area.

Do I have to take part? What happens if I say no? Can I withdraw?

No, you do not have to take part. You do not have to give any reason for not taking part and it will not affect the standard of care you receive. Yes, you can decide to stop at any time. This will not affect the standard of care you receive.

What will happen to me if I agree to take part?

Firstly, you will be asked to watch a short animation or given a leaflet which will explain what exercise prehabilitation is and what it entails. You will then complete a short questionnaire. Once you have completed the questionnaire you will be invited to participate

in an interview with the research team. You do **not** have to take part in the interview if you complete the questionnaire. If you would like to receive further information about the interview you will be asked to provide contact details at the end of the questionnaire. These contacts details will be collected independently, stored securely and will not be linked to your initial responses.

Are there any benefits to me or others if I take part in the study?

There are no direct benefits to you. The results of this study will help to inform the future design of exercise prehabilitation interventions.

How do I provide consent?

Consent is given in question one of the questionnaire.

PART 2- DATA PROTECTION

What data about me will be collected

All data collected will be anonymised.

Data	**Patient/ Family Member**	**Healthcare Provider**
Age	**X**	
Cancer and Surgery Type	**X**	
Neoadjuvant Chemotherapy and/or Radiotherapy	**X**	
Time point in treatment i.e before surgery or after surgery	**X**	
Preoperative Activity Levels	**X**	
Current Activity Levels	**X**	**X**
Years of Clinical Experience		**X**
Occupation		**X**
Experience with Prehabilitation	**X**	**X**
Experience with Exercise Prehabilitation	**X**	**X**

At the end of the questionnaire you may be invited to take part in an interview. If you wish to take part personal data (see table below) will be collected to allow the research team to contact you for participation in the interview. Importantly any personal information provided will be collected through a separate online form which will not be matched to your questionnaire responses.

Data to be Collected	Name
	Address
	Contact Number
	Email Address

What will happen to my personal data?

If you decide to take part in the questionnaire your responses will be anonymous. These will be kept securely for up to 7 years after which they will be destroyed.

Personal data will only be collected and processed if you think you may be interested in taking part and wish to hear more information about the interview. Only personal data necessary to achieve the objectives of this research project will be collected. You will be allocated a study number, which will be used as a code to identify you on all documentation. Your name and contact details will not be passed to anyone other than members of the research team. Your personal data will be kept securely for up to 7 years after which it will be destroyed. Your data will not be transferred outside the EU. An anonymous version of the study data set will be made available on a secure online data repository post study completion in line with open access publication requirements.

Who will access and use my personal data?

Members of the research team will access and use your personal data as part of the study only if you elect to take part in the interview. Research team members will only be granted access to your data when they have completed training in data protection.

Will my personal data be kept confidential?

If you decide to take part in the questionnaire, responses to the questionnaire will be anonymous and therefor confidential. If you elect to take part in the interview your personal data will be kept confidential. We will keep it in a password protected file. Your study data will be identified with a code number which will not include your name or other information that directly identifies you. Your data will not be identifiable in any future presentations/publications on the study.

To protect the security of data collected for this study a Data Protection Impact Assessment has been completed.

What are my rights?

Questionnaire will be anonymous and therefore once submitted cannot be identified. For this reason, once your responses have been submitted we will be unable to access, restrict, correct, delete or transfer data.

If you provide personal data for participation in the interview you have the following rights regarding your personal data.

- Right to access data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability

Will my data be used in future research?

Your data will not be used in future research without your consent.

PART 2- FUNDING & APPROVAL

Who is funding this study?

This study is funded by the Health Research Board (HRB) and the Medical Research Charities Group (MRCG).

Has this study been approved by an Ethics Committee?

Ethical approval has been granted by the Faculty of Health Science, Research Ethics Committee, Trinity College Dublin (reference number 210202) and the Research Ethics Committee Beacon Hospital (reference number BEA0197).

PART 3- FURURE INFORMATION

Where can I get further information?

Research Team: Emily Smyth
Email: exerciseoncology@tcd.ie

Prehabilitation Research Study

WE WOULD LIKE TO INVITE YOU TO

TAKE PART IN A SHORT INTERVIEW

This interview will allow us to delve into your opinions on exercise prehabilitation and will help to guide programme design in the further.

If you wish to be contacted by the research team to participate in the interview please provide your contact details below.

Please enter your name.....

Please enter your best contact number.....

Please enter your address.....

.....

Please enter your email address.....

If you have any questions, please feel free to contact us at exerciseoncology@tcd.ie

Trinity St James's Cancer Institute

CONSENT FORM

The Acceptability of Exercise Prehabilitation Before Cancer Surgery: Semi structured Interview

To be completed by the **PARTICIPANT:**

I confirm I have read and understood the Information Leaflet for the above study. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.	□**YES**	□**NO**
I know that participation is completely voluntary, and I can withdraw at any point without giving a reason and without any consequences.	□**YES**	□**NO**
I understand that I will not be paid for taking part in this study.	□**YES**	□**NO**
I know how to contact the research team if I need to	□**YES**	□**NO**
I agree to being contacted by researchers by phone as part of this research study	□**YES**	□**NO**
I agree to allow the researchers to use my information (personal data) as part of this study as outlined in the information leaflet	□**YES**	□**NO**
I am aware that the information I provide are handled confidentially and according to applicable data protection laws.	□**YES**	□**NO**
I understand that the results of the research are published in a way that does not compromise the identity of the participants.	□**YES**	□**NO**
I am happy to be contacted in future about future research projects by the research team	□**YES**	□**NO**
I understand that there are no direct benefits to me from participating in this study. I understand that results from analysis of my personal information will not be given to me	□**YES**	□**NO**
I understand that personal information about me, including the transfer of this personal information about me outside of the EU, will be protected in accordance with the General Data Protection Regulation.	□**YES**	□**NO**
A transcript of the interview is available upon request. Please advise us if you would like to receive a copy by emailing us at: exerciseoncology@tcd.ie		

Patient Name (Block Capitals) Patient Signature Date

PARTICIPANT INFORMATION LEAFLET

The Acceptability of Exercise Prehabilitation Before Cancer Surgery: Semi structured Interview

You are being invited to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. If you have any questions you can contact the research team at exerciseoncology@tcd.ie Take time to decide whether or not to take part.

PART 1- THE STUDY

Why is this study being done?

Exercise prehabilitation is a growing area of interest in cancer care. The aim of exercise prehabilitation prior to surgery is to prepare the body for the physical stresses of surgery. There is a growing body of evidence to support prehabilitation, however prehabilitation requires significant patient engagement. Therefore, in order to establish an intervention which is applicable in practice, we must first consider how acceptable the intervention is perceived to be. Acceptability refer to how tolerable you consider prehabilitation to be. Understanding your opinions on the acceptability of prehabilitation will enable us to implement a preoperative exercise intervention which can be implemented in a care pathway.

Why am I being asked to take part?

You are being asked to participant as you fall within the category of key stakeholder and have already completed part one of this study.

Do I have to take part? What happens if I say no? Can I withdraw?

No, you do not have to take part. You do not have to give any reason for not taking part and it will not affect the standard of care you receive. Yes, you can decide to stop at any time. This will not affect the standard of care you receive.

What will happen to me if I agree to take part?

You will first be contacted to arrange delivery of a consent form and a stamped return envelope. The consent form must be returned to the team or via a pre-stamped addressed envelope or scanned prior to participation in the interview. Once consent is received a member of the research team will contact you to arrange a time to carry out the interview at a time which is convenient for you. This will be carried out over the telephone or videoconference. All interviews will be recorded. The interview will last approximately 20 minutes.

Are there any benefits to me or others if I take part in the study?

There are no direct benefits to you. The results of this study will help to inform the future design of exercise prehabilitation interventions.

How do I provide consent?

Written consent will be obtained prior to participation in the interview and returned to the research team.

PART 2- DATA PROTECTION

What will happen to my personal data?

If you decide to take part your personal details and interview responses will be kept confidential at all times. Personal data will be processed only as is necessary to achieve the objectives of this research project.

You will be allocated a study number, which will be used as a code to identify you on all documentation. Your name and contact details will not be passed to anyone other than members of the research team. Your personal data and recordings will be kept securely for up to 7 years after which it will be destroyed. Your data will not be transferred outside the EU. An anonymous version of the study data set will be made available on a secure online data repository post study completion in line with open access publication requirements. Audio recordings will not be used in future unrelated studies.

Who will access and use my personal data?

Members of the research team will access and use your personal data as part of the study. Research team members will only be granted access to your data when they have completed training in data protection.

Will my personal data be kept confidential?

Your personal data will be kept confidential. We will keep it in a secured file. Your study data will be identified with a code number which will not include your name or other information that directly identifies you. Your data will not be identifiable in any future presentations/publications on the study. To protect the security of data collected for this study a Data Protection Impact Assessment has been completed.

What are my rights?

You have the following rights regarding your data.

- Right to access data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability

Will my data be used in future research?

Your data will not be used in future research without your consent.

PART 2- FUNDING & APPROVAL

Who is funding this study?

This study is funded by the Health Research Board (HRB) and the Medical Research Charities Group (MRCG).

Has this study been approved by an Ethics Committee?

Ethical approval has been granted by the Faculty of Health Science, Research Ethics Committee, Trinity College Dublin (reference number 210202) and the Research Ethics Committee Beacon Hospital (reference number BEA0197).

PART 3- FURURE INFORMATION

Where can I get further information?

Research Team: Emily Smyth

Email: exerciseoncology@tcd.ie

22 Study III Informed Consent

CONSENT FORM

STUDY NAME: Part 2 Semi structured Interview: The Acceptability of Exercise Prehabilitation Before Cancer Surgery. **Participant Code:**

To be completed by the **PARTICIPANT:**

I confirm I have read and understood the Information Leaflet for the above study. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.	□**YES**	□**NO**
I know that participation is completely voluntary and I can withdraw at any point without giving a reason and without any consequences.	□**YES**	□**NO**
I understand that I will not be paid for taking part in this study.	□**YES**	□**NO**
I know how to contact the research team if I need to	□**YES**	□**NO**
I agree to being contacted by researchers by phone as part of this research study	□**YES**	□**NO**
I agree to allow the researchers to use my information (personal data) as part of this study as outlined in the information leaflet	□**YES**	□**NO**
I am aware that the information I provide are handled confidentially and according to applicable data protection laws.	□**YES**	□**NO**
I understand that the results of the research are published in a way that does not compromise the identity of the participants.	□**YES**	□**NO**

I am happy to be contacted in future about future research projects by the research team	□**YES**	□**NO**
I understand that there are no direct benefits to me from participating in this study. I understand that results from analysis of my personal information will not be given to me	□**YES**	□**NO**
I understand that personal information about me, including the transfer of this personal information about me outside of the EU, will be protected in accordance with the General Data Protection Regulation.	□**YES**	□**NO**
A transcript of the interview is available upon request. Please advise us if you would like to receive a copy by emailing us at: exerciseoncology@tcd.ie		

Patient Name (Block Capitals) Patient Signature Date

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Witness Name (Block Capitals) Witness Signature Date