Multidisciplinary Rehabilitation in Oesophago-gastric Cancer Survivorship

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Declaration

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Summary

Cancers of the oesophagus and stomach, although traditionally associated with poorer outcomes, have seen gradual improvements in survival rates in recent decades. Curative treatment for oesophago-gastric cancer is inherently complex with significant risk of morbidity and mortality, involving radical surgical reconstruction of the upper gastrointestinal tract, often in combination with chemotherapy or chemoradiotherapy. Although associated with significant survival advantages, along with the effects of the cancer itself, these treatments can have a devastating impact on both nutritional status, and physical functioning, which in turn can have detrimental consequences for health related quality of life (HRQOL). As these deficits prevail into survivorship, there is considerable rationale for the development of strategies which aim to minimise these impairments and therefore improve the quality of survivorship. Accordingly, this thesis aimed to examine i) the feasibility, and ii) the efficacy of multidisciplinary rehabilitation in oesophago-gastric cancer survivorship.

Work for this thesis began with a systematic review of the literature, to investigate the effects of curative treatment for oesophago-gastric cancer on objectively measured physical functioning. Neoadjuvant chemotherapy/chemoradiotherapy and oesophago-gastric cancer surgery was found to impact negatively on physical functioning, particularly cardiorespiratory fitness, the gold standard measure. Furthermore, the systematic review highlighted the dearth of literature examining rehabilitative strategies to improve or maintain physical functioning in the oesophago-gastric cohort.

In order to address this gap in the literature, Study I and Study II of this thesis involved the development of a multidisciplinary rehabilitation programme for survivors of oesophago-gastric cancer which aimed to improve cardiorespiratory fitness and HRQOL. Study I aimed to establish the feasibility of such a programme. A 12 week exercise programme consisting of supervised group and individual home-based sessions was combined with 1:1 dietary counselling to ensure unintentional weight loss did not occur as a result of increased exercise participation. In addition the programme also consisted of 8 multi-disciplinary led education sessions. Feasibility was demonstrated by the recruitment rate (55%), adherence to the supervised (82(13)%) and homebased (78(32)%) exercise sessions, lack of adverse events, and positive improvements achieved in cardiorespiratory fitness (VO_{2max}) ($p=0.004$), physical performance (6MWT)

(p=0.003), and global HRQOL (p=0.006). Importantly, body composition remained stable during the 12 week programme.

Given the positive findings of Study I, the efficacy of the multidisciplinary rehabilitation programme was further investigated by Randomised Controlled Trial in Study II. Forty-three disease free survivors of oesophago-gastric cancer median (range) 30(6-62) months post-surgery, were randomised to either a usual care control group, or to an intervention group that were asked to take part in the 12 week rehabilitation programme. The exercise component was modified slightly from Study I to incorporate a resistance training element, to target the muscle loss associated with oesophago-gastric cancer and its treatments. Correcting for baseline values, the intervention group had significantly higher VO_2max than the control group, both at programme completion ($p<0.001$), and at three month follow-up ($p=0.001$). Similarly to Study I, body composition remained stable throughout the study period. No significant changes occurred in secondary measures following participation in Study II.

Whilst Study I and Study II of this thesis explored the feasibility and efficacy of a structured rehabilitation programme for survivors of oesophago-gastric cancer at least 6 months post curative treatment, the rehabilitative needs of those within the first six months of oesophago-gastric surgery recovery also warranted exploration. Study III utilized qualitative methods to explore the challenges faced in returning to physical activity in the first few months' post-oesophagogastric cancer surgery. Participants in Study III identified a myriad of issues which are barriers to returning to physical activity post-oesophagogastric surgery, and also reported the need for rehabilitative input within the first six months of oesophago-gastric cancer surgery recovery.

The results of this thesis, establish the efficacy of multidisciplinary rehabilitation to improve cardiorespiratory fitness in oesophago-gastric survivorship. Importantly this gain in cardiorespiratory fitness may be achieved without compromise to body composition in this nutritionally challenged cohort. Study III of this thesis also highlighted the need for rehabilitation in the earlier phase post-oesophago-gastric surgery. This thesis highlights that rehabilitation is effective, safe, and achievable in this complex cohort.

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1RM	1 repetition max
5-FU	5 Fluorouracil
6MWT	Six minute walk test
95%CI	95% Confidence Interval
ACCP	American College of Chest Physicians
ACROBAT-NRSI	Cochrane Risk of Bias Assessment Tool for Non-Randomised Studies of Interventions
ACS	American Cancer Society
ACSM	American College of Sports Medicine
AEE	Activity energy expenditure
AF	Atrial fibrillation
AHP	Allied Health Professional
AICR	American Institute of Cancer Research
AJCC	American Joint Committee on Cancer
AMB	Annemarie Bennett
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AT	Anaerobic Threshold
ATS	American Thoracic Society
BIA	Bioelectrical impedance analysis
BLS	Basic Life Support
BMI	Body mass index
BP	Blood pressure
CHF	Congestive heart failure
CM	Conor Murphy
CPET	Cardiopulmonary Exercise Test
CPM	Counts per minute
CRF	Clinical Research Facility
CRP	C-reactive protein
DCF	Docetaxel, cisplatin and 5-fluorouracil

DEE	Diet induced energy expenditure
DLW	Doubly labelled water
DXA	Dual-energy X-Ray Absorptiometry
ECF	Epirubican, cisplatin and 5-fluorouracil
ECG	Electrocardiogram
ECW	Extracellular water
EG	Emer Guinan
EORTC	European Organisation for the Research and Treatment of Cancer
ERAS	Enhanced recovery after surgery
ERS	European Respiratory Society
EUS	Endoscopic ultrasound
FFM	Fat free mass
FM	Fat mass
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GS	Grainne Sheill
HEN	Home enteral nutrition
HER-2	Human epidermal growth factor receptor 2
HGD	High grade dysplasia
HGS	Hand grip strength
HPV	Human papilloma virus
HR	Hazard ratio
HRQOL	Health related quality of life
HRR	Heart rate reserve
ICC	Intraclass correlation coefficient
ICU	Intensive care unit
ICW	Intracellular water
IMT	Inspiratory muscle training
IQR	Inter-quartile range
ISWT	Incremental Shuttle Walk Test
JM	Jonathan Moran

LL	Lower limb
LON	Linda O'Neill
LOS	Length of stay
LPG	Laparoscopic partial gastrectomy
MD	Mean difference
MDT	Multidisciplinary team
MET	Metabolic equivalent
MVPA	Moderate and vigorous physical activity
NAC	Neoadjuvant chemotherapy
NCI	National Cancer Institute
NCRI	National Cancer Registry Ireland
NCRT	Neoadjuvant chemoradiotherapy
NSAIDs	Non-steroidal anti-inflammatory drugs
ODG	Open distal gastrectomy
OR	Odds ratio
OTG	Open total gastrectomy
PET	Positron emission tomography
PFT	Pulmonary function test
POC	Post-operative complication
PPCs	Post-operative pulmonary complications
PROM	Patient reported outcome measure
QUIPs tool	Quality in Prognostic Studies tool
RCT	Randomised controlled trial
RER	Respiratory exchange ratio
RMR	Resting metabolic rate
RP	Radiation Pneumonitis
RPE	Rate of Perceived Exertion
RR	Relative risk
SCC	Squamous cell carcinoma
SD	Standard deviation
SEM	Standard error of measurement

SJH	St James's Hospital
SMD	Standardised mean difference
SMM	Skeletal muscle mass
SWT	Shuttle walk test
TBW	Total body water
TEE	Total energy expenditure
UL	Upper limb
VATs	Video assisted thoracotomy
VEGF	Vascular endothelial growth factor
VO_2max	Maximum oxygen consumption
VO_2peak	Peak oxygen consumption
W	Watts
WCRF	World Cancer Research Fund
WHO	World Health Organisation

List of Appendices

Dissemination of Research

Published Papers:

- **O'NEILL, L**., GUINAN, E., DOYLE, S., ELLIOT, J., O'SULLIVAN, J., REYNOLDS, J. V. & HUSSEY, J. 2017. Rehabilitation strategies following esophageal cancer(the ReStOre trial); a feasibility study. *Diseases of the Esophagus* 30**,** 1-8.
- **O'NEILL, L**., GANNON, J., GUINAN E., REYNOLDS JV. & HUSSEY, J. 2017. Letter to the Editor. Multidisciplinary rehabilitation across the esophageal cancer journey. *Journal of Thoracic Diseases*, doi: 10.21037/jtd.2017.11.72.

Papers under review:

- **O'NEILL, L**., MORAN, J., GUINAN, E., REYNOLDS, JV., HUSSEY, J. Physical Decline and its Implications in the Management of Oesophageal and Gastric Cancer; a Systematic Review (2017)
  Currently under review at the Journal of Cancer Survivorship

Abstracts under review:

- **O'NEILL, L**., GUINAN, EM., DOYLE, S., BENNETT, AE., MURPHY, C., ELLIOTT, JA., O'SULLIVAN, J., HUSSEY, J & REYNOLDS, JV. The Restore Randomized Controlled Trial - Impact of a multidisciplinary rehabilitative programme on cardiorespiratory fitness in esophagogastric cancer survivorship
  Abstract submitted for presentation to the European Surgical Association Annual Meeting 2018

Conference Presentations:

Oral Presentations:

Clinical Research Facility, St James's Hospital Annual Scientific Meeting, December 2017

- **O'NEILL, L**., GUINAN, EM., DOYLE, S., BENNETT, AE., MURPHY, C., ELLIOTT, JA., O'SULLIVAN, J., REYNOLDS, JV, & HUSSEY, J. Impact of a multidisciplinary rehabilitative programme on cardiorespiratory fitness in oesophago-gastric cancer survivorship – the RESTORE randomized control trial (RCT)

Irish Society of Chartered Physiotherapists Conference 2017, Galway

- **O'NEILL, L**., MORAN, J., GUINAN, E., REYNOLDS, JV., HUSSEY, J. Physical Decline and its Implications in the Management of Oesophageal and Gastric Cancer; a Systematic Review

Poster Presentations:

Irish Society of Chartered Physiotherapists Conference 2017, Galway

- **O'NEILL, L**., BENNETT, AB., GUINAN, EM., REYNOLDS, JV, & HUSSEY, J
  Patient's perspectives of physical recovery following oesophago-gastric cancer surgery

World Cancer Research Fund/ World Obesity Hot Topics Conference, London, 2016 and Irish Society of Chartered Physiotherapists conference, Wexford, 2016

- **O'NEILL, L**., DOYLE, S., GUINAN, EM., O'SULLIVAN, J., REYNOLDS, JV, & HUSSEY, J.
  ReStOre- Rehabilitation following oesophageal cancer: Achieving exercise guidelines in a nutritionally vulnerable group without undesirable weight loss – a feasibility study.

Irish Association of Cancer Research Conference, Cork, 2016

- **O'NEILL, L**., DOYLE, S., GUINAN, EM., O'SULLIVAN, J., REYNOLDS, JV, & HUSSEY, J.
  Rehabilitation strategies following oesophageal cancer – the ReStOre trial – a feasibility study.

Public and Patient Dissemination:

Cancer Week Ireland, EU Researchers' Night, Public Symposium 'Cancer Research Frontiers', Trinity College Dublin, 29 September 2017

- Presentation: 'Exercise Rehabilitation in Cancer: Supporting Patients throughout their Cancer Journey'

St James's Hospital Patient and Family Information Evening, Oesophageal Cancer Research, Clinical Research Facility, May 2017

- Presentation : 'Rehabilitation Strategies following Oesophago-gastric Cancer'

Chapter 1 Introduction

1.1 Oesophageal Cancer

The oesophagus is a muscular tube connecting the pharynx with the stomach, which is approximately 18 to 26 centimetres in length. The oesophagus is positioned within the thoracic cavity behind the trachea and the heart, and in front of the spinal column. The function of the oesophagus is to facilitate the downward passage of food to the stomach for digestion and absorption, and it also allows for the passage of gastrointestinal contents superiorly during vomiting and reflux. The upper oesophageal sphincter, located at the top of the oesophagus, facilitates the passage of food into the oesophagus by relaxing when it detects the presence of food. The junction of the oesophagus with the stomach is termed the oesophageal-gastric junction, and there contains another sphincter, the lower oesophageal sphincter which prevents the backflow of stomach contents into the oesophagus. Anatomically, the oesophagus consists of three distinct sections; the cervical, thoracic, and abdominal oesophagus (Figure 1.1).

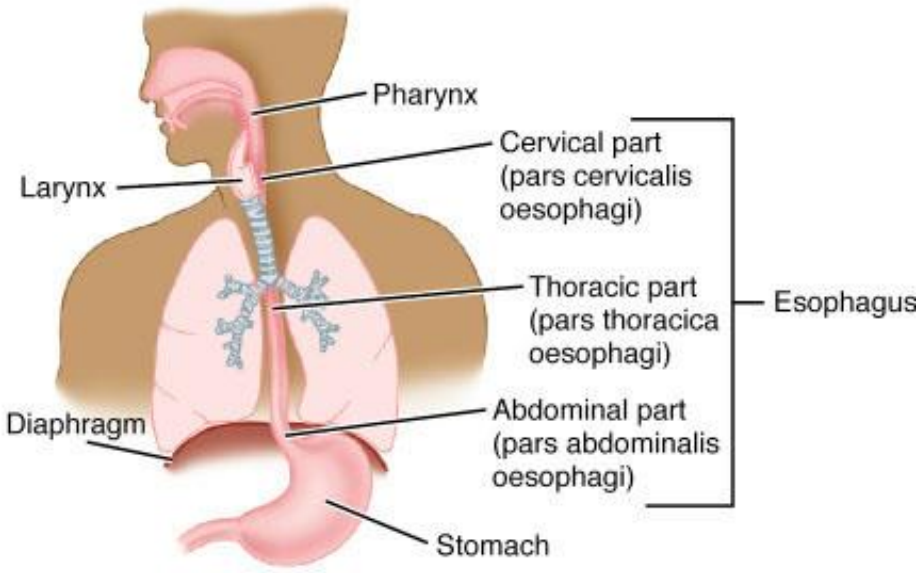

Figure 1.1 The oesophagus - cervical, thoracic and abdominal components

The cervical oesophagus extends from the pharyngoesophageal junction to the suprasternal notch, the thoracic oesophagus extends from the suprasternal notch to the diaphragmatic hiatus, and the abdominal oesophagus extends from the diaphragmatic hiatus to the orifice of the cardia of the

stomach. The oesophageal wall consists of four layers; the innermost mucosa, the submucosa, the muscularis propria, and the adventitia (Figure 1.2)(Kuo and Urma, 2006).

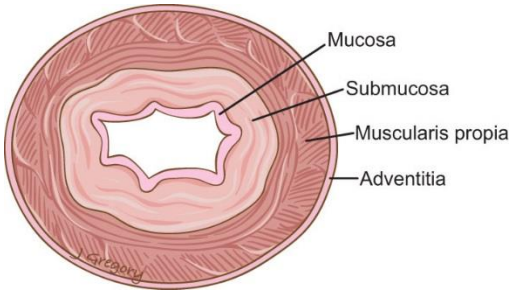

Figure 1.2 Layers of oesophageal wall

Cancer is a group of diseases which are characterised by abnormal, uncontrolled cellular growth. In cancer, normal cell regulation is disrupted due to damaged DNA, which may result in old damaged cells surviving when they should die, or, new cells forming when they are not required (ACS, 2014b, Urruticoechea et al., 2010). These extra cells may divide further and form growths known as tumours. Cancerous tumours are malignant, and may grow and spread into nearby tissues. As tumours grow, cancer cells may break off, and travel through the blood or lymph system and form new tumours in distant places to the original tumour. When this occurs the cancer is termed metastatic. There are many different types of cancers. Approximately 85% of cancers are carcinomas which involve the epithelial cells of internal organs. Other forms of cancer include sarcomas, which involve the cells of bones and soft tissues, and haematological cancers such as leukaemia (involving the blood forming cells in the bone marrow) and lymphoma (involving lymphocytes) (NCI, 2015, WCRF/AICR, 2007).

There are two main histological types of oesophageal cancer; adenocarcinoma and squamous cell carcinoma (SCC). Adenocarcinomas are typically found in the distal part of the oesophagus, and arise from the glandular cells that are responsible for mucous production in the lining of the oesophagus. SCCs occur in the upper and middle parts of the oesophagus and form from the squamous cells of the inner lining of the oesophagus (ACS, 2014b). Cancers of the oesophagus may also be termed undifferentiated. Undifferentiated means it is not possible to distinguish what type of cell the cancer cells originated from. Rarely other forms of cancer are identified in the oesophagus such as small cell carcinomas, lymphomas, carcinoids, and melanomas (Napier et al., 2014).

1.1.1 Incidence and aetiology

Globally oesophageal cancer is the 8th most common cancer, and it ranks 6th amongst all cancers in terms of mortality (Zhang, 2013). Along with the United Kingdom and the Netherlands, Ireland has one of the highest incidences of oesophageal cancer in Europe. From 2011 to 2013 an average of 387 new cases of oesophageal cancer were diagnosed in Ireland per annum (137 female and 251 male) (NCRI, 2017a). Worldwide oesophageal cancer has a much higher prevalence in males (2.4:1) compared to females (GLOBOCON, 2012a). Risk of oesophageal cancer increases steadily with age, with fewer than 15% of all incidences occurring in those under the age of 35 (ACS, 2014b). In recent decades the epidemiology of oesophageal cancer has changed greatly. Previously, SCC was the most frequently detected histological type of oesophageal cancer across the world. Today SCC is the most common histological type of oesophageal cancer in the developing world. However, in the western world rates of SCC have declined greatly, and incidence of adenocarcinoma is rapidly increasing largely due to dietary factors and the ever increasing obesity epidemic (Napier et al., 2014, Zhang, 2013). For example, in Ireland from 1994 to 2009, the rate of SCC dropped by 0.9% in females and 1.4% in males per year, whereas each year the rate of adenocarcinoma increased by 2.2% for females and 3.0% for men (NCRI, 2011b).

Many convincing risk factors for oesophageal cancer have been identified in the literature including; gastroesophageal reflux disease (GERD), Barrett's oesophagus, tobacco smoking, alcohol consumption, obesity, and lower socioeconomic status (NCRI, 2013). GERD is commonly termed reflux and describes the process whereby stomach acids and enzymes escape from the stomach into the distal part of the oesophagus (Zhang, 2013). There is strong evidence of the association between GERD and the adenocarcinoma subtype of oesophageal cancer, however it is important to note that the risk of an individual with GERD developing oesophageal cancer is low. Shaheen and Ransohoff (2002) reported that individuals with long term GERD have a less than 1/1000 risk of developing adenocarcinoma of the oesophagus. Patients with GERD are highly susceptible to the development of Barrett's Oesophagus (Lagergren, 2005), a condition which involves a metaplastic change in the lining of the oesophagus, whereby squamous cells are converted to glandular cells (Shaheen et al., 2000). With Barrett's Oesophagus cells become more abnormal over time, and may develop in to pre-cancerous cells (dysplasia). Dysplasia may be described as low-grade or high grade. In low grade dysplasia cells are more normal, whereas in high grade dysplasia cells are more abnormal, and there is a greater cancer risk. Similarly to GERD, there is a strong association between Barrett's Oesophagus and oesophageal adenocarcinoma. In large population studies the relative risk of a patient with a diagnosis of Barrett's Oesophagus developing oesophageal adenocarcinoma has been found to be 30-60 fold more likely than the general population. However, it is important

to note the actual risk of a person with Barrett's Oesophageal developing oesophageal cancer is low (Lagergren, 2005). A meta-analysis of 57 studies comprising of 11,434 patients and 58,547 patient-years of follow-up, reported the pooled annual incidence of oesophageal adenocarcinoma amongst patients with Barrett's oesophagus was 0.33% (95% CI 0.28% to 0.38%) (Desai et al., 2012).

Tobacco smoking is strongly associated with both SCC and adenocarcinoma of the oesophagus. The risk of oesophageal cancer for smokers is twice as high as that for non-smokers (NCRI, 2013). There is a direct correlation between both the number of cigarettes smoked per day, and the length of time the smoker spends smoking, with incidence of oesophageal cancer (Zhang, 2013). The consumption of smokeless tobacco products such as snuff and chewing tobacco, is also strongly linked with oesophageal cancer (NCRI, 2013). Alcohol consumption is strongly associated with development of SCC cancer of the oesophagus (Blot, 1999). The consumption of both tobacco and alcohol heavily increases the risk of oesophageal cancer compared to either alone (Zhang, 2013). As aforementioned increased incidence of adenocarcinoma cancer of the oesophagus in the western world is heavily linked to the growing obesity epidemic. The relative risk of a person with a BMI >30kg/m^2 of developing adenocarcinoma of the oesophagus is 16 compared to a person with a lean BMI (<22 kg/m^2) (Lagergren, 2005). Contrastingly, obesity is not associated with development of SCC (Zhang, 2013). Lower socioeconomic status is also highly associated with the development of oesophageal cancer (Wu et al., 2016).

Other suggested risk factors for development of oesophageal cancer include; consuming high temperature drinks, eating processed or red meats, achalasia, infection with human papilloma viruses (HPV)(SCC), history of other cancers such as lung, mouth, or throat cancer, Plummer-Vinson Syndrome (SCC), previous injury to the oesophagus, and occupational exposure to hexavalent chromium (ACS, 2014b, NCRI, 2013).

A number of factors have also been identified as having a protective effect on the development of oesophageal cancer. For example, diets rich in fruit and vegetables have been linked with a lower risk of oesophageal cancer. In particular foods containing beta-carotene, and Vitamin C have been found to reduce oesophageal cancer risk (NCRI, 2013). Non-steroidal anti-inflammatory drugs (NSAIDS), and the presence of the helicobacter pylori infection, also reduces risk of AD oesophageal cancer (Lagergren, 2005). Furthermore, there is growing evidence that risk of oesophageal cancer may be reduced by engaging in regular moderate-vigorous intensity physical activity. A meta-

analysis by Behrens et al. (2014), reported the risk of oesophago-gastric cancer was most reduced among individuals engaging in moderate to vigorous physical activity five times per week (RR = 0.67, 95% CI, 0.58-0.79).

1.1.2 Signs and symptoms

Typically signs and symptoms of oesophageal cancer do not manifest until the disease is at an advanced stage. Signs of advancing disease include difficulty swallowing (dysphagia) and unexplained weight loss. Other reported symptoms include; GERD, odynophagia (pain when swallowing), persistent vomiting or regurgitation, fatigue, pain (retrosternal or between shoulder blades), gastrointestinal bleeding, hoarseness, dyspnoea (shortness of breath), persistent coughing, and abdominal pain (ACS, 2014b, Zhang, 2013).

1.1.3 Diagnosis and staging

Diagnosis of oesophageal cancer is usually by an upper gastrointestinal (GI) contrast study and endoscopy with biopsy. When cancer is present the upper GI contrast study may show a stricture, the endoscopy identifies the tumour size and location, and the biopsy allows for a histological diagnosis of the cancer. Other tests including computerised tomography (CT) scans, positron-emission tomography (PET) scans, and endoscopic ultrasound (EUS) are used in the staging of the disease (Berry, 2014).

Oesophageal cancer staging is defined by the American Joint Committee on Cancer (AJCC) which established the TNM staging system (Rice et al., 2010). The T refers to the primary tumour, N refers to lymph node involvement, and M describes the extent of any metastatic disease. The 7th Edition of the AJCC Cancer Staging Manual: Oesophageal also contains a separate factor, grade, which refers to how normal the cancer cells look like under the microscope. The grade of a cancer is often simplified to low (G1 or G2) or high grade (G3 or G4). Low grade cancers tend to spread slower than high grade cancers (ACS, 2014b). There are slight differences in the staging of adenocarcinoma and SCC of the oesophagus, with the SCC classification also considering the location of the tumour. The stages of adenocarcinoma and SCC of the oesophagus are presented in Table 1.1 and 1.2 respectively. Details of the relationship between cancer stage and the TNM and grade classification are presented in Table 1.3 and 1.4.

Table 1-1 Stages of adenocarcinoma of the oesophagus (Source: National Cancer Institute)

Stage		Description
Stage 0		Abnormal cells in the mucosa or submucosa (high-grade dysplasia).
Stage I	**Stage IA**	Cancer has formed in the mucosa or submucosa. Cancer cells are grade 1 or 2.
	Stage IB	Cancer has formed in the mucosa or submucosa. Cancer cells are grade 3, or, has formed in the mucosa or submucosa and spread into the muscle layer of the oesophagus. Cancer cells are grade 1 or 2.
Stage II	**Stage IIA**	Cancer has spread into the muscle layer of the oesophagus wall. Cancer cells are grade 3.
	Stage IIB	Cancer has spread into the connective tissue layer of oesophagus wall, or, is in the mucosa or submucosa and may have spread into the muscle layer of oesophagus wall. Cancer is found in one or two lymph nodes near the tumour.
Stage III	**Stage IIIA**	Cancer is in the mucosa or submucosa layer and may spread into the muscle layer of the oesophagus wall. Cancer is found in 3 to 6 lymph nodes near the tumour, or, has spread into the connective tissue layer of the oesophagus wall. Cancer is found in 1 or 2 lymph nodes near the tumour, or, has spread into the diaphragm, pleura, or membrane around the heart. The cancer can be removed by surgery.
	Stage IIIB	Cancer has spread into the connective tissue layer of the oesophagus wall. Cancer is found in 3 to 6 lymph nodes near the tumour.
	Stage IIIC	Cancer has spread into the diaphragm, pleura, membrane around the heart. The cancer can be removed by surgery. Cancer is found in 1 to 6 lymph nodes near the tumour, or, in nearby organs such as aorta, trachea or spine, and the cancer cannot be removed by surgery, or, 7 or more lymph nodes near the tumour.
Stage IV		Cancer has spread to distant tissues or organs

Table 1-2 Stages of squamous cell carcinoma of the oesophagus (Source: National Cancer Institute)

Stage		Description
Stage 0		Abnormal cells in the mucosa or submucosa (high-grade dysplasia).
Stage I	**Stage IA**	Cancer has formed in the mucosa or submucosa. Cancer cells are grade 1.
	Stage IB	Cancer has formed in the mucosa or submucosa. Cancer cells are grade 2 and 3 or has formed in the mucosa or submucosa and spread into the muscle, or, connective tissue layer of the oesophagus.
Stage II	**Stage IIA**	Cancer has spread into the muscle layer or the connective tissue layer of the oesophagus wall. Cancer cells are grade 1. The tumour is in either the upper or middle oesophagus, or, into the muscle or connective tissue layer of the oesophagus. Cancer cells are grade 2 and 3. Tumour is in the lower oesophagus or location is unknown.
	Stage IIB	Cancer has spread into the muscle layer or connective tissue layer of oesophagus wall. Cancer cells are graded 2 or 3. Tumour is in the upper or middle oesophagus, or, is in the mucosa or submucosa and may have spread into the oesophagus wall. Cancer is found in one or two lymph nodes near the tumour.
Stage III	**Stage IIIA**	Cancer is in the mucosa or submucosa layer and may spread into the muscle layer of the oesophagus wall. Cancer is found in 3 to 6 lymph nodes near the tumour, or, has spread into the connective tissue layer of the oesophagus wall. Cancer is found in 1 or 2 lymph nodes near the tumour, or, has spread into the diaphragm, pleura, or membrane around the heart. The cancer can be removed by surgery.
	Stage IIIB	Cancer has spread into the connective tissue layer of the oesophagus wall. Cancer is found in 3 to 6 lymph nodes near the tumour.
	Stage IIIC	Cancer has spread into the diaphragm, pleura, membrane around the heart. The cancer can be removed by surgery. Cancer is found in 1 to 6 lymph nodes near the tumour, or, in nearby organs such as aorta, trachea or spine, and the cancer cannot be removed by surgery, or, 7 or more lymph nodes near the tumour.
Stage IV		Cancer has spread to distant tissues or organs

Table 1-3 Relationship between Stage and TNM, and grade classification for adenocarcinoma of the oesophagus (Source: 7th Edition of the AJCC Cancer Staging Manual *(Rice et al., 2010)*)

Stage	T	N	M	G
0	is (HGD)	0	0	1
IA	1	0	0	1-2
IB	1	0	0	3
	2	0	0	1-2
IIA	2	0	0	3
IIB	3	0	0	Any
	1-2	1	0	Any
IIIA	1-2	2	0	Any
	3	1	0	Any
	4a	0	0	Any
IIIB	3	2	0	Any
IIIC	4a	1-2	0	Any
	4b	Any	0	Any
	Any	N3	0	Any
IV	Any	Any	1	Any

Abbreviations: Tis (HGD) = carcinoma in situ (high grade dysplasia)

Table 1-4 Relationship between stage and TNM, grade, and location for squamous cell carcinoma of the oesophagus (Source: 7th Edition of the AJCC Cancer Staging Manual *(Rice et al., (2010)*)

Stage	T	N	M	G	Location
0	is (HGD)	0	0	1	Any
IA	1	0	0	1	Any
IB	1	0	0	2-3	Any
	2-3	0	0	1	Lower
IIA	2-3	0	0	1	Upper, middle
	2-3	0	0	2-3	Lower
IIB	2-3	0	0	2-3	Upper middle
	1-2	1	0	Any	Any
IIIA	1-2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
IIIB	3	2	0	Any	Any
IIIC	4a	1-2	0	Any	Any
	4b	Any	0	Any	Any
	Any	N3	0	Any	Any
IV	Any	Any	1	Any	Any

Abbreviations: Tis (HGD) = carcinoma in situ (high grade dysplasia)

The most recent statistics from the National Cancer Registry Ireland (NCRI) report that 6.6% of oesophageal cancers in Ireland are diagnosed at Stage I, 15.5% at Stage II, 19% at Stage III, and 25.7% at Stage IV. Often staging for oesophageal cancer is incomplete, and the NCRI reported that staging was undetermined for 33.2% of cases of oesophageal cancer recorded in Ireland from 2010 to 2013 (NCRI, 2017c).

1.1.4 Treatment

The primary treatment for oesophageal cancer is surgical resection (oesophagectomy). Typically a multimodality approach is favoured over surgery alone as neoadjuvant chemotherapy (NAC), neoadjuvant chemoradiotherapy (NCRT), and perioperative chemotherapy combined with surgery, have all been found to have significant survival advantages when compared to surgery alone for locally advanced disease (Burt et al., 2017).

For early stage oesophageal cancers, superficial treatments such as endoscopic mucosal resection, radiofrequency ablation, cryotherapy, and photodynamic therapy are considered a good option for tumours that only involve the mucosa (Stage IA). For tumours that extend into the submucosa oesophagectomy is required (Berry, 2014). Oesophagectomy is a complex procedure associated with considerable risk of morbidity and mortality. In order to improve outcomes, oesophagectomies are typically performed in high volume specialised centres. Post-operative mortality in high volume centres is reported as less than 5% (Wolf et al., 2011). Research has shown there is an inverse relationship between mortality and hospital volume. Not only do high volume centres offer surgical expertise, but the high standard of post-operative critical and clinical care using standardised care pathways allow for early detection of post-operative complications, and therefore facilitating prompt treatment of complications, and therefore reduced mortality risk (Paul and Altorki, 2014).

There are two main types of oesophagectomy; transthoracic or transhiatal. Transthoracic oesophagectomy can be described as two-stage (Ivor Lewis procedure) or three-stage (McKeown procedure) (Klevebro et al., 2017). Two-stage oesophagectomy involves a thoracotomy and laparotomy, and the oesophagogastric anastomosis is in the upper chest, whereas three-stage oesophagectomy involves a thoracotomy, laparotomy, and neck incision, and the oesophagogastric anastomosis is in the neck (Enzinger and Mayer, 2003). Transhiatal oesophagectomy allows for removal of the tumour without a thoracotomy, therefore reducing the risk of post-operative pulmonary complications (Klevebro et al., 2017). However, transthoracic oesophagectomy facilitates greater visualisation of the tumour, and consequently a more thorough dissection. No significant differences between surgical approaches (transthoracic or transhiatal) have been observed in terms of overall survival or operative mortality (Enzinger and Mayer, 2003), however, there is a trend that 5 year survival is better following transthoracic oesophagectomy (Wolf et al., 2011). In many centres open oesophagectomies have been replaced with minimally invasive procedures in an attempt to reduce post-operative morbidity, however research is yet to

demonstrate significant advantages in favour of minimally invasive techniques compared to open oesophagectomy (Tapias et al., 2016).

Multimodality treatment (NAC/ NCRT/ perioperative chemotherapy, combined with surgery) has become the standard of care for locally advanced oesophageal cancer. The aims of multimodality treatment are to reduce tumour activity, enhance resectability, and improve disease free and overall survival (Kidane et al., 2015). NAC typically involves the administration of a combination of 2 or 3 drugs over 2 to 6 cycles in the months preceding oesophagectomy. Allum et al. (2009) reported on the long-term results of the Medical Research Council (MRC) OE02 trial, which compared the effects of surgery combined with NAC (cisplatin and 5-Fluorouracil (5-FU)) (n=400) versus surgery alone (n=402), in a cohort with a mix of SCC (30.8%), adenocarcinoma (66.5%), and undifferentiated oesophageal carcinoma (2.6%). A significant 5-year survival advantage of 23% vs 17% was experienced by the group that received NAC (Hazard Ratio (HR) =0.84, 95% Confidence Interval (CI), 0.72-0.98, p=0.03). Furthermore, a meta-analysis of 10 RCTs, involving 2122 participants with either SCC or adenocarcinoma of the oesophagus by Kidane et al. (2015) reported that compared to surgery alone, NAC combined with surgery results in significantly improved survival (HR=0.88, 95%CI, 0.80-0.96), and increased rate of complete resection (Relative Risk (RR)=1.11, 95%CI, 1.03-1.19).

NCRT involves the administration of both chemotherapy and radiotherapy in advance of surgery. The CROSS (Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study) is considered the benchmark trial for the NCRT treatment of oesophageal cancer (Donohoe and Reynolds, 2017). Shapiro et al. (2015) randomised 366 patients with clinically resectable, locally advanced cancer (SCC or adenocarcinoma) of the oesophagus or oesophagogastric junction (clinical stage T1N1M0 or T2-3N0-1M0) to receive either neoadjuvant chemoradiotherapy (paclitaxel, carboplatin, and 41.4 Gy/23 fraction) and surgery, or surgery alone. There was a 92% complete resection rate in the group that received NCRT. Median survival was 49 months for the NCRT group vs 24 months for the surgery alone group (95%CI, 0.49-0.87, p=0.87). Furthermore, five year survival was reported to be 47% in the NCRT group which greatly exceeds the survival rates reported in any previous studies regarding multimodality treatment for oesophageal cancer (Shapiro et al., 2015).

Perioperative chemotherapy is considered the treatment of choice for lower oesophageal and junctional tumours. Both the French FNCLCC and FFCD trial (Ychou et al., 2011) and the MAGIC

(Medical Research Council Adjuvant Gastric Infusional Chemotherapy) (Cunningham et al., 2006) trial reported significant survival advantages for perioperative chemotherapy for lower and junctional adenocarcinoma oesophageal tumours combined with surgery versus surgery alone (HR=0.69 95%CI, 0.5-0.95, and HR=0.75, 95%CI, 0.6-0.93).

Although it is clear that multimodality treatment for oesophageal cancer offers significant survival benefits when compared to surgery alone, the optimum multi-modality treatment regime has yet to be defined, and neither NAC nor NCRT has been found to have a significant survival advantage over the other (Burt et al., 2017, Klevebro et al., 2015). Numerous research projects are on-going to identify the optimum multimodality regime. For example, the NeoAegis trial is a multicentre, international trial which is ongoing at this research centre at St James's Hospital, comparing the CROSS regime (Shapiro et al., 2015) to a modified MAGIC regime, (Cunningham et al., 2006) including capecitabine and oxaliplatin as alternatives to 5-FU and cisplatin, in patients with locally advanced adenocarcinoma of the oesophagus or oesophageal-gastric junction (Reynolds et al., 2017).

The area of targeted and immune based therapies is a promising area of oesophageal cancer research. Research is ongoing at present examining the effects of the addition of targeted therapies, and immune therapies to multimodality treatment. For example, with regards to targeted therapies, there is a trial ongoing by the National Cancer Institute, investigating the addition of trastuzumab to neoadjuvant chemoradiotherapy (carboplatin/paclitexal and concurrent radiotherapy) in 591 HER-2 overexpressing patients with Stage Ib to IIIC AD oesophageal cancer, and in terms of immune-therapy, the potential of Nivolumab in preventing inactivation of anti-tumour cells is currently being investigated (Donohoe and Reynolds, 2017).

As symptoms of oesophageal cancer tend to only become apparent when the disease has advanced, 50% of patients present with evidence of metastatic disease at diagnosis. Palliative treatment may include chemotherapy and supportive care (Enzinger and Mayer, 2003). Radiation and endoscopic techniques such as stenting and dilation are used to reduce dysphagia and oesophageal bleeding, and in very rare cases, oesophagectomy may be carried out as a palliative procedure (Berry, 2014).

1.1.5 Prognosis and survival

Despite advances in surveillance techniques, diagnostic procedures, surgical approaches, and multimodality therapies, 5 year survival for oesophageal cancer remains considerably poor (Lagergren and Lagergren, 2013). For patients with localised disease global survival rates range from 30-47% (Donohoe and Reynolds, 2017). Oesophageal cancer is associated with a poor prognosis as many patients are not diagnosed until the disease is too advanced for curative treatment. Oesophageal tumours can be quite advanced before they cause symptoms, as the oesophagus is a very mechanically compliant structure which allows for symptomless tumour expansion, and rapid tumour invasion is also facilitated by the lack of serosa layer in the wall of the oesophagus, and its rich lymphatic plexus (Cowie et al., 2014). In recent decades, survival rates have seen small improvements which can be attributed to advances in endoscopic detection and multimodality treatment (Holmes and Vaughan, 2007). The improvements in survival rates for oesophageal cancer in Ireland from 1994-2013 are presented in Table 1.5.

Table 1-5 Five year net survival for oesophageal cancer in Ireland (1994-2014 (Source: National Cancer Registry Ireland (NCRI, 2017c))

Diagnosed	Net survival (age standardised)	95% Confidence interval
1994-1998[c]	11.4%	9.63-13.1%
1999-2003[c]	12.7%	11.0-14.5%
2004-2008[c]	14.9%	13.1-16.6%
2009-2013[c]	22.6%	20.0-25.1%
2010-2014[h]	21.5%	19.3-23.8%

[c]= cohort, by year of diagnosis, [h]=hybrid, by year of follow-up (all patients alive at some point 2010 -2013, or diagnosed in 2009 and follow-up to 31/12/2014)

The most important prognostic factor for survival is tumour stage (Lagergren and Lagergren, 2013). In Ireland the five year survival rate for Stage I cancer is 67.1% compared to just 3.8% for Stage IV cancer. The five year oesophageal cancer survival rate per stage from 2008 to 2012 in Ireland are presented in Figure 1.3. Other prognostic factors include the tumour location, presence of other comorbidities, dysphagia at presentation, histological type of cancer, and acute surgical complications (Lagergren and Lagergren, 2013). Weight loss is also a well-documented prognostic risk factor for oesophageal cancer, patients with loss of muscle mass and strength (sarcopenia) have reduced overall survival when compared to non-sarcopenic patients (HR=1.87, 95%CI, 1.15-3,03,

p=0.011) (Tamandl et al., 2016). Pre-operative performance status (Polee et al., 2003), and physical function are also prognostic of outcome (Jack et al., 2014, Murray et al., 2007, Liedman et al., 2001).

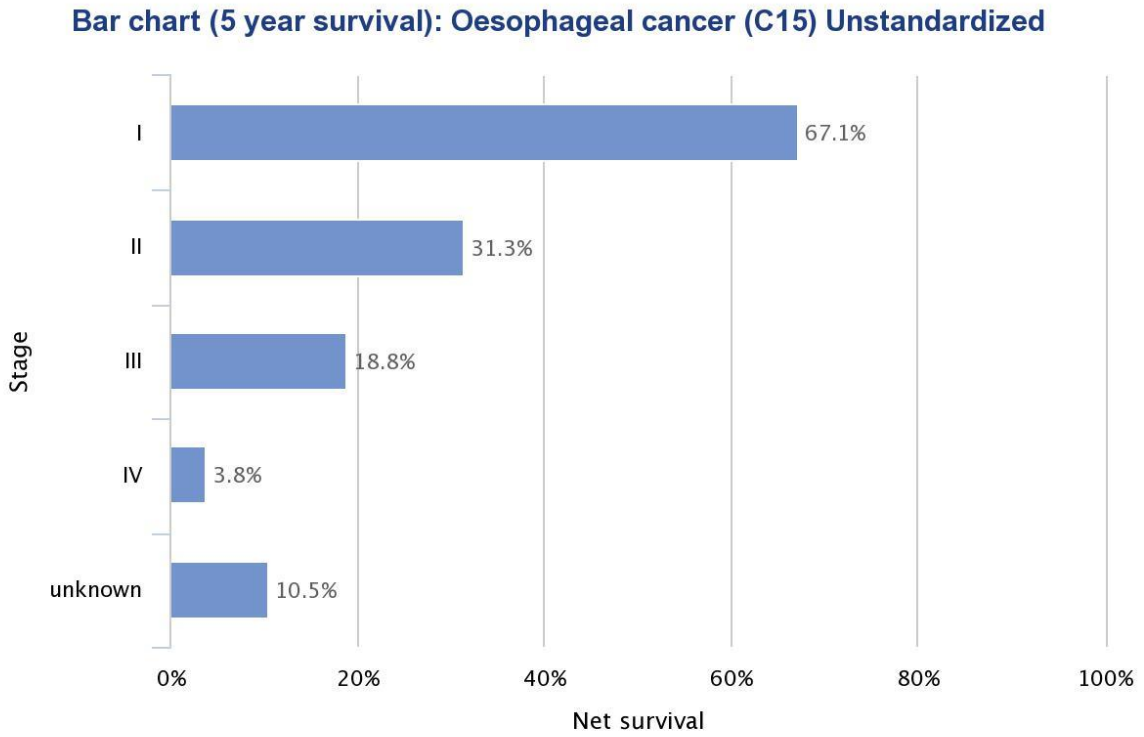

Figure 1.3 Five year stage specific survival rates for oesophageal cancer in Ireland between 2008 and 2012 (Source: National Cancer Registry Ireland)

1.1.6 Treatment side-effects

Curative treatment for oesophageal cancer is associated with significant mortality and morbidity. Firstly, as previously discussed, oesophagectomy is the only curative treatment for oesophageal cancer. However, it is a high risk procedure. Even in high volume centres, oesophagectomy is associated with significant risk of morbidity, with morbidity rates varying from 40% to 60%. The most significant complications following oesophagectomy include; atrial fibrillation, post-operative pulmonary complications, and anastomotic leakage. Other reported complications include anastomotic stricture, recurrent laryngeal nerve injury, diaphragmatic hernia, thromboembolic complications, haemorrhage, and delayed gastric emptying (Paul and Altorki, 2014). New onset atrial fibrillation presents in approximately 13% to 46% of patients following oesophagectomy. Age, diabetes, neoadjuvant treatment, and previous cardiac history have all been identified as risk factors for development of AF (Mc Cormack et al., 2014). Although most cases of post-oesophagectomy AF resolve without impact on outcomes, the development of AF has been

associated with concurrent development of other serious post-operative complications including pneumonia, respiratory sepsis, systemic inflammation (Mc Cormack et al., 2014), and anastomotic leaks (Stawicki et al., 2011).

Post-operative pulmonary complications (PPCs) are common following oesophagectomy, with an incidence rate in high volume centres of 20-50%. Examples, include pneumonia, pleural effusions, atelectasis, acute respiratory distress syndrome (ARDS), aspiration and respiratory insufficiency requiring prolonged intubation (Mc Cormack et al., 2014, Paul and Altorki, 2014). Pneumonia in particular has a significant impact on survival (HR=1.456, 95% CI 1.020-2.079, p=0.039) (Booka et al., 2015). Consequently the focus of much research is on strategies to reduce the risk of pneumonia following oesophagectomy. Intervention strategies to reduce post-oesophagectomy pneumonia include; i) interventions to optimise pre-operative performance status such as pre-operative nutritional support, and inspiratory muscle training (Valkenet et al., 2014), ii) perioperative corticosteroids and neutrophil elastase inhibitors to reduce the inflammatory response to surgery, and iii) adequate post-operative analgesia to reduce pain and promote improved post-operative pulmonary function, coughing ability, and early return to mobilisation (Weijs et al., 2013).

The incidence of anastomotic leakage has been reported to be as high as 50%, and is associated with significant morbidity, and a mortality rate of 30% to 60% (Schaheen et al., 2014). Cervical anastomoses are associated with a higher incidence of leak, but have a lower morbidity and mortality risk, whereas thoracic anastomotic leaks are less frequent but can result in significant morbidity and mortality (Paul and Altorki, 2014). There is conflicting evidence regarding the long term effects of post-operative complications following oesophagectomy. Some studies have found strong associations between development of post-operative complications and reduced overall and disease free survival (Luc et al., 2015, Rizk et al., 2004), whereas other studies have reported no relationship (Xia et al., 2013). Incidence of post-operative complications, particularly anastomotic leakage, cardiopulmonary complications, and operative technical complications (Scarpa et al., 2011), are associated with long term deficits in health related quality of life that may persist up to 5 years post-operatively (Derogar et al., 2012). Therefore, it is imperative that continued efforts are made to reduce morbidity following oesophagectomy.

Although associated with significant survival benefits, multimodality treatment for oesophageal cancer involving the use of chemotherapy and/or radiotherapy in conjunction with surgery is

associated with significant side effects and toxicities that may increase the risk of surgical morbidity (Sjoquist et al., 2011). Chemotherapy is a type of cancer treatment that uses cytotoxic medication to kill cancer cells. Commonly used chemotherapeutic drug regimes in oesophageal cancer are carboplatin and paclitaxel, cisplatin and 5-FU, ECF: epirubican, cisplatin, and 5-FU, cisplatin with capecitabine, and DCF: docetaxel, cisplatin, and 5-FU. Chemotherapy for oesophageal cancer may also damage healthy tissue cells resulting in side effects such as; nausea and vomiting, loss of appetite, hair loss, diarrhoea, constipation, anaemia, immunosuppression, and fatigue (ACS, 2014b), and is associated with cardiac, renal, neurological and hepatic toxicities (Livshits et al., 2014). Anthracycline drugs such as epirubican are most associated with cardiotoxicity, which can result in cardiomyopathy, dysrhythmias, ischaemic ECG changes, congestive heart failure (CHF), left ventricular dysfunction, and pericarditis (Plenderleith, 1990). Trastuzumab, the HER-2 targeted therapy is also linked to development of CHF (Livshits et al., 2014). Cisplatin is the chemotherapeutic agent most commonly associated with renal failure, and is linked to hepatic toxicity also (Plenderleith, 1990). Peripheral neuropathies, which may lead to irreversible sensori-motor loss are most frequently observed following administration of cisplatin or paclitaxel (Livshits et al., 2014). Longer term side-effects of chemotherapy include infertility, and risk of secondary malignancies such as leukaemia (Plenderleith, 1990).

External beam radiation therapy is often used in combination with chemotherapy to shrink the tumour in advance of surgery. Side effects of radiation include; nausea and vomiting, diarrhoea, pain with swallowing, painful sores in the mouth and throat, skin changes such as blistering and peeling, and fatigue. Radiation therapy for oesophageal cancer can cause damage to body tissues, and may cause stricture in the oesophagus and radiation pneumonitis (ACS, 2014b). Radiation pneumonitis is associated with significant morbidity and mortality, and is more prevalent in patients with upper or middle thoracic tumours, and incidence is directly proportional to radiation dose (Shaikh et al., 2016).

The most pronounced side-effect of oesophageal cancer and its treatments is weight loss (Ouattara et al., 2012). As mentioned in section 1.1.2, unexplained weight loss is often one of the presenting symptoms of oesophageal cancer, with 79% of patients reporting unintentional weight loss pre-diagnosis (Martin and Lagergren, 2009). Across the oesophageal cancer journey, from before diagnosis and into survivorship, weight loss is a significant issue and is strongly associated with treatment outcomes. Weight loss in oesophageal cancer can involve both the loss of fat mass and fat free mass (muscle) (Yip et al., 2014). In oesophageal cancer, a reduction in fat free mass is likely

due to a combination of sarcopenia and cancer cachexia. Sarcopenia is described as the loss of skeletal muscle mass and strength (Stene et al., 2013, Muscaritoli et al., 2010), and cancer cachexia has been defined as 'a multifactorial syndrome characterized by severe body weight, fat and muscle loss and increased protein catabolism due to underlying disease' (Muscaritoli et al., 2010).

It has been reported that 26-75% of patients with oesophageal cancer present with sarcopenia at diagnosis (Elliott et al., 2017). Two recent studies have shown that the prevalence of sarcopenia is raised following neoadjuvant chemotherapy. Both Yip et al. (2014) and Elliott et al. (2017) noted a marked increase in the percentage of patients with sarcopenia following completion of neoadjuvant chemotherapy, with reported increases from 26% to 43%, and 16% to 31% respectively. Weight loss and sarcopenia during neoadjuvant treatment is likely due to a combination of the effects of the disease and the previously mentioned side-effects of treatment. Factors accelerating sarcopenia during neoadjuvant treatment include reduced nutrient intake, increased sedentary behaviour, increased metabolic rate, and systemic inflammation (Elliott et al., 2017). Moreover, sarcopenia has been shown to reduce neoadjuvant treatment tolerance, with higher incidence rates of chemotherapeutic toxicities in sarcopenic patients (Vega et al., 2016). Furthermore, pre-operative sarcopenia is associated with adverse surgical outcomes, in particular PPCs. Recently, Ida et al. (2015) reported sarcopenic patients had significantly lower pre-operative pulmonary function and experienced a higher rate of PPCs in comparison to non-sarcopenic patients ($p=0.01$).

Weight loss is most pronounced at the 6 month post-surgery mark (Martin and Lagergren, 2009), with up to 50% of patients reporting up to 20% weight loss at that time point (Ouattara et al., 2012). Clinically significant involuntary weight loss is defined as loss of > 5% of body weight in a 6 to 12 month period, with weight loss of greater than 10% considered indicative of malnutrition (Collins, 2003). The aetiology of weight loss following oesophagectomy is multifactorial. Firstly, following oesophagectomy the anatomy of the upper gastrointestinal tract has been significantly altered, and henceforth the body must adapt to a new way of digesting and absorbing food. As a result nutritional issues such as dysphagia, dumping syndrome, and delayed gastric emptying are common (Martin and Lagergren, 2009). Risk factors for weight loss following oesophagectomy include; female gender, pre-operative weight loss, or being over-weight preoperatively, disease reoccurrence, and post-operative complications (Ouattara et al., 2012). Weight loss of in excess of 10% is strongly associated with poorer prognosis following oesophageal cancer treatment

(D'Journo et al., 2012), and is linked with greater risk of reoccurrence (du Rieu et al., 2013), and reduced survival (Adenis et al., 2013).

As survival rates for oesophageal cancer slowly improve, greater emphasis has been placed on developing strategies to improve the quality of survivorship (Chen, 1995). Given the severity of the described treatment associated morbidities, it is understandable that survivors report significantly reduced health related quality of life (HRQOL). A systematic review by Scarpa et al. (2011) reported that global quality of life and physical function remain significantly reduced at six months post-oesophagectomy, and that symptoms including fatigue, diarrhoea, and dyspnoea are highly prevalent. Physical functioning is an important aspect of HRQOL, that has been found to continue to decline even up to 3 years of survivorship (Lagergren et al., 2007), and is considered prognostic of survival (Jack et al., 2014). The impact of oesophageal cancer and its treatments on physical functioning will be discussed in detail in section 1.5.

1.2 Gastric Cancer

The stomach is a J-shaped, distensible, muscular, sac like organ, located between the oesophagus and duodenum in the left side of the upper abdomen. Anatomically, the stomach is divided into four distinct regions; the cardia a small area at the oesophago-gastric junction, the fundus which is the bulge of the stomach superior to the cardia, the body which is the area between the fundus and the curve of the J, and the pylorus which is the distal part of the stomach (Martini and Bartholomew, 2017). Similar to the oesophagus, the stomach has a sphincter at either end that controls the entrance and exit of materials from the stomach. Superiorly the lower oesophageal sphincter is found at the junction of the oesophagus and stomach, and inferiorly the pyloric sphincter is located at the junction of the stomach and the duodenum. The anatomy of the stomach is presented in Figure 1.4.

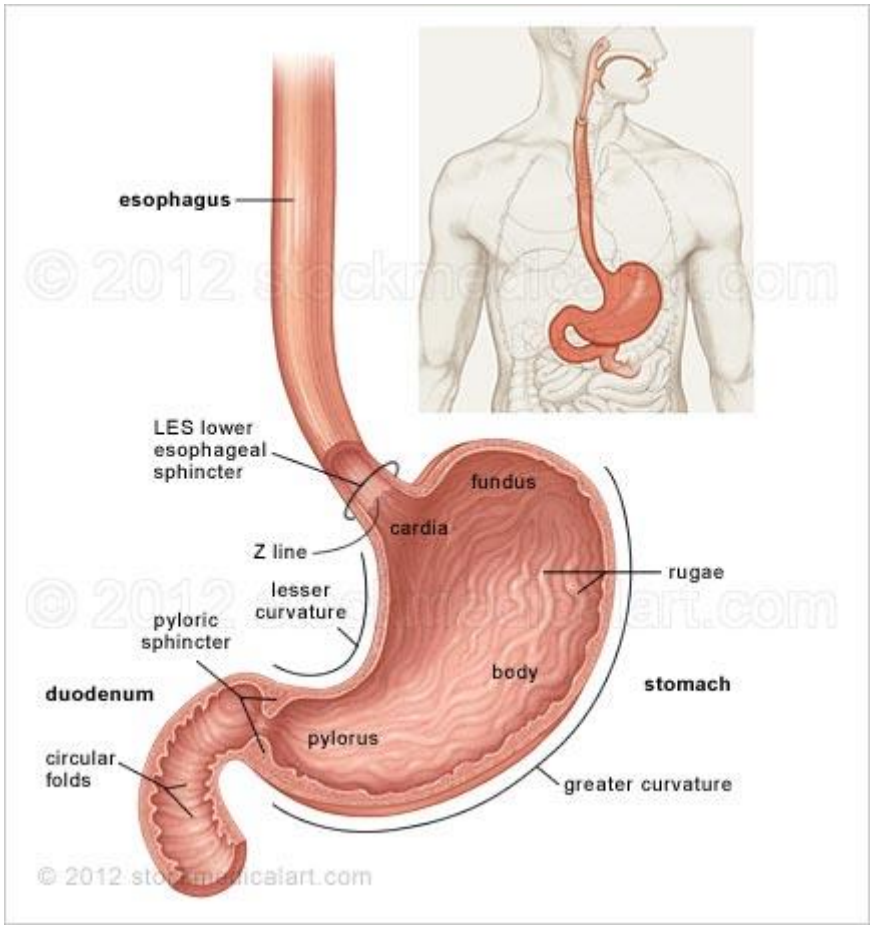

Figure 1.4 Anatomy of the stomach

The main function of the stomach is to receive ingested food from the oesophagus, breakdown ingested food, and store it until it is delivered to duodenum. Ingested food mixes with the enzymes

of the stomach to form an acidic mixture termed chyme. The stomach also functions in initial digestion of proteins, and produces intrinsic factor which is a compound necessary for production of vitamin B12 in the small intestine (Martini and Bartholomew, 2017). The stomach wall consists of four layers; the mucosa, submucosa, muscularis externa, and serosa which are depicted in Figure 1.5.

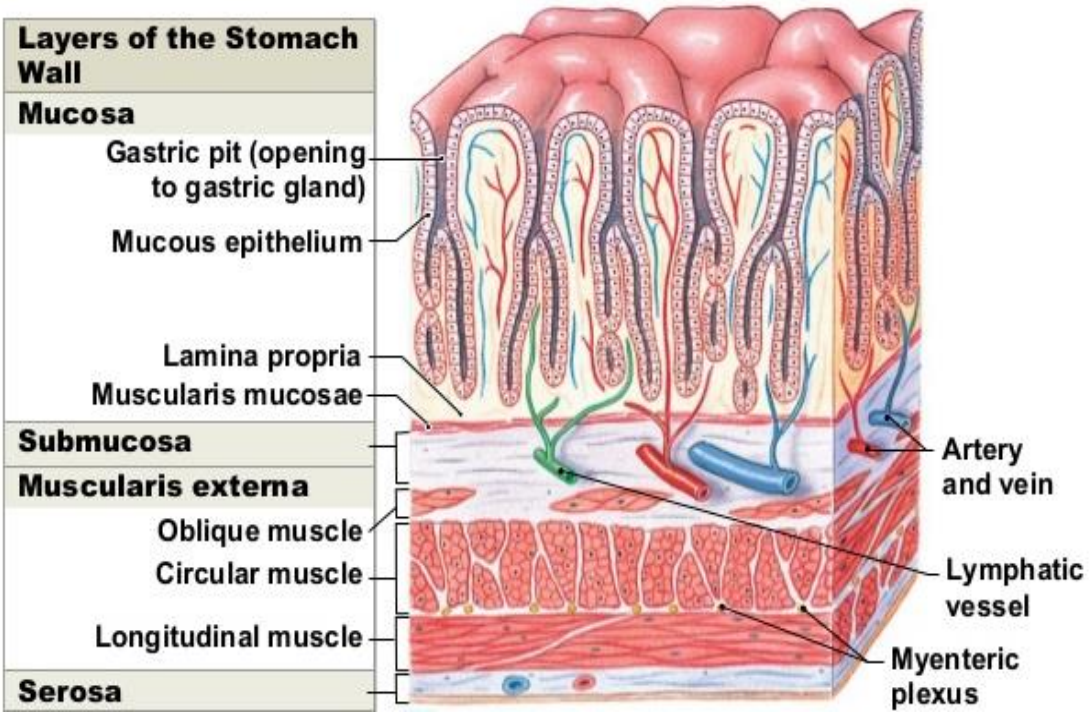

Figure 1.5 Layers of the gastric wall (Source: Essentials of Anatomy and Physiology, 7th Edition *(Martini and Bartholomew, 2017)*)

Cancer of the stomach is termed gastric cancer. Adenocarcinomas, involving the epithelial cells of the mucosa, account for 90-95% of gastric cancers (Correa, 2013). Four percent of cancers that occur in the stomach are lymphomas. Rarer tumours include; gastrointestinal stromal tumours, carcinoid tumours, squamous cell carcinoma, small cell carcinoma, and leiomyoscarcoma (ACS, 2014a).

1.2.1 Incidence and aetiology

After lung, breast, colorectal, and prostate cancer, gastric cancer is the 5th most common cancer world-wide, and is the third leading cause of cancer related deaths (GLOBOCON, 2012b). In Ireland, gastric cancer is the 6th most common cancer, with an average 565 new cases per annum (204 female, and 361 male) reported from 2011 to 2013 (NCRI, 2017b). In most parts of the world, the overall incidence of gastric cancer is actually decreasing. For example, in the USA there was a 1.7% for men and 0.8% reduction for women in incidence of gastric cancer from 1992 to 2010. Despite this overall reduction, incidence of cancer of the gastric cardia has remained stable or increased, and this has been associated with the increasing obesity epidemic (Karimi et al., 2014).

The aetiology of gastric cancer is multifactorial, and a number of risk factors have been identified including; age, gender, helicobacter pylori (H-pylori) infection, smoking tobacco, lower socioeconomic status, and radiation (Correa, 2013, NCRI, 2011a). Firstly, the risk of gastric cancer increases with age, with the average age of diagnosis reported to be 69 years (ACS, 2014a). Gender differences in the incidence of gastric cancer vary, with men two to three times more likely to develop gastric cancer (Karimi et al., 2014). Gastric cancer is one of few cancers that are directly linked to an infectious agent. H-pylori is a gram negative bacteria which has the ability to colonize the mucosa and induce an immune response. There are different strains of the bacteria, and they vary in their pathogenic and carcinogenic abilities. Approximately 50% of adults harbour the H-pylori bacteria, but fewer than 1% will develop gastric cancer (Correa, 2013). Gastric cancer is also associated with the Epstein-Barr Virus (NCRI, 2011a). Similar to oesophageal cancer, Tobacco smoking significantly increases the risk of developing gastric cancer (Karimi et al., 2014). Lower socioeconomic class is also a risk factor for developing gastric cancer, highlighting the link between tobacco use and social class (NCRI, 2011a). Exposure to radiation has also been established as a risk factor for gastric cancer through long-term follow-up of survivors of the Hiroshima and Nagasaki atomic bombings. Finally, comparably to adenocarcinoma of the oesophagus, obesity and GERD have been associated with development of cardia gastric cancer (Karimi et al., 2014).

A number of gastric cancer risk reducing factors have also been identified. Alike oesophageal cancer, consuming a healthy diet including fresh fruit and vegetables reduces the risk of gastric carcinoma (NCRI, 2011a) , and diets high in salt, processed meat, pickled vegetables, and fermented soya should be avoided (Correa, 2013). Refrigeration of foods is also associated with reduced risk of gastric cancer (Karimi et al., 2014). Akin to oesophageal cancer, the use of NSAIDs such as aspirin is associated with reduced gastric cancer risk (NCRI, 2011a). The use of statins to reduce low-density

lipoprotein cholesterol, and engagement in regular physical activity have also been identified as having a protective effect on the risk of developing gastric cancer (Karimi et al., 2014).

1.2.2 Signs and symptoms

Comparable to oesophageal cancer, early stage gastric cancer rarely causes symptoms and as a result the disease is usually not detected until it is at an advanced stage. Signs of gastric cancer include; appetite loss, early satiety, unintentional weight loss, heart burn, abdominal pain or discomfort, nausea, vomiting, anaemia, and abdominal swelling (ACS, 2014a, Maconi et al., 2008).

1.2.3 Diagnosis and staging

Diagnosis of gastric cancer is usually by endoscopy with biopsy in conjunction with endoscopic ultrasound (EUS) to determine the staging of the cancer (Pasechnikov et al., 2014, Kuntz and Herfarth, 1999, Caletti et al., 1993). Other tests involved in the diagnosis and staging of gastric cancer include; upper gastrointestinal (GI) series testing, CT, MRI, PET, and laparoscopy (surgical exploration of the stomach) (Pasechnikov et al., 2014). Gastric cancer staging is also defined by the American Joint Committee on Cancer (AJCC) TNM staging system. At present the 7th Edition of the AJCC Cancer Staging Manual: Stomach, is used for classification of gastric cancer (Washington, 2010). The stages of gastric cancer are presented in Table 1.6 and the relationship between gastric cancer stage and the TNM classification is presented in Table 1.7. Comparably to oesophageal cancer, cancer of the stomach is typically diagnosed at a later stage (Figure 1.6).

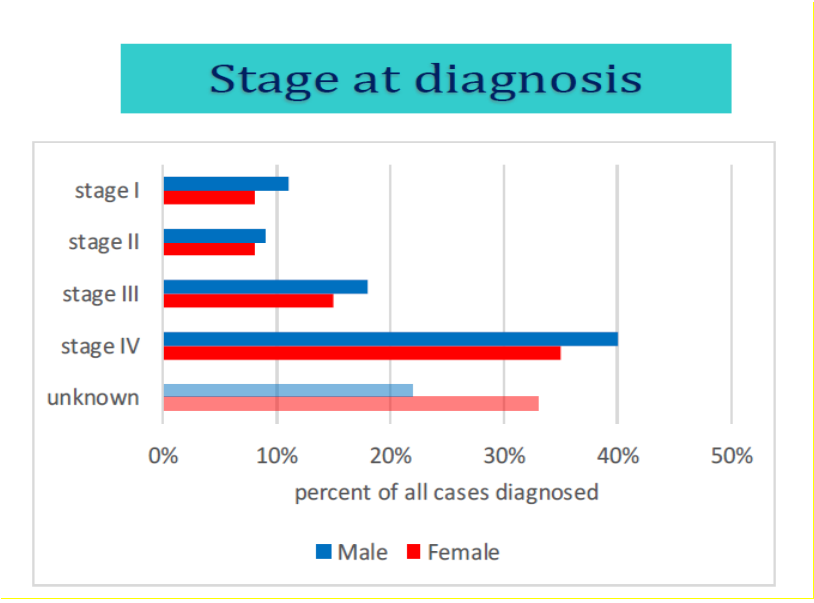

Figure 1.6 Gastric cancer - Stage at diagnosis in Ireland 2012 -2014 (NCRI, 2017b)

Table 1-6 Stages of gastric cancer (Source: National Cancer Institute)

Stage		Description
Stage 0		Abnormal cells are found in the lining of the mucosa of the stomach wall. Stage 0 is also called carcinoma in situ.
Stage I	**Stage IA**	Cancer may have spread into the submucosa of the stomach wall.
	Stage IB	Cancer may have spread into the submucosa of the stomach wall, and is found in 1 or 2 nearby lymph nodes, or, has spread to the muscle layer of the stomach wall.
Stage II	**Stage IIA**	Cancer has spread to the subserosa of the stomach wall, or has spread to the muscle layer of the stomach wall, and is found in 1 or 2 lymph nodes near the tumour, or, may have spread to the submucosa of the stomach wall and is found in 3 to 6 lymph nodes near the tumour.
	Stage IIB	Cancer has spread to the serosa of the stomach wall, or, has spread to the subserosa of the stomach wall and is found in 1 or 2 lymph nodes near the tumour, or, has spread to the muscle layer of the stomach wall and is found in 3 to 6 lymph nodes near the tumour, or, may have spread to the submucosa of the stomach wall and is found in 7 or more lymph nodes near the tumour.
Stage III	**Stage IIIA**	Cancer has spread to the serosa layer of the stomach wall and is found in 1 to 2 lymph nodes near the tumour, or, the subserosa of the stomach wall and is found in 3 to 6 lymph nodes near the tumour, or, the muscle layer of the stomach wall and is found in 7 or more lymph nodes near the tumour.
	Stage IIIB	Cancer has spread to nearby organs such as spleen, transverse colon, liver, diaphragm, pancreas, kidney, adrenal gland, or small intestine, and may be found in 1 or 2 lymph nodes near the tumour, or, the serosa and is found in 3 to 6 lymph nodes, or, the subserosa and is found in 7 or more lymph nodes.
	Stage IIIC	Cancer has spread to nearby organs, and may be found in 3 or more lymph nodes, or, the serosa and is found in 7 or more lymph nodes.
Stage IV		Cancer has spread to distant parts of the body.

Table 1-7 Relationship between stage and TNM status for gastric cancer (Source: 7th Edition of the AJCC Cancer Staging Manual: Stomach *(Washington, 2010)*)

Stage	T	N	M
Stage 0	is	0	0
Stage IA	1	0	0
Stage IB	2	0	0
	1	1	0
Stage IIA	3	0	0
	2	1	0
	1	2	0
Stage IIB	4a	0	0
	3	1	0
	2	2	0
	1	3	0
Stage IIIA	4a	1	0
	3	2	0
	2	3	0
Stage IIIB	4b	0 or N1	0
	4a	2	0
	3	3	0
Stage IIIC	4b	2 or 3	0
	4a	3	0
Stage IV	Any	Any	1

Abbreviations: Tis = carcinoma in situ

1.2.4 Treatment

Surgical resection (gastrectomy) is the only potentially curative treatment for cancer of the stomach. Comparably to oesophagectomy, gastrectomy is associated with significant risk of serious morbidity and mortality. Following total gastrectomy, thirty day mortality varies from 0.8% to 13%. Two recent studies reported 30 day mortality rates of 4.7%, and 4.1% respectively (Bartlett et al., 2014, Papenfuss et al., 2014). Risk factors for 30 day mortality include; age greater than 70, reduced physical function, hypertension, pre-operative weight loss, and presence of ascites (Bartlett et al., 2014). Splenectomy or pancreatectomy in conjunction with gastrectomy also significantly increase mortality rates (Nanthakumaran et al., 2005).

Early stage gastric tumours may be treated with endoscopic submucosal dissection. This approach has comparable long term outcomes to open surgery (Shen et al., 2013). For more advanced tumours (Stage IB – III), surgical resection either subtotal gastrectomy or total gastrectomy is required (Waddell et al., 2014). Subtotal gastrectomy involves the removal of the part of the stomach that contains the cancer, nearby lymph nodes, and parts of other tissues and organs near the tumour, and total gastrectomy involves the removal of the whole stomach, nearby lymph nodes, and parts of the oesophagus, small intestine, and other tissues near the tumour. In a total gastrectomy, the oesophagus is connected to the small intestine to facilitate the passage of food (ACS, 2014a). Gastrectomy is traditionally an open procedure, but the use of laparoscopic surgery has been evaluated as an alternative surgical approach to reduce surgical morbidity and mortality. However, there are concerns that the laparoscopic approach to surgery might reduce the ability to harvest all cancerous nodes, and further research is required to compare the long term outcomes of open versus laparoscopic gastrectomy (Haverkamp et al., 2013).

Gastric resections are described in terms of the extent of nodal dissection. A D1 resection involves the removal of the perigastric lymph nodes, whereas a D2 resection involves the removal of perigastric lymph nodes plus those along the left gastric, common hepatic and splenic arteries, and the coeliac axis (Waddell et al., 2014). There is contrasting evidence from Asian versus Western studies regarding D2 versus D1 resections. Asian studies have found significant survival advantaged for D2 resections (Shen et al., 2013), whereas western studies including the Dutch MRC study (Cuschieri et al., 1999) have found no survival benefits. However, a recent meta-analysis by Mocellin et al. (2015) reported that D2 lymphadenectomy improves disease specific survival (HR=0.81, 95%CI, 0.71-0.92), and the consensus in international guidelines is that D2 resections (without routine pancreatectomy and splenectomy) are recommended and should be performed in high

volume centres, with surgical expertise, and specialised post-operative care (Waddell et al., 2014, Shen et al., 2013).

Akin to oesophageal cancer, a multimodality approach (surgery and perioperative chemotherapy/ adjuvant chemotherapy/ adjuvant chemoradiotherapy) is favoured for gastric cancers that are greater than Stage IB (Waddell et al., 2014). Perioperative chemotherapy has been implemented as the standard of care in Europe (Waddell et al., 2014). The results of the MAGIC trial (Cunningham et al., 2006), reported significant 5 year survival benefits towards perioperative chemotherapy (epirubicin, cisplatin, and infused fluorouracil (ECF)) and surgery (n=250) vs surgery alone (n=253)(5 year survival 36.3% (95%CI, 29.5-43.0) vs 23.0% (95% CI, 16.6-29.4)) in patients with resectable tumours of lower oesophagus, oesophago-gastric junction, and stomach. The smaller French FNCLCC and FFCD trial (Ychou et al., 2011), had comparable results with a perioperative chemotherapy regime of cisplatin and fluorouracil combined with surgery, versus surgery alone (5 year survival rate 34% vs 19%, HR=0.65, 95%CI, 0.48-0.89, p=0.003). An alternative treatment option for patients that undergo surgery and have >Stage IB disease is adjuvant chemotherapy or adjuvant chemoradiotherapy. However, evidence is lacking to inform the choice between these two treatment regimens (Waddell et al., 2014).

As with oesophageal cancer, in recent years there has been growing research focus into targeted therapies for gastric cancer. In gastric cancer there is a growing interest in the use of monoclonal antibody therapy, for example trastuzumab has been used in combination with chemotherapy to block the effects of the growth factor HER-2, and ramucirumab as a second line treatment to block the effect of the protein (VEGF (Vascular endothelial growth factor)) in gastric cancer that has recurred (ACS, 2014a, Waddell et al., 2014).

Approximately 40% of gastric tumours have already progressed to Stage IV at diagnosis (Alberts et al., 2003). Palliative treatment options include chemotherapy, radiotherapy, and supportive care. Palliative chemotherapy has been found to increase survival compared to best supportive care (Wagner et al., 2006), and palliative radiotherapy can be used to reduce symptoms of bleeding, pain, and stomach obstruction (Waddell et al., 2014).

1.2.5 Prognosis and survival

Similar to oesophageal cancer, gastric cancer is typically diagnosed late, and therefore the prognosis is poor with an average 5-year survival rate of less than 20% (Correa, 2013). Screening is useful for identifying early stage gastric cancers, however it is only considered cost effective in countries such as Japan and Korea which have a high incidence of gastric cancer (Waddell et al., 2014). In Japan barium studies or serum-pepsinogen testing is used for screening, and patients with abnormal results are referred on for diagnostic endoscopy (Shen et al., 2013). The five year survival rate for gastric cancer can reach upwards of 90%, if early stage tumours are detected and treated before they invade the muscular layer of the stomach (Correa, 2013). With the advancement of multimodality treatment regimens there has been a gradual improvement in gastric cancer survival rates (ACS, 2014a). For example, the National Cancer Registry Ireland's most recent statistics show the average five year survival for gastric cancer in Ireland has improved from 17.4% (1994-1998) to 27.4% (2009-2013) (Table 1.8). Gastric cancer survival in Ireland is dependent on the stage of the disease with 5 year survival ranging from 67.4% for Stage I disease, to only 4% for Stage IV disease (Figure 1.7).

Table 1-8 Five year net survival for gastric cancer in Ireland (1994-2013) (Source: National Cancer Registry Ireland(NCRI, 2017c))

Diagnosed	Net survival (age standardised)	95% confidence interval
1994-1998[c]	17.4%	15.6-19.1%
1999-2003[c]	17.3%	15.6-19.0%
2004-2008[c]	23.2%	21.3-25.0%
2009-2013[c]	27.4%	25.1-29.8%
2009-2014[h]	27.3%	25.3-29.4%

[c]= cohort, by year of diagnosis, [h]=hybrid, by year of follow-up (all patients alive at some point 2010 -2013, or diagnosed in 2009 and follow-up to 31/12/2014)

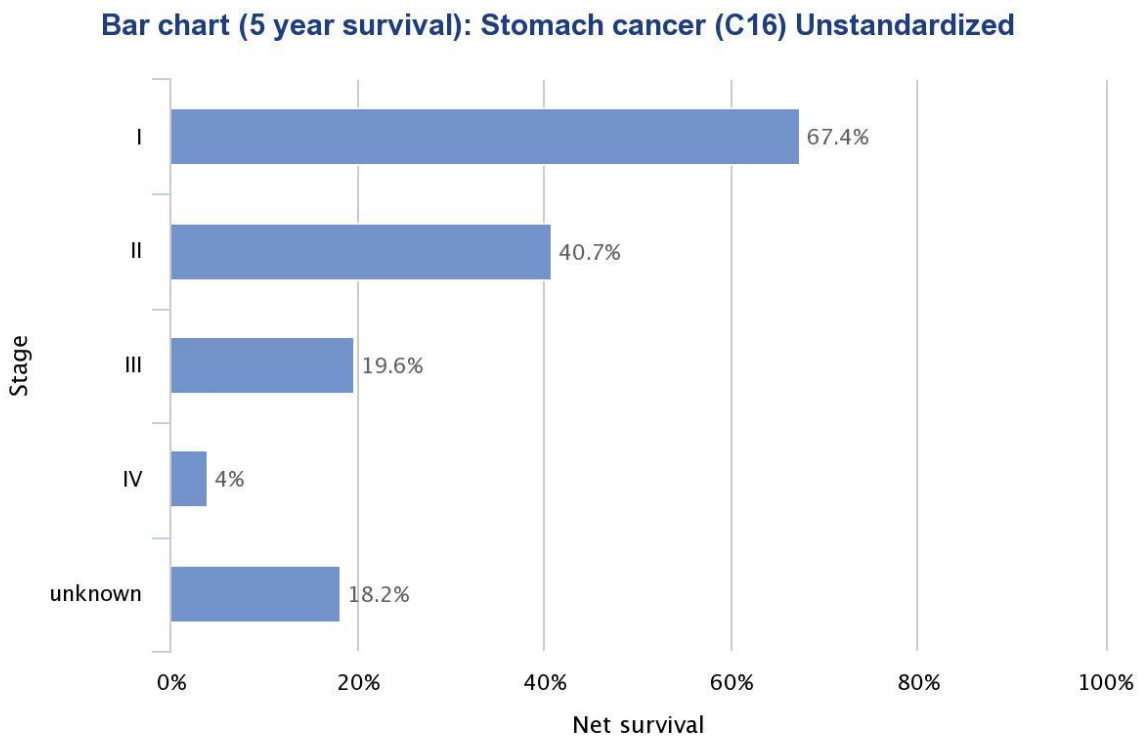

Figure 1.7 Five year stage specific survival rates for gastric cancer in Ireland 2008 -2012 (Source: National Cancer Registry Ireland)

A number of tumour-related and patient-related factors have been linked with gastric cancer prognosis. Following a 10 year follow-up study of German gastric cancer patients, Siewert et al. (1998) reported that the ratio of invaded to removed lymph nodes was the single most important prognostic factor for gastric cancer survival, highlighting the importance of extended lymph node dissection during gastrectomy. Other tumour related factors include the residual tumour category, tumour T staging and the presence of distant metastases. Siewert et al. (1998) also reported post-operative complications were prognostic of survival. More recently HER-2 overexpression has been associated with poorer gastric cancer outcomes and more aggressive disease (Gravalos and Jimeno, 2008). As previously discussed research is ongoing investigating the efficacy of anti-HER-2 therapies. As with oesophageal cancer, sarcopenia has also been identified as an independent predictor for poorer overall survival (HR = 1.653, 95%CI, 1.332-2.052, $p < 0.001$) and disease-free survival (HR = 1.620, 95%CI, 1.295-2.027, $p < 0.001$) from gastric cancer (Zhuang et al., 2016).

1.2.6 Treatment side-effects

The risk of serious morbidity following gastrectomy is reported to range from 13 to 38%, with an increased risk of post-operative complications observed in patients undergoing total gastrectomy in comparison to sub-total gastrectomy (Bartlett et al., 2014). Common post-gastrectomy complications include; anastomotic leak, wound infections, pulmonary complications, thromboembolic complications, ascites, and sepsis (Papenfuss et al., 2014, Sano et al., 2004). Risk factors associated with morbidity include; age greater than 70, reduced physical function, and pre-operative weight loss (Bartlett et al., 2014).

As previously discussed in section 1.2.4, perioperative chemotherapy is considered the standard of care for gastric tumours in western centres. The high incidence of serious morbidity following gastrectomy is particularly worrying, as those with serious complications are much less likely to receive post-operative chemotherapy, which subsequently impacts on overall and disease-free survival. In the MAGIC trial, Cunningham et al. (2006) reported that only 66% of patients randomised to receive perioperative chemotherapy were able to continue chemotherapy post-surgery, and in the French FNCLCC and FFCD trial (Ychou et al., 2011) only 48% of patients randomised to perioperative chemotherapy were able to commence chemotherapy post-gastrectomy. As with all chemotherapy, perioperative chemotherapy for gastric cancer is associated with numerous side effects including nausea and vomiting, immunosuppression, peripheral neuropathies, and hepatic and renal toxicity (Zhao et al., 2016).

Akin to oesophageal cancer, malnutrition, weight loss, and sarcopenia are prevailing symptoms in gastric cancer. Pre-operative chemotherapy can accelerate weight loss, and increase incidence of sarcopenia (Mirkin et al., 2017). Weight loss during chemotherapy, reduces the treatment response rate, and increases the risk of chemotherapeutic toxicity. Pre-operative weight loss in excess of 10% is significantly associated with morbidity and mortality (Cui et al., 2014). Post-gastrectomy malnourished patients are at greater risk of post-operative complications, have longer length of hospital stay, and reduced long-term overall and disease free survival (Mirkin et al., 2017, Wang et al., 2016). Patients with significant weight loss are also less likely to commence scheduled chemotherapy post-operatively (Aoyama et al., 2013), thus negatively affecting overall outcomes.

Quality of survivorship has gained appreciation as an outcome of importance for gastric cancer (McCall et al., 2016). Side effects of gastric cancer and its treatments, particularly dietary issues

such as early satiety, appetite loss, heartburn, dysphagia, nausea and vomiting, can have a detrimental effect on health-related quality of life. Global quality of life is reported to be significantly reduced post-gastrectomy (McCall et al., 2016), and deficits can persist up to one year post-operatively (Yu et al., 2016). Reduced social function and the symptoms of nausea and vomiting, and pain also prevail at one year post-gastrectomy. As with oesophageal cancer, physical function deficits are reported in up to five years of survivorship (Yu et al., 2016). The impact of gastric cancer treatment on physical functioning will be discussed in section 1.5.

1.3 Impact of cancer and cancer treatment on physical functioning

Physical functioning is an important aspect of health related quality of life (HRQOL), and refers to an individual's capacity to undertake essential activities of daily living independently (Atkinson et al., 2017). Physical functioning in cancer has been predominantly investigated in cancer populations using physical function subscales of patient reported outcome measures (PROMs) such as the EORTC-QLQ-C30 and the SF-36. Although these physical function subscales exhibit good reliability (EORTC-QLQ-C30 Physical Function Subscale: internal consistency Cronbach α=0.68 (pre-treatment), and α=0.71 (during treatment), test-retest reliability r=0.91, and SF-36 Physical Function Subscale: internal consistency Cronbach α=0.94, test-retest reliability r=0.74 after 1 week, and r=0.85 at 4 weeks), neither have been validated for use in isolation and must be used in conjunction with the core questionnaire (Atkinson et al., 2017). Moreover, a criticism of these subscales is that they are self-reported, and such measures are limited in their ability to reflect true physical function (Boyle et al., 2015, Thorsen et al., 2006). Indeed there is often no relationship between self-reported physical function and objectively measured exercise capacity (Thorsen et al., 2006). Consequently, more focus has been placed on objective measures of physical function in cancer populations including tests of; cardiorespiratory fitness, physical performance such as six minute walking test (6MWT), muscle strength tests, and quantification of physical activity engagement by accelerometry. The assessment of physical function will be described in Chapter 2 of this thesis.

Physical function deficits are common across the cancer continuum due to the effects of the cancer itself and its treatments, both of which can have widespread effects on the body systems, resulting in impairments of the cardiovascular, respiratory, nervous, musculoskeletal, immune and endocrine systems (Brown et al., 2012). As previously discussed in sections 1.1.6 and 1.2.6, cancer treatments can result in numerous side effects including fatigue, pain, weakness, cardiovascular

and pulmonary complications, and gastrointestinal symptoms which can all hamper the ability of patients with cancer to engage in their usual physical activities.

There is substantial evidence that physical functioning is impaired in cancer survivorship (Schmitz et al., 2010). When compared to individuals who have never had cancer, physical function deficits are more frequent in both recent (<5years) and long term (>5years) survivors of cancer (OR=1.85, 95%CI, 1.23-2.77, and OR=1.49, 95%CI, 1.07-2.08) (Ness et al., 2006). Physical functioning has been increasingly investigated in cancer populations, and deficits are widely reported. For example, in survivors of breast cancer, which is the most well studied cancer with regard to physical functioning, cardiorespiratory fitness has been reported to range from 17.5 to 25.2 ml/min/kg, which is below population reference values (Campbell et al., 2012). Furthermore, most breast cancer survivors do not meet the recommended levels of physical activity (Irwin et al., 2004). Impaired physical function can negatively impact on cancer survivors' abilities to engage in societal and familial roles, and can inhibit return to work. Cancer survivors who are older, less educated, overweight or obese, and less active are more likely to experience physical function deficits (Campbell et al., 2012). Increasingly, physical function is being investigated as a prognostic biomarker in cancer survivors. A recent study by Brown et al. (2015) investigated the relationship between physical function and mortality in 413 cancer survivors. Brown et al. (2015) reported that a one unit increase in a short physical performance battery or a 0.1 $m.s^{-1}$ increase in a gait speed test was associated with a 12% reduction in mortality (Hazard Ratio(HR)= 0.88, 95%CI, 0.82-0.94, p<0.001, and HR=0.88, 95%CI, 0.82-0.96, p=0.003).

The impact of oesophageal and gastric cancer treatment on physical functioning is investigated in section 1.5.

1.4 Exercise interventions in cancer populations

With a growing number of cancer survivors, health research has increasingly focused on strategies to improve the quality of survivorship. One method is through primary prevention of other chronic health conditions that have a detrimental effect on HRQOL. Survivors of cancer with impaired physical function are at much greater risk of co-morbid conditions, such as cardiovascular disease, diabetes, osteoporosis, and other cancers. Risk factors for these co-morbidities include cancer treatment, genetic predispositions, and lifestyle factors (Demark-Wahnefried et al., 2006). Lifestyle factors are inherently modifiable, and attempts to change behaviour and improve lifestyle choices

are becoming an important focus of research in cancer survivorship. An example of a modifiable lifestyle factor is physical activity. Akin to the general population most survivors of cancer live predominantly sedentary lifestyles (Demark-Wahnefried et al., 2006), and, have sub-optimal levels of physical functioning. Consequently, in recent times the efficacy of exercise interventions to improve physical functioning across the cancer continuum has become an important field of cancer research.

In the past, clinicians advised patients with cancer to rest and avoid activity. However, now exercise is considered an important self-care intervention throughout the cancer journey from pre-diagnosis into survivorship (Schmitz et al., 2010). Exercise is a subcategory of physical activity that is planned, structured, and repetitive, and aims to improve one or more aspect of physical fitness. The components of physical fitness are described in section 2.3.1 of this thesis. Exercise is advocated in cancer populations due to its positive effects on physical function, quality of life, fatigue, body composition, cardiovascular health, mental health, and disease free and overall survival (Brown et al., 2012, Demark-Wahnefried et al., 2006). Increasingly the aetiology of the protective effects of exercise in cancer have been investigated. Exercise has been associated with a number of biochemical processes that are thought to reduce risk of cancer development, reoccurrence, and improve survival (Thomas et al., 2017, Koelwyn et al., 2015). Indirect effects of exercise include; changes in vitamin D, weight reduction, and improved mood, and reported direct effects of exercise include; reduced levels of insulin-like growth factor, reduced leptin levels, transient rise and then reduction in testosterone and vasoactive intestinal peptide, improved immune response including enhanced activity of natural killer cells and white bloods cells, reduced inflammation through a reduction in C reactive protein, interleukin-6, TNFα, prostaglandins, and COX-2, and finally increased antioxidant activity (Thomas et al., 2017).

The current exercise recommendations for patients with cancer are the same as those for the general population. Patients with cancer are advised to 'avoid inactivity', and for optimum health benefits are advised to engage in 150 minutes of moderate intensity physical activity per week and two-to-three resistance training sessions per week (ACSM, 2010). A number of precautions should be adhered to when prescribing exercise interventions for patients with cancer. Firstly, exercise is contraindicated in those with severe and unrelenting fatigue, severe anaemia, or ataxia. Thorough screening for cardiovascular issues is also required, particularly of patients who have undergone or are undergoing anthracycline chemotherapy which has a risk of cardiac toxicity. Furthermore, there are numerous cancer specific precautions that need to be considered for example, the possibility

of bone metastases in advanced prostate cancer, and the risk of hernia post-oesophagectomy (Schmitz et al., 2010).

To date research regarding cancer and exercise has predominantly focused on breast, colorectal, lung, and prostate cancers (Schmitz et al., 2010). The Physical Activity Cancer Control Framework was proposed by Courneya and Friedenreich (2007), and describes 6 key time-points across the cancer continuum from diagnosis into survivorship where exercise and physical activity have been found to be beneficial, and identifies key objectives for exercise programmes at each time-point (Figure 1.8). There is growing research regarding the benefits of exercise across the cancer journey. For example, with regards to prehabilitation, a recent systematic review by Treanor et al. (2017) found that exercise in advance of lung cancer surgery reduced the length of hospital stay (mean difference (MD) -4.18 days, 95%CI, -5.43 to -2.93) and reduced the incidence of post-operative complications (OR=0.25, 95%CI 0.10-0.66). In relation to exercise during active treatment e.g. chemotherapy, there is substantial literature advocating exercise during adjuvant chemotherapy for breast cancer. In their recent systematic review Furmaniak et al. (2016) reported significant improvements in fitness (SMD=0.42, 95%CI, 0.25-0.59, based on 15 studies with 1310 participants), and fatigue (SMD=-0.28, 95%CI, -0.41 to -0.16, based on 19 studies with 1698 participants) could be achieved through exercise during adjuvant chemotherapy. Furthermore, one of the rationale behind exercise interventions during adjuvant chemotherapy for breast cancer is to minimise the cardiotoxic effects of chemotherapy, by enhancing cardiovascular functioning, and therefore increasing treatment tolerance and completion rates (Yu and Jones, 2016). Numerous benefits of exercise interventions in cancer survivorship, particularly in breast cancer have been reported. In a meta-analysis, Fong et al. (2012) reported cancer survivors experienced significant improvements in measures of physical performance including VO_{2peak} (2.2 ml/min/kg, 95%CI, 1.0-3.4, p=0.01), six minute walk test distance (29m, 95%CI, 4-55, p=0.03), leg press strength (19kg, 95%CI, 9-28, p=0.01), and hand grip strength (3.5kg, 0.3-6.7, p=0.03) following participation in a structured exercise programme. In further support for exercise interventions in cancer survivorship, exercise participation has been associated with improved survival in breast and colorectal cancer cohorts (Schmitz et al., 2010).

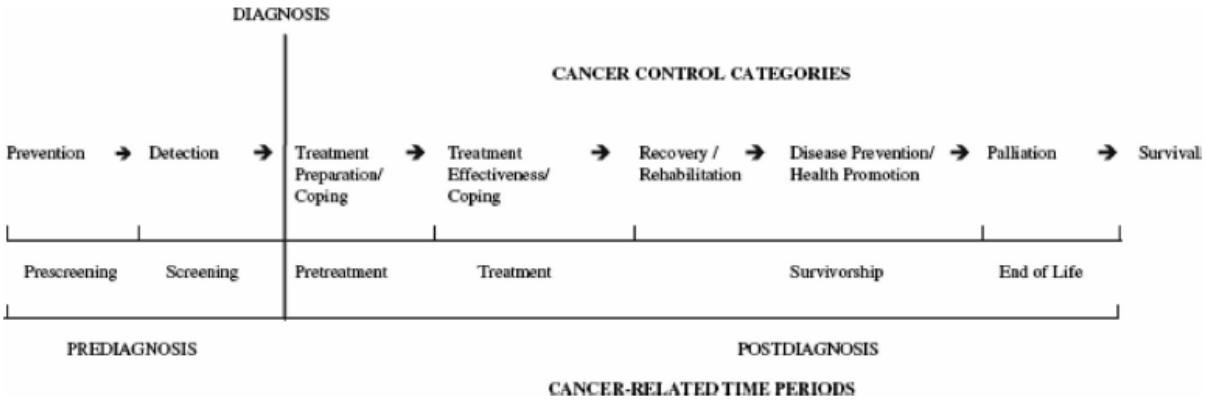

Figure 1.8 Physical Activity and Cancer Control Framework (Courneya and Friedenreich, 2007)

Despite the growing supportive evidence for exercise in cancer, a large number of research questions still require investigation. Firstly, further research is required to determine the exercise prescription parameters (Frequency Intensity Type Time (FITT)) required for specific gains in functional status, quality of life and well-being. The underlying therapeutic mechanisms of exercise requires further exploration. Further research is required to determine the optimum exercise regime to maximise therapeutic responses to chemotherapy. The optimal timing of exercise interventions across the cancer continuum is yet to be determined. Strategies to improve the translation from research into evidenced based clinical practice are required, as are strategies to improve the long term adherence of survivors to exercise. Further research is also required to establish the long term effects of exercise in survivorship e.g. impact on mortality rates. And finally more research is required to examine the efficacy of exercise interventions in lesser studied cancers such as oesophageal and gastric cancer (Brown et al., 2012, Schmitz et al., 2010).

Section 1.5 will now review the impact of oesophago-gastric cancer and its' treatment on objectively measured physical functioning, and therefore identify the need for rehabilitative interventions involving exercise in oesophago-gastric cancer

1.5 Physical functioning and rehabilitative strategies in oesophago-gastric cancer

A systematic review of the literature was carried out to investigate the impact of curative treatment for oesophago-gastric cancer on physical functioning, and also investigate rehabilitative strategies to help maintain or improve physical function.

A version of this systematic review is currently under review at the Journal of Cancer Survivorship.

O'Neill, L., Moran, J., Guinan, E., Reynolds, JV., Hussey, J. Physical Decline and its Implications in the Management of Oesophageal and Gastric Cancer; a Systematic Review (2017)

As aforementioned, curative treatment for oesophago-gastric cancer involves a multimodality approach consisting of NAC/NCRT/ perioperative chemotherapy in conjunction with resectional surgery (Kidane et al., 2015, Carcas, 2014, Ronellenfitsch et al., 2013, Barbour et al., 2008, van Meerten et al., 2008). The existing condition at presentation may be associated with significant nutritional and physical impairment, and in this context, each treatment intervention may result in further attrition of key domains of physical well-being (Sato et al., 2016, Heneghan et al., 2015, Chang et al., 2014). Oesophagectomy for instance can impair cardiopulmonary fitness due to changes in respiratory mechanics, in particular open thoracic surgery with one-lung anaesthesia, and nutritionally, up to 50% of patients following surgery lose 20% of body weight by 6 months postoperatively, with attendant significant risk of physical decline (Ouattara et al., 2012, Scarpa et al., 2011, Chasen and Bhargava, 2010). Deficits in physical function result in difficulties completing activities of daily living which can have a devastating impact on HRQOL for cancer survivors (Chasen and Bhargava, 2010). Assessment of physical function in oesophago-gastric cancer cohorts may be important before treatment begins with chemotherapy or chemoradiation, again pre-surgery to assess fitness and address deficits, and again in recovery from surgery, particulary during the first year (Jack et al., 2014, Forshaw et al., 2008).

Heretofore, in most published work physical function in oesophago-gastric cancer has largely been captured using QOL questionnaires with a physical function subscale. These include the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire- C30 (EORTC-QLQ-C30) (Chang et al., 2014, Daster et al., 2014), the Functional Assessment of Cancer Therapy - for patients with oesophago-gastric cancer (FACT-E (Darling et al., 2006) and FACT-Ga (Munene et al.,

2012)), and the Short Form-36 (SF36) (Maas et al., 2015). Studies using these domains consistently show physical function is significantly impaired through oesophago-gastric cancer treatment and in long-term survivorship (Daster et al., 2014, Malmstrom et al., 2013a, Scarpa et al., 2011). However as previously discussed in section 1.3 these subscales correlate poorly with more objective measures of physical functioning (Thorsen et al., 2006) and accordingly, an objective assessment is desirable to accurately and reliably evaluate physical function in patients with oesophago-gastric cancer, and prescribe interventions with defined targets of improvement.

Across oncology, the objective measurement of physical function is increasingly the subject of study (Steins Bisschop et al., 2012, Schmitz et al., 2010). Higher physical function has been associated with better HRQOL, emotional well-being, treatment tolerance, and survival in cancer populations (Leitzmann et al., 2015, Jack et al., 2014). Cardiopulmonary Exercise Testing (CPET) (Steins Bisschop et al., 2012, Moran et al., 2016), the six minute walking test (6MWT) (Schmidt et al., 2013), the incremental shuttle walking test (ISWT) (Gannon et al., 2017), hand grip strength (HGS) (Chen et al., 2011), and accelerometer measured physical activity levels (Feeney et al., 2011), are examples of objective measures of physical function that have been applied in oesophago-gastric cancer research. Considering the physical challenge of modern oesophageal and gastric treatment protocols for patients with locally advanced disease being treated with curative intent, studies are somewhat limited, and further knowledge is required regarding objective measures of physical functioning to i) help determine suitability for treatment and ii) help identify their rehabilitation requirements. Moreover, exercise rehabilitation, increasingly studied with proven efficacy of outcomes, including mortality, in breast and colorectal cancer (Schmitz et al., 2010), is an area of increasing research activity in oesophago-gastric cancer (Xu et al., 2015, Lococo et al., 2012, Chasen and Bhargava, 2010).

1.5.1 Aims and objectives

The aim of this systematic review was to investigate the effects of curative treatment (oesophagectomy/gastrectomy +/_ neoadjuvant/ perioperative chemo/chemoradiotherapy) on physical functioning in patients with oesophago-gastric cancer.

Secondary objectives were to:

i. To explore associations between physical function and postoperative outcomes.
ii. To determine the effects of rehabilitation programmes across the oesophago-gastric cancer journey on physical function.

1.5.2 Methods

This systematic review was performed using the PRISMA standardised reporting guidelines (Moher et al., 2009).

1.5.2.1 Inclusion/ Exclusion criteria

Studies were included in this review only where they reported on:

- **P**articipants: Patients with a histological confirmed diagnosis of oesophageal, oesophageal junction, or gastric cancer who underwent treatment with curative intent.
- **E**xposure: Neoadjuvant therapy (chemotherapy/ chemoradiotherapy), perioperative chemotherapy, and or surgery (oesophagectomy/gastrectomy) with curative intent.
- **O**utcomes: Physical function measured objectively e.g. cardiopulmonary fitness, physical performance, physical activity levels, and muscle strength.
- **S**tudy type: Randomised controlled trials (RCTs), non-randomised trials of an intervention, or a cohort study.

Studies were excluded if i) physical function was measured by subjective means only e.g. questionnaire, ii) if articles were unavailable in English, iii) systematic reviews, iv) meta-analysis, v) case studies, vi) letters to the editor, vii) conference proceedings, or viii) abstracts with no full text available.

1.5.2.2 Search strategy and selection

The search strategy was developed in consultation with a medical librarian (David Mockler) which was tailored to each individual database. The databases of PubMed, EMBASE CINAHL, Cochrane Library, SCOPUS, PEDro, and the WHO Trial Registry were searched up to June 2016 by one author (Linda O'Neill (LON)). The following search algorithm was used to identify suitable articles on PubMed: ("esophageal surgery"[Title/Abstract] OR "oesophageal surgery"[Title/Abstract] OR "esophageal cancer"[Title/Abstract] OR "oesophageal cancer"[Title/Abstract] OR "esophageal neoplasm*"[Title/Abstract] OR "oesophageal neoplasm*"[Title/Abstract] OR "esophageal resection"[Title/Abstract] OR "oesophageal resection"[Title/Abstract] OR "esophageal adenocarcinoma*[Title/Abstract] OR "oesophageal adenocarcinoma*"[Title/Abstract] OR "esophagectom*"[Title/Abstract] OR "oesophagectom*"[Title/Abstract] OR "esophagogastroplast*"[Title/Abstract] OR "oesophagogastroplast*"[Title/Abstract] OR "esophagogastrectom*"[Title/Abstract] OR "oesophagogastrectom*"[Title/Abstract] OR "Esophageal Neoplasms"[Mesh] OR "Esophagectomy"[Mesh] OR "Esophagoplasty"[Mesh]) AND ("Exercise Test"[Mesh] OR "Muscle Strength"[Mesh] OR "Motor Activity"[Mesh] OR "Muscle Strength Dynamometer"[Mesh] OR "Exercise Therapy"[Mesh] OR "Physical Endurance"[Mesh] OR "Physical Exertion"[Mesh] OR "Oxygen Consumption"[Mesh] OR "Physical Fitness"[Mesh] OR "Ergometry"[Mesh] OR "exercise"[Title/Abstract] OR "cpet"[Title/Abstract] OR "cpex"[Title/Abstract] OR "cpx"[Title/Abstract] OR "muscle strength"[Title/Abstract] OR "VO_2"[Title/Abstract] OR "walking"[Title/Abstract] OR "physical activit*"[Title/Abstract] OR "physical performance"[Title/Abstract] OR "fitness"[Title/Abstract] OR "physical endurance"[Title/Abstract] OR "physical training"[Title/Abstract] OR "resistance training"[Title/Abstract] OR "treadmill test"[Title/Abstract] OR "ergomet*"[Title/Abstract] OR "bicycle test"[Title/Abstract]). The complete search strategy for each database is included in Appendix I.

Two authors (LON and Jonathan Moran (JM)) reviewed all titles and abstracts and screened for eligibility. Both authors then independently reviewed full text articles. Any discrepancies that occurred were reviewed by a third author (Dr Emer Guinan (EG)).

1.5.2.3 Data extraction

Two authors (LON and JM) used a pre-defined data extraction sheet to record study characteristics and results. Data extracted included author, patient characteristics, treatment type, outcome of

physical performance, timing of outcome assessment, and exercise intervention if applicable. Authors of full texts were contacted by email if insufficient data was available in the full text.

1.5.2.4 Quality assessment of included studies

The methodological quality of the included studies was assessed using three different risk of bias tools. Prognostic studies (n=13) were assessed using the Quality in Prognostic Studies (QUIPS) tool (Hayden et al., 2013) (Appendix II), which assesses for risk of bias under the following domains; study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. RCTs (n=2) were evaluated using the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011) (Appendix III), which analyses for risk of bias in terms of sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Other non-randomised experimental studies (n=3) and the observational studies (n=7) were evaluated using the Cochrane Risk of Bias Assessment Tool for Non-Randomised Studies of Interventions (ACROBAT-NRSI) (Sterne JAC, 2014)(Appendix IV). This screens for bias due to confounding, selection of participants into the study, measurement of intervention, departures from the intended, missing data, measurement of outcomes, selection of the reported result, and overall bias.

1.5.3 Results

1.5.3.1 Identification and selection of studies

A total of 2629 papers were identified using the search strategy (2044 excluding duplicates). LON and JM excluded 2019 articles based on titles and abstracts. Any disagreements were resolved by EG. Twenty-five articles were included in the data extraction (Figure 1.9).

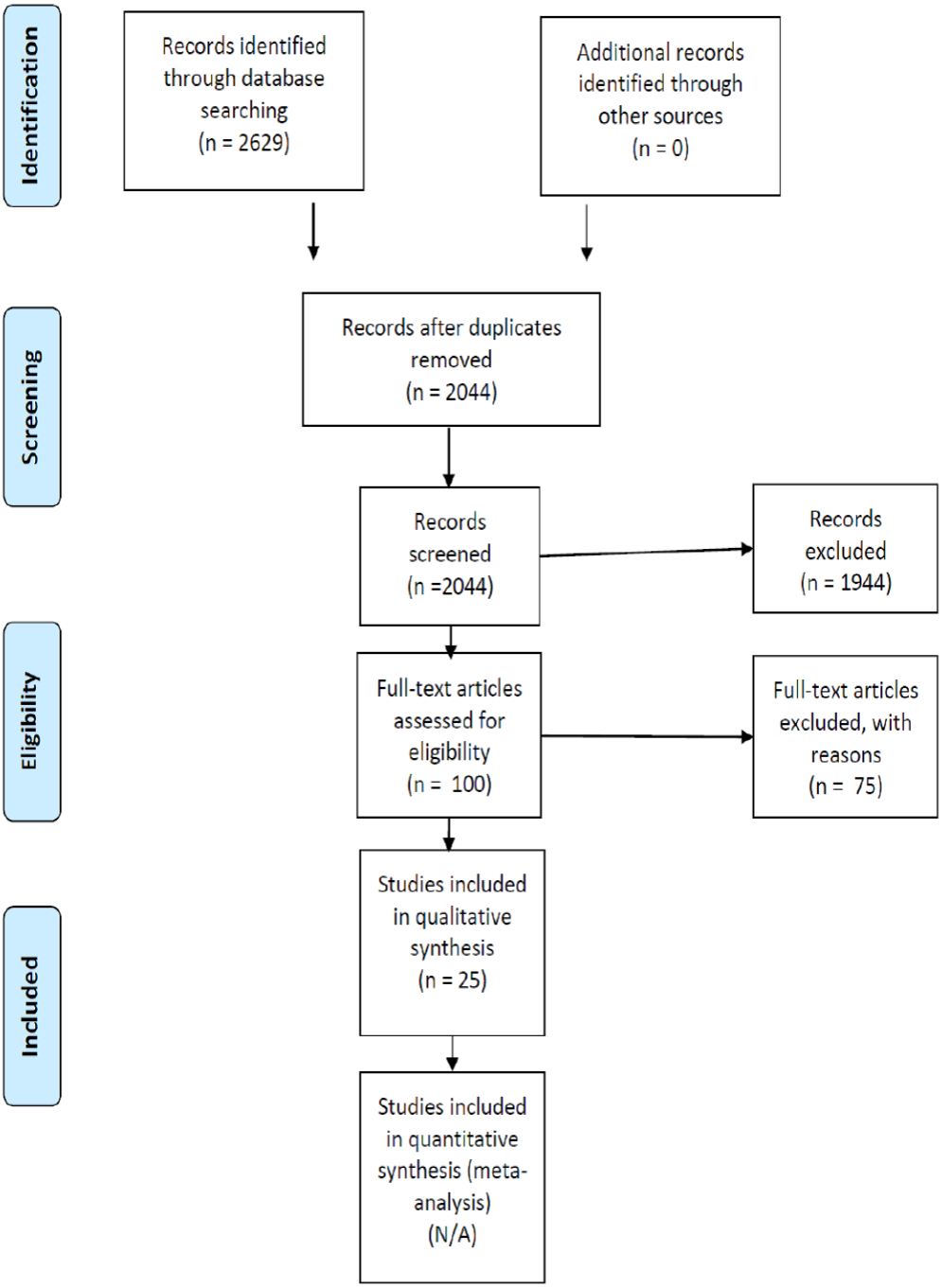

Figure 1.9 Prisma diagram

1.5.3.2 Study participants and characteristics

A total of 1897 patients were included. For the purpose of data analysis the papers reviewed were analysed in three categories; i) observational studies (n=8) (Table 1.9a) which assessed change in physical function at different time-points during the cancer journey ii) prognostic studies (n=13) (Table 1.9b) where the relationship between physical function and morbidity/ mortality risk post treatment was assessed, , and iii) experimental studies of exercise interventions to improve physical function in patients with oesophageal, junctional or gastric cancer (n=4) (Table 1.9c). A meta-analysis was not indicated due to the large heterogeneity of the included papers. Studies varied in terms of methodology (prognostic/ observational/ experimental), measure of physical function, physical function variables included in the analysis, timing of measurements, type of cancer, and cancer treatment being received (surgery/ chemo/radiotherapy).

Table 1-9 Demographic characteristics

1.9a Demographic characteristics of observational studies

Author (Date)	Treatment Type	Sample Size (n)	Age (years)	Gender	Location	Measure of Physical Function	Variables reported	Time-points
Inoue et al (2003)	Laparoscopic Partial Gastrectomy (LPG)	20	62.4 (12.8)	14 M, 6 F	Japan	Accelerometer Activity Levels	% recovery of pre-op activity levels	Pre + post LPG
	Open Distal Gastrectomy (ODG)	35	64.2 (13.6)	21 M, 14 F				Pre + post ODG
	Open Total Gastrectomy (OTG)	20	61.5 (14.3)	13 M, 7 F				Pre + post OTG
Taguchi et al (2003)	Oesophagectomy with Open Thoracotomy	29	61.7 (6.4)	24 M, 5 F	Osaka, Japan	CPET (cycle ergometer)	VO_2max, AT	Pre + post open oesophagectomy
	Oesophagectomy with Video Assisted Thoracotomy (VATs)	22	61.6 (9.3)	20 M, 2 F				Pre + post VATs oesophagectomy
Fagevik Olsen et al (2005)	Thoracoabdominal Oesophageal Resection	18	62.5 (Range: 20-76)	13 M, 5 F	Goteborg, Sweden	Stand-up test	Time to perform 10 stand ups	Pre-op, 2 years follow-up
						Hand Grip Force	Newtons	
Tatematsu et al (2013)	Neoadjuvant Chemotherapy	27	63.4 (6.8)	22 M, 5 F	Kyoto, Japan	Knee extensor muscle strength	Newton metres per kilogram	Pre + post NAC
						6MWT	6 minute walking	

							distance (metres)	
Tatematsu et al (2013)	Oesophagectomy	30	63.6 (7.1)	25 M, 5 F	Kyoto, Japan	Knee extensor muscle strength 6MWT	Newton metres per kilogram 6 minute walking distance (metres)	Pre + post oesophagectomy
Bowrey et al (2015)	Oesophagectomy or Gastrectomy + HEN	20	64.6 (8.0)	18 M, 2 F	Leicester, United Kingdom	HGS	HGS(kg)	Pre surgery, 6 weeks, 3 months, 6 months
	Oesophagectomy or Gastrectomy -HEN	21	63.1 (8.7)	18 M, 3 F				
Lund et al (2015)	Neoadjuvant Chemotherapy	23	62 (Range 46-71)	19 M, 4 F	Stockholm, Sweden	CPET (cycle ergometer)	Working capacity (Watts)	Pre + post NAC
	Neoadjuvant Chemoradiotherapy	17	66 (Range 56-75)	15 M, 2 F				Pre + post NCRT
von Dobeln et al (2016)	Neoadjuvant Chemotherapy and Oesophagectomy	53	63 (median)	45 M, 8 F	Sweden and Norway	CPET (cycle ergometer)	Max exercise capacity (Watt)	Pre + post NAC + 1-2 year follow-up
	Neoadjuvant Chemoradiotherapy and Oesophagectomy	44	64 (median)	37 M, 7 F				Pre + post NCRT + 1-2 year follow-up

Continuous variables e.g. age, presented as mean (standard deviation) unless otherwise stated.

Abbreviations: CPET= Cardiopulmonary Exercise Testing, VO_2max = Maximum oxygen consumption, AT = Anaerobic Threshold, 6MWT = 6 Minute Walking Test, HGS = Hand Grip Strength, HEN= Home Enteral Nutrition, LPG = Laparoscopic Partial Gastrectomy, ODG = Open Distal Gastrectomy, OTG = Open Total Gastrectomy, VATs = Video Assisted Thoracotomy, NAC = Neoadjuvant Chemotherapy, NCRT= Neoadjuvant Chemoradiotherapy

1. 9b Demographic characteristics of prognostic studies

Author (Date)	Treatment Type	Sample Size (n)	Age (years)	Gender	Location	Physical Function Measure	Variables reported	Outcome
Liedman et al (1995)	Laparotomy/Gastrectomy or Thoracoabdominal Resection	213	66 (Range37-88) / 65 (Range31-81)	1.7:1 M:F/ 4.0:1 M:F	Sweden	CPET (cycle ergometer)	Working capacity (Watts)	Morbidity, Mortality
Liedman et al (2001)	Pre-operative Radiochemotherapy and Oesophagectomy	29	63 (Range: 45-78)	25 M, 4 F	Goteborg, Sweden	CPET (cycle ergometer)	Working capacity (Watts)	PPC, Mortality
	Oesophagectomy	10	62 (Range: 46-76)	10 M, 0 F				
Nagamatsu et al (2001)	Oesophagectomy and Lymphadenectomy	91	59 (Range: 38-74)	88 M, 3 F	Fukuoka, Japan	CPET (cycle ergometer)	VO_2peak, AT	Morbidity
Murray et al (2007)	Oesophagectomy	51	64.3 (8.86)	NR	Sheffield, United Kingdom	SWT	Shuttle walk test distance (m)	Mortality
Forshaw et al (2008)	Oesophagectomy (Transthoracic Oesophagectomy (n=39) Transhiatal Oesophagectomy (n=39))	78	65 (Range: 40-81)	64 M, 14 F	London, United Kingdom	CPET (cycle ergometer)	VO_2peak, AT	LOS, Morbidity, Mortality
Chen et al (2011)	Transthoracic Oesophagectomy	52	60.6	48 M, 4 F	Taipei, Taiwan	HGS	HGS (kg)	LOS, Morbidity, Mortality
	Transhiatal Oesophagectomy	9	61	6 M, 3 F				

Feeney et al (2011)	Oesophagectomy	37	61 (9.5)	29 M, 8 F	Dublin, Ireland	Physical Activity Levels	Time/day spent inactive/light/ moderate/vig orous activity	PPC, LOS
Rawat et al (2011)	Oesophagectomy and Neoadjuvant Chemoradiotherapy	45	<50 years (12), >50 years (33)	29 M, 16 F	New Delhi, India	6MWT	Walking distance change (m)	Morbidity
Moyes et al (2013)	Oesophagogastric Cancer surgery	103	<65 (43%) 65-74(45%), >75 (12%)	83M, 25 F	United Kingdom	CPET (cycle ergometer)	VO_2peak, AT	PPC
Jack et al (2014)	Neoadjuvant Chemotherapy and Oesophagogastric Cancer Surgery	89	67.52 (10.04)	NR	United Kingdom	CPET (cycle ergometer)	VO_2peak, AT	Survival
Sato et al (2016)	Gastric Cancer Surgery	293	66 (Range: 33-85)	192 M, 101 F	Yokohama, Japan	HGS	HGS (kg)	Morbidity
van Egmond et al (2016)	Oesophagectomy	94	63.8(9.4)	74 M, 20 F	Amsterdam , Holland	HGS	HGS (kg)	POC, LOS, Mortality
Wang et al (2016)	Gastrectomy	255	65.14	190 M, 65 F	China	HGS/ Gait Speed	HGS (kg)/ Gait speed (m/s)	POC, LOS

Continuous variables (e.g. age) reported as mean (standard deviation) unless otherwise stated.

Abbreviations: NR= Not Reported in article, HGS=Hand Grip Strength, CPET= Cardio Pulmonary Exercise Testing, SWT = Shuttle Walk Test, 6MWT = 6 Minute Walking Test, VO_2peak = Peak Oxygen Consumption, AT = Anaerobic Thresholds, PPC = Post-operative Pulmonary Complication, POC = Post-operative complication, LOS= Length of Stay.

1.9c Demographic characteristics of exercise intervention studies

Author (Date)	Intervention Type	Sample Size (n)	Age (years)	Gender	Location	Physical Function Measure	Variables reported	Time-points
Chasen et al (2010)	MDT rehabilitation programme	53	63 (Range: 22-80)	42 M, 11 F	Canada	6MWT	6 minute walking distance (metres)	Pre + Post Intervention
Timmerman et al (2011)	Pre-operative exercise programme	5	62.6 (8.5)	4 M, 1 F	Nijmegen, Netherlands	CPET (cycle ergometer) Muscle Strength	VO_2max Newtons	Pre + Post Rehabilitation
Lococo et al (2012)	Post-oesophagectomy pulmonary rehabilitation program	8	70 (5.45)	6 M, 2 F	Rome, Italy	6MWT	6 minute walking distance (metres)	Pre + Post Rehabilitation
Xu et al (2015)	Walk and eat intervention during NCRT intervention Usual care control group	28 28	58.1 (9.6) 61.1 (9.0)	26 M, 2 F 26 M, 2 F	Taipei, Taiwan	6MWT HGS	6 minute walking distance (metres) Kilograms	Pre + Post Intervention

Continuous variables (e.g. age) reported as mean (standard deviation) unless otherwise stated.

Abbreviations: 6MWT= 6 Minute Walking Test, CPET= Cardiopulmonary Exercise Test, VO_2max = maximal oxygen consumption, HGS= Hand Grip Strength, NCRT = Neoadjuvant Chemoradiation Therapy

1.5.3.3 Results of risk of bias assessment of studies

Results of risk of bias assessment are detailed in Table 1.10. With regards to observational studies most were considered low risk of bias, however most had high risk of bias with regard to measurement of outcomes due to lack of blinding. Most prognostic studies had low to moderate risk of bias in most domains, however study confounding ranked moderate to high for all studies. With the interventional studies, all had moderate to serious risk of bias with exception of the study by Xu et al. (2014). The main bias inducing factors of the interventional studies included in this review were i) the lack of blinding of participants and assessors, and ii) the lack of randomisation to the intervention.

Table 1-10 Risk of bias assessment

1.10a Risk of bias for observational studies

Cochrane Risk of Bias Assessment Tool for Non-randomised Studies of Interventions (ACROBAT-NRSI)

Author (date)	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias in departures from intended	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Inoue et al (2003)	Moderate favours comparator	Moderate, favours comparator	Moderate, favours comparator	NI	Low	Moderate, favours comparator	Moderate, favours comparator	Moderate, favours comparator
Taguchi et al (2003)	Low	Low	Moderate	Low	Low	Moderate	Low	Low
Fagevik Olsen et al (2005)	Moderate	Moderate	Low	NI	Low	Low	Moderate	Moderate
Tatematsu et al (2013)	Low	Low	Low	Low	Low	Moderate	Low	Low
Tatematsu et al (2013)	Low	Low	Low	Low	Low	Moderate	Low	Low
Lund et al (2015)	Low	Low	Low	Low	Low	Moderate	Low	Low
von Dobeln et al (2016)	Low	Low	Low	Low	Moderate	Low	Low	Low

The Cochrane Collaboration's tool for assessing risk of bias

Author (date)	Sequence Generation	Allocation Concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Bowrey et al (2015)	Low	Low	High	Unclear	Unclear	Low

1.10b Risk of bias of prognostic studies

Quality in Prognostic Studies (QUIPS) Tool

Author (date)	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Liedman et al (1995)	Low	Low	Low	Low	High	Low
Liedman et al (2001)	Moderate	Low	Low	Low	Moderate	Moderate
Nagamatsu et al (2001)	Low	N/A	Low	Low	Moderate	Low
Murray et al (2007)	High	High	Moderate	Low	High	High
Forshaw et al (2008)	Low	Low	Low	Low	Moderate	Low
Chen et al (2011)	High	High	High	High	High	High
Feeney et al (2011)	Low	N/A	Low	Low	Moderate	Low
Rawat et al (2011)	Moderate	High	Moderate	Moderate	High	High
Moyes et al (2013)	Low	Low	Low	Low	Moderate	Low
Jack et al (2014)	Low	Low	Low	Low	Moderate	Low
Sato et al (2016)	Low	N/A	Low	Low	Moderate	Low
van Egmond et al (2016)	Low	Moderate	Low	Low	Moderate	Low
Wang et al (2016)	Low	Low	Low	Low	Moderate	Low

1.10c Risk of Bias of Exercise Intervention Studies

Cochrane Risk of Bias Assessment Tool for Non-randomised Studies of Interventions (ACROBAT-NRSI)

Author (date)	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias in departures from intended	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Chasen et al (2010)	Serious, favours experimental	Serious, favours experimental	Moderate, favours experimental	Serious, favours experimental	Serious, favours experimental	Moderate, favours experimental	Moderate, favours experimental	Serious, favours experimental
Timmerman et al (2011)	Moderate, experimental	Low	Low	Low	Low	Moderate, favours experimental	Moderate	Moderate
Lococo et al (2012)	Serious	Critical, favours experimental	Serious, favours experimental	NI	Serious, favours experimental	Serious, favours experimental	Serious, favours experimental	Serious, favours experimental

The Cochrane Collaboration's tool for assessing risk of bias

Author (date)	Sequence Generation	Allocation Concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Xu et al (2015)	Low	Unclear	Unclear	Low	Low	Low

1.5.3.4 Impact of Neoadjuvant Therapy and Surgery on Physical Function (Table 1.11)

This review included four studies (von Dobeln et al., 2016, Lund et al., 2015, Jack et al., 2014, Tatematsu et al., 2013a) which examined changes in physical function during NAC/NCRT for oesophago-gastric cancer. In a prospective cohort pilot study within a RCT, Lund et al. (2015) compared changes in cardiorespiratory fitness as measured by CPET in 40 patients with oesophageal cancer undergoing either NAC or NCRT (cisplatin and 5-fluorouracil +/- 40 Gy radiotherapy). Patients undergoing both treatment regimens experienced significant within-group reductions in cardiorespiratory fitness. The NAC group (n=23) experienced a mean change of -17W, 95% CI [-129,-5], p=0.03, and the NCRT group (n=17) experienced a mean change of -33W, 95% CI [-48,-18], p=0.001. The between group comparison was insignificant p=0.10. In another study by this research group in 97 patients with oesophageal cancer treated with NAC/NCRT von Dobeln et al. (2016) reported a reduction in cardiorespiratory fitness from 150 (125-175) W to 125 (103-153) W was observed. In a similar cohort of 39 patients treated with NAC for oesophago-gastric cancer participants experienced a mean reduction in AT from 14.5(3.8) ml/min/kg pre-NAC to 12.3(3.0) ml/min/kg post-NAC ($p<0.001$) and also a reduction in VO_{2peak} from 20.8(6.0) ml/min/kg pre-NAC to 18.3(5.1) ml/min/kg post-NAC ($p<0.001$) (Jack et al., 2014). While there is consistent evidence of a reduction in cardiorespiratory fitness during neoadjuvant therapy, walking tests of exercise performance are less sensitive to change. In a cohort of 27 participants undergoing NAC (cisplatin and 5-fluorouracil) for oesophageal cancer, Tatematsu et al Tatematsu et al. (2013a) observed no significant reductions in walking distance during a 6MWT, or in knee flexor strength from pre to post neoadjuvant treatment.

The impact of oesophago-gastric cancer surgery on physical function was explored in six studies (von Dobeln et al., 2016, Bowrey et al., 2015, Tatematsu et al., 2013b, Fagevik Olsen et al., 2005, Inouez et al., 2003, Taguchi et al., 2003). Acute post-operative changes in physical function were examined in two studies (Tatematsu et al., 2013b, Inouez et al., 2003). Tatematsu et al. (2013b) observed significant reductions in both walking distance achieved in a 6MWT (563.3(73.3) m vs 485.3(85.6) m, $p<0.001$), and knee flexor strength (2.3(0.6) Nm/kg vs 2.1(0.6) Nm/kg, $p<0.001$) from pre-oesophagectomy to post-oesophagectomy discharge (n=30). Inouez et al. (2003) examined the recovery time (time to return to pre-operative accelerometer measured physical activity levels) in 65 patients undergoing gastric surgery. Recovery time following open total gastrectomy (7.8(1.2) days) or open distal gastrectomy (6.6(2.1) days) was significantly longer than the recovery time post laparoscopic partial gastrectomy (2.8(0.9) days). Taguchi et al. (2003) examined the change in CPET measured cardiorespiratory fitness from pre-oesophagectomy to three months post-

oesophagectomy, following two different surgical approaches, open thoracotomy (n=29), and video assisted thoracoscopy (n=22). Cardiorespiratory fitness was significantly reduced at three months in both groups ($p<0.0001$) with both groups experiencing similar reductions in VO_2max and AT.

In a RCT comparing home enteral nutrition (HEN) (n=21) to no HEN (n=20), Bowrey et al. (2015) reported that patients who did not receive HEN had greater deficits in HGS when compared to baseline at six weeks (mean difference 3.9kg, 95% CI [1.6, 6.2]), three months (mean difference 2.5kg, 95% CI [-0.5, 5.6]), and six months post-surgery (mean difference 2.5kg, 95% CI [-1.21 to 6.1]). Fagevik Olsen et al. (2005), and von Dobeln et al. (2016) investigated the longer term impact of oesophagectomy on physical function. Fagevik Olsen et al. (2005) measured physical function using HGS and aerobic performance (time to perform ten sit-to-stand manoeuvres) in 18 participants at 2 years post-oesophagectomy. HGS was not measured at baseline (pre-oesophagectomy). Mean HGS at 2 years post-oesophagectomy was 313.6(80.8) Newtons. Compared to reference values, strength values for female participants HGS compared well to aged matched peers, whereas the male HGS were significantly lower than reference values ($p<0.001$). Time to perform 10 sit-to-stand (seconds(s)) was significantly better at two years follow-up compared to pre-oesophagectomy (23.05(5.4) s vs 30.6(15.5) s, $p<0.05$). von Dobeln et al. (2016) performed repeat CPETs at 1-2 years post-surgery in 15 patients who had completed NAC/NCRT and oesophagectomy, and cardiorespiratory fitness was significantly reduced when compared to baseline pre-treatment values (128W (115-170) to 107W (80-125), $p<0.001$).

This review indicates that a significant decline in physical function is observed in the first three months following oesophagectomy. However, little can be concluded regarding the longer term impact of oesophago-gastric cancer surgery on physical function due to the limited amount of literature.

Table 1-11 Results of observational studies examining the impact of oesophagogastric cancer treatment (surgery and or chemo/chemoradiotherapy) on physical function

Author (date)	Physical Fitness Measure	Time points measured	n	Impact of treatment on physical fitness
Inoue et al (2003)	Accelerometer measured activity Levels	Pre + post gastrectomy (first week)	20 25 20	Recovery time (Day that cumulative acceleration had recovered to more than 90% of the pre-operative level): **LPG:** 2.8(0.9) days **ODG**: 6.6(2.1) days **OTG**: 7.8(1.2) days
Taguchi et al (2003)	CPET	Pre + Post oesophagectomy	29 22	VO_2max (ml/min): **Controls Group:** Pre-op 1185.6(300.3) vs post-op 916.1(238.6) p<0.0001 **VATS Group:** Pre-op 1112.8 (220.12) vs post-op 835.6(233.0) p<0.0001 Anaerobic Threshold (ml/min): **Controls Group:** Pre-op 885.0(223.6) vs post-op 681.7(157.6) p<0.0001 **VATS Group:** Pre-op 817.1(161.2) vs post-op 662.1 (153.5) p<.0001 No significant difference between groups for VO_2max (p=0.865) or AT (p=.222)
Fagevik Olsen et al (2005)	HGS	2 years post-oesophagectomy	18	Mean HGS 313.6(80.8) Newtons Women's HGS compared well to reference values, men's HGS was lower than reference values p<0.001
	Time to perform ten stand ups	Pre-oesophagectomy + 2 years post-op		Pre-oesophagectomy 23.0(5.4)seconds(s) vs 2 years post-op 30.6 (15.5)s p<0.05
Tatematsu et al (2013)	6MWT	Pre + Post NAC	27	Pre-NAC 574.9(77.8)m vs post-NAC 565.1(75.3), p-value NR
	Knee ext strength			Pre-NAC 2.5 (0.5)Nm/kg vs post-NAC 2.4(0.5) Nm/kg, p-value NR
Tatematsu et al (2013)	6MWT	Pre+ Post oesophagectomy (day of discharge)	30	Pre-oesophagectomy 563.3(73.3)m vs Post-oesophagectomy 485.3(85.6)m p<0.001
	Knee ext strength			Pre-oesophagectomy 2.3(0.6) Nm/kg vs Post-oesophagectomy 2.1(0.6)Nm/kg p<0.001

Bowrey et al (2015)	HGS	Baseline, 6 weeks, 3 months, 6 months	21 20	Changes from base line (pre-op): **Intervention** 6 weeks post-op (n=20) -2.5(4.4)kg, 3 months post-op (n=18) -2.9(4.6)kg, 6 months post-op (n=16) -1.5 (4.4) kg **Control** 6 weeks post-op (n=21) -4.1(4.9)kg, 3 months post-op (n=21) -4.1(4.3), 6 months post-op (n=21) -2.0(4.1)kg
Lund et al (2015)	CPET	Pre + post NAC/NCRT	23 17	**NAC** Exercise Test (Watts) Mean (95% CI): Pre-NAC 150 (135-165) vs post-NAC 133 (115-151) p= 0.03 **NCRT** Exercise Test (Watts) Mean (95% CI): Pre-NCRT 151 (133-151) vs Post-NCRT 118(96-140) p=0.001 NAC mean change -17W (-29, -5), NCRT mean change -33W CI(-48, -18) interaction effect p=0.10
von Dobeln et al (2016)	CPET	Pre + Post NAC/NCRT and 1-2 years post oesophagectomy	97	Before treatment : Max exercise capacity(W) : 150 (125-175) , After neoadjuvant treatment 125(103-153) p<0.001 (n=65) Before treatment : Max exercise capacity(W) : 128 (115-170) , After 1-2 years 107(80-125) p<0.001 (n=15)

Abbreviations: NR= Not reported in Article, CPET = Cardiopulmonary Exercise Test, 6MWT =6 Minute Walking Test, LPG = Laparoscopic Partial Gastrectomy, ODG = Open Distal Gastrectomy, OTG= Open Total Gastrectomy, VATs = Video Assisted Thoracotomy, NAC = Neoadjuvant Chemotherapy, NCRT = Neoadjuvant Chemoradiotherapy.

1.5.3.5 Physical Function and Outcome post-oesophagectomy/ gastrectomy (Table 1.12)

The relationship between cardiorespiratory fitness as measured by CPET and outcome post-oesophagectomy/gastrectomy was investigated in six studies included in this review (Jack et al., 2014, Moyes et al., 2013, Forshaw et al., 2008, Liedman et al., 2001, Nagamatsu et al., 2001, Liedman et al., 1995). Three studies reported a strong relationship between lower cardiorespiratory fitness as measured by CPET and risk of developing a postoperative pulmonary complications (PPC) following oesophago-gastric cancer surgery (Moyes et al., 2013, Forshaw et al., 2008, Nagamatsu et al., 2001). In a study of 103 participants, Moyes et al. (2013) found PPCs occurred post-oesophago-gastric resection in 42% of patients with an AT of <9ml/min/kg compared with 29% of patients with an AT of > 9ml/min/kg but <11ml/min/kg, and 20% with an AT of >11ml/min/kg (p=0.04). And similarly, Forshaw et al. (2008) (n=78) reported significantly lower cardiorespiratory fitness (VO_{2peak}) in patients who developed a PPC post-oesophagectomy versus those that didn't (19.2(5.1) ml/min/kg vs 21.4(4.8) ml/min/kg, difference 2.3ml/min/kg, 95% CI [-0.06, 4.5], p=0.04). Nagamatsu et al. (2001) (n=91) also found VO_{2max} to be significantly lower in those that developed a PPC post-oesophagectomy (789(152) $ml.min^{-1}.m^{-2}$ vs 966(124) $ml.min^{-1}.m^{-2}$, p<0.001). In contrast, this review identified no associations between cardiorespiratory fitness and development of non-cardiopulmonary complications (Forshaw et al., 2008), and unplanned ICU admissions (Moyes et al., 2013, Forshaw et al., 2008).

Three studies reported an association between lower cardiorespiratory fitness as measured by CPET and mortality post oesophago-gastric resection (Jack et al., 2014, Liedman et al., 2001, Liedman et al., 1995). In an observational study of 213 participants who underwent gastrectomy, Liedman et al. (1995) reported risk of postoperative death increased steeply at a working capacity of 80W or below. In another study, the same authors Liedman et al. (2001), compared the prognosis of 29 patients treated with neoadjuvant chemoradiation (NCRT) and oesophagectomy to 10 controls scheduled for oesophagectomy only. Working capacity was significantly reduced preoperatively in those who had NCRT compared with surgery alone (p<0.001). Furthermore, no patients that achieved a working capacity of >100W pre-operatively died in the first three post-operative months. Jack et al. (2014) assessed cardiorespiratory fitness in 89 patients with oesophago-gastric cancer, and reported reduced VO_{2peak} and AT were associated with greater one year mortality in patients (n=39) that completed neoadjuvant chemotherapy (NAC) and surgery (p=0.014). Baseline cardiorespiratory fitness was not associated with 1-year survival in patients who received surgery alone (p=0.92), indicating the dual hit of NAC and surgery may increase the

mortality risk in those with lower baseline fitness. The results of these three studies suggest that lower cardiorespiratory fitness may be associated with greater risk of post-operative mortality.

The relationship between pre-oesophagectomy physical activity levels and PPCs was examined in one study (n=37) using accelerometry (RT3, (StayHealthy, Monrovia, CA, USA) (Feeney et al., 2011). Patients who developed a PPC spent significantly more time inactive preoperatively (20.0(1.5) vs 18.4(2.1) hours per day, p=0.037) when compared to those that did not experience a PPC, and spent significantly less time in moderate intensity activity (20(13.7) vs 36(20.7) minutes per day, p=0.03).

Performance during a structured walk test and outcome post oesophago-gastric surgery was explored in three studies (Wang et al., 2016, Rawat et al., 2011, Murray et al., 2007). Wang et al. (2016) reported significantly reduced gait speed in sarcopenic patients (n=32) (mean gait speed 0.80(0.38) m/s) undergoing gastrectomy compared to non-sarcopenic (n=223) (mean gait speed 1.05(0.21) m/s) ($p<0.01$). Sarcopenic patients also had a much higher rate of major complications ($p<0.01$). Rawat et al. (2011) reported that a ratio of 6MWT/vital capacity of greater than 4ft/litre was found to correlate with incidence of clinically symptomatic radiation induced pneumonitis at 9 months post-oesophagectomy. Murray et al. (2007) reported that in a population of 51 participants (mean pre-oesophagectomy 6MWT 489.33(144.23) m), there was a 0% one month mortality rate in those that achieved a pre-oesophagectomy 6MWT distance of >350m. No clear conclusions regarding walking performance and outcomes post upper-gastrointestinal surgery could be identified from this review.

This review identified conflicting evidence regarding the relationship between muscle strength as measured by HGS and outcomes post upper-gastrointestinal cancer surgery. Chen et al. (2011) investigated the use of HGS as a predictor of outcome in 61 patients scheduled for oesophagectomy. Weak HGS defined as <25kg was identified in 20 participants. Participants with weak HGS had a longer ICU stay (days) (12.75 vs 4.05, p=0.003), longer hospital stay (days) (32.3 vs 21.4, $p<0.003$), and higher mortality (7 vs 2, p=0.016) when compared to those with normal HGS. In contrast van Egmond et al. (2016) found no relationship between HGS and risk of post-operative complications in 91 patients undergoing oesophagectomy [OR 0.99; p=0.250]. Both Sato et al. (2016) and Wang et al. (2016) investigated the predictive ability of HGS in determining outcome post-gastric cancer surgery. Sato et al. (2016) reported the risk of post-operative mortality was significantly higher in patients with low HGS (n=54) when compared to patients with high HGS

(n=239) (p=0.004). Wang et al. (2016) found that sarcopenic patients (n=32) had significantly lesser HGS than non-sarcopenic patients (n=223) ($p<0.001$) and that sarcopenic patients were more likely to experience a major complication ($p<0.001$).

Table 1-12 Results of prognostic studies investigating the relationship between physical function and outcomes post-oesophagogastric cancer surgery

Physical Function Measure	Author (date)	Timing of Physical Function Measurement	n	Mean Physical Function (unless otherwise stated)	Results
Cardiopulmonary Fitness	Liedman et al (1995)	Pre-laparotomy/ gastrectomy/ thoraco-abdominal resection	132	Laparotomy/gastrectomy mean working capacity 100.9 Watts (Range 40-220)	Risk of postoperative death increased steeply at a working capacity of 80W or below.
			81	Thoracoabdominal resection mean working capacity 109.7 Watts (Range 40-190)	
	Liedman et al (2001)	Post diagnosis and pre-oesophagectomy	39	Working Capacity displayed in graph format only	No patients that performed >100W at their preoperative assessment died In the NCRT group, 3 patients died during treatment. The 26 remaining had a mean decrease in working capacity of 30W ($p<0.0001$) This decrease in working capacity was significantly more pronounced than the controls ($p<0.001$) 10 patients had a reduction of working capacity to less than 90W, of whom 6 died within 3 months postoperatively. The number of post-operative complications was comparable between groups.
	Nagamatsu et al (2001)	Pre-oesophagectomy	91	$VO_2max.m^{-2}$ ($ml.min^{-1}.m^{-2}$) Present 789(152) vs Absent 966(124) $p<.001$ $AT.m^{-2}$ ($ml.min^{-1}.m^{-2}$)	Cardiopulmonary complication rate: 86% in patients with a $VO_2max.m^{-2}$ of less than 699 $ml.min^{-1}.m^{-2}$ 44% in patients with a $VO_2max.m^{-2}$ of 700-799$ml.min^{-1}.m^{-2}$

				Present 488(121) vs Absent 436(138) p=0.12.	10% in patients with a $VO_{2max}.m^{-2}$ of 800-1099 $ml.min^{-1}.m^{-2}$ 0% in patients $VO_{2max}.m^{-2}$ >1100$ml.min^{-1}.m^{-2}$.
	Forshaw et al (2008)	Pre-oesophagectomy	78	VO_{2peak} 20.5(5.0) ml/min/kg, AT 13.9(2.9) ml/min/kg	Cardiopulmonary complications: **VO_{2peak} (ml/min/kg)** Present 19.2 (5.1) vs Absent 21.4(4.8) Difference(95% CI) 2.3(-0.06 to 4.5) p=0.04 **AT (ml/min/kg)** Present 13.2(3.1) vs Absent 14.4(2.6) Difference (95% CI) 1.2 (-0.09 to 2.6) p=0.07 Non-cardiopulmonary complications: **VO_{2peak} (ml/min/kg)** Present 20.4(5.2) vs Absent 20.7(4.3) Difference(95% CI) 0.27(-2.4 to 2.9) p=0.84 **AT (ml/min/kg)** Present 14.1(3.0) vs Absent 13.9(2.9) Difference(95% CI) 0.22(-1.3 to 1.8) p=0.77 Unplanned ITU admissions: **VO_2peak (ml/min/kg)** Present 18.9(5.1) vs Absent 20.8(5.0) Difference(95% CI) 1.9(-1.1 to 4.9) p=0.21 **AT (ml/min/kg)** Present 12.6 (3.2) vs Absent 14.2(2.8) Difference (95% CI) 1.6 (-0.12 to 3.3) p=0.07 An AT cut off of 11 mL/kg/min was a poor predictor of postoperative cardiopulmonary morbidity
	Moyes et al (2013)	Pre-oesophagogastric resection	108	VO_{2peak} 15.2 (5.3) ml/min/kg Mean AT 10.8 (2.8) ml/min/kg,	Cardiopulmonary complication occurred in 42% of patients with an AT of <9ml/min/kg compared with 29% of patients with an AT of >9ml/min/kg but<11ml/min/kg and 20% with and AT of >11ml/min/kg (p=0.04).

					Trend that those with AT<11ml/min/kg and a low VO_2peak had a higher rate of unplanned ICU admission.
	Jack et al (2014)	Pre-neoadjuvant chemotherapy Post-neoadjuvant chemotherapy	89	**Group 1 (no NAC)** (n=50) Baseline AT 13.4(2.3) ml/kg/min VO_2peak 18.9(4.2) ml/kg/min. **Group 2 (NAC)** (n=39) Baseline AT 14.5(3.8) ml/kg/min VO_2peak 20.8(6.0) ml/kg/min **Group 2 Post NAC:** AT 12.3 (3.0) ml/kg/min (mean difference 2.19 (95% CI 1.47 to 2.91). VO_2peak 18.3 (5.1) ml/kg/min (mean difference2.51 (1.55 to 3.47)	Decreased baseline VO_2peak at AT and peak associated with greater one year mortality in patients that completed NAC and surgery p=0.014. No association between 1-year mortality and baseline VO_2peak/ AT in those that received surgery only p=0.81.
Physical Activity Levels	Feeney et al (2011)	Pre-oesophagectomy	37	Inactive 18.9 (2.1) hours/day (h/day) Light activity 4.5 (1.8) h/day Moderate activity 0.5(0.2) h/day Vigorous activity 0.1(0.2) h/day	Post-operative Pulmonary Complication (PPC) n=10, Non PPC n=27 **Inactive:** PPC 20(1.5)h/day vs Non-PPC 18.4(2.1) h/day p<0.05 **Light activity**: PPC 3.5(1.4)h/day vs Non-PPC4.9(1.9) h/day p=0.037 **Moderate activity**: PPC 20(13.7) min/day vs Non-PPC 36(20.7) min/day p=0.03 **Vigorous activity:** PPC 6(12)min/day vs 6(12) min/day NS

Walking Performance Tests	Murray et al (2007)	Pre-oesophagectomy	51	SWT distance 489.22(144.23)m	Overall mortality 10%. No patient who walked >350m died. 5/8 patients who walked<350m died and 2 others remained in ICU at 30 days.
	Rawat et al (2011)	Pre-NACRAD, 1,3,6,9 months	45	NR	Changes in 6MWT distance correlated with changes in PFT values. p<0.001 6MWT/vital capacity (VC) values of <4ft/l had a correlation with incidence of clinically symptomatic RP at 9 months
	Wang et al (2016)	Pre-gastrectomy	255	Gait speed =1.03(0.24) m/s (median(IQR))	Sarcopenic (n=32) mean gait speed 0.80 (0.38)m/s , non-sarcopenic (n=223) mean gait speed 1.05(0.21)m/s p<0.001 Total major complications(n%) =46(18.0), sarcopenic =14(43.8), non-sarcopenic 32(14.3) p<0.001
Muscle Strength	Chen et al (2011)	Pre-oesophagectomy	52 9	Transthoracic Group mean HGS 29.1kg Transhiatal Group mean HGS 26.5kg	Weak HGS defined as >25kg Weak HGS (n=20), Normal HGS (n=41) Weak HGS ICU stay (days) 12.75 vs Normal HGS ICU stay(days) 4.05 p=0.003 Weak HGS Hospital stay(days) 32.3 vs Normal HGS Hospital stay(days) 21.4 p=0.003 Weak HGS mortality 7 vs Normal HGS Mortality 2 p=0.016
	Sato et al (2016)	Pre-gastric cancer resection	293	Median HGS 28.6 (11.2-75.5)kg	Low HGS (n=54) 22.2% mortality compared to high HGS (n=239) 11.3% morbidity (p=0.004)

	Van Egmond et al (2016)	Pre-oesophagectomy	92	Median (i.q.r) HGS = 42.5 (15.0) (% of predicted mean(s.d) =114.0(20.8)	HGS was not associated with POC after oesophagectomy [OR 0.99; p=0.250].
	Wang et al (2016)	Pre-gastrectomy	255	HGS 29.74(9.55)kg	Sarcopenic (n=32) mean HGS 19.94(7.83)kg , non-sarcopenic (n=223) mean HGS 31.14 (8.95)kg p<0.001 Total major complications(n%) =46(18.0), sarcopenic =14(43.8), non-sarcopenic 32(14.3) p<0.001

Abbreviations: NR =Not Reported in Article, VO_2max = maximum oxygen consumption, VO_2peak = peak oxygen consumption, AT = Anaerobic Threshold, HGS = Hand Grip Strength, 6MWT= Six Minute Walking Test, SWT = Shuttle Walk Test, PFT = Pulmonary Function Test, ICU = Intensive Care Unit, POC = Post-Operative Complication, RP = Radiation Pneumonitis, I.Q.R = Inter Quartile Range, SD=Standard Deviation, OR = Odds Ratio, NS=Not significant.

1.5.3.6 Impact of Exercise Interventions (Table 1.13)

Exercise interventions designed to improve or maintain physical function at different time points during the oesophageal or gastric cancer patient journey were investigated in four studies (Xu et al., 2015, Lococo et al., 2012, Timmerman et al., 2011, Chasen and Bhargava, 2010). Xu et al. (2015) implemented a randomised controlled trial which investigated the efficacy of a supervised walk and eat intervention during NCRT to maintain physical function. Physical function was assessed by walking distance during the 6MWT and HGS. When compared to the intervention group (n= 28), the control group (n=28) which received no intervention experienced a 100.0m, 95% CI [29.9-170.2], p=0.012 greater decline in 6MWT distance, and a 3.0kg, 95% CI [1.3, 4.9)], p=0.002 reduction in HGS post-NCRT. Timmerman et al. (2011) piloted a pre-surgery therapeutic aerobic exercise programme in 15 cancer patients (n=5 oesophageal cancer) to improve pre-operative exercise capacity as assessed by CPET. In patients with oesophageal cancer, VO_{2peak} improved by a mean of 6.22(2.38) ml/min/kg. Lococo et al. (2012) implemented a 4 week inpatient programme involving aerobic, resistance, and inspiratory muscle training post-operatively for eight oesophageal cancer patients. 6MWT distance improved significantly post-intervention (159.63(29.34) m vs 223.63(33.81) m, p=0.0117). Chasen and Bhargava (2010) prescribed an 8 week pilot multidisciplinary programme incorporating supervised exercise sessions in oesophago-gastric cancer survivors and found 6MWT walking distance improved from 384m to 435m (p=0.01). Details of the exercise interventions in each of the studies are presented in Table 1.14.

Table 1-13 Results of studies examining the effects of exercise interventions on physical function in oesophagogastric cancer

Author (date)	Physical Fitness Outcome	Time of Intervention	n	Results
Chasen et al(2010)	6MWT	Gastroesophageal cancer survivorship	22	6 min walk distance improved from 384 to 435m (p=0.01)
Timmerman et al (2011)	CPET	Pre-surgery	5	Cardio Respiratory Fitness VO_2 (ml/min/kg) Pre-rehabilitation 24.74(6.27) vs Post-rehabilitation 30.96(6.74), Mean change 6.22(2.38)
Lococo et al (2012)	6MWT	Post-surgery	8	Pre-rehabilitation 159.63(29.34)m vs 223.63(33.81)m p<.0117
Xu et al (2015)	6MWT	Neoadjuvant Chemotherapy	30	Intervention Group: Baseline 471.4(84.5)m, Mean change at completion (-18m (75.3))
			29	Control Group: 437(97.2)m, Mean change at completion (-118(160.5)m)
	HGS			Group difference in mean change 100.0 (29.9-170.2)(95% CI) p= 0.012 Intervention Group: Baseline 32.4(9.5)kg, Mean change at completion (-1.1(2.5)kg) Control Group: 31.8(8.5)kg, Mean change at completion (-4.1(4.0)kg) Group difference in mean change 3.0(1.3-4.9) (95% CI) p=0.002

Abbreviations: 6MWT= Six Minute Walking Test, CPET = Cardiopulmonary Exercise Test, HGS = Hand Grip Strength

Table 1-14 Details of exercise interventions

Author (date)	Duration of Intervention	Frequency	Intensity	Type of Exercise	Time	Supervised vs Unsupervised	Inpatient vs Outpatient	Group vs Individual	MDT Input
Chasen et al (2010)	8 weeks	2/7	NR	Therapeutic exercise to maintain or increase range of motion, endurance, and mobility training	NR	Supervised	Outpatient	Individual	Fortnightly visits to dietitian, occupation therapist, nurse, physician, other Allied Health Professionals.
Timmerman et al (2011)	4-5 weeks	2/7	65-85% HRR 60-80%1RM	30 -50 minutes of aerobic exercise using a stationary bike, cross trainer or treadmill. Resistance training of large muscle groups using weighted fitness equipment	2 hours	Supervised	Outpatient	Individual	N/A
Lococo et al (2012)	4 weeks	5/7	NR	Incremental exercise cycle ergometer, abdominal muscle activities, inspiratory resistive sessions, treadmill, UL + LL training, full arm circling	NR	Supervised	Inpatient	NR	Twice weekly education sessions on chest physio, pharmacology, dietary counselling, relaxation and stress management, energy conservation, breathing re-training.

Xu et al (2015)	4-5 weeks	3/7	5 minute warm-up followed by 20 minutes hallway walking	60% HR Max	25 mins	Supervised	Outpatient	NR	Weekly dietary advice from dietitian

Abbreviations: NR = Not Reported in Article, HR = Heart Rate, HRR =Heart Rate Reserve, 1RM =1 Repetition Max, UL =Upper Limb, LL =Lower Limb, N/A = Not Applicable.

1.5.4 Discussion of systematic review

The results of this review concur largely with the assumption that physical function deficits are likely to occur across the oesophago-gastric cancer journey. Although large scale conclusions are difficult due to the heterogeneity of the current literature base regarding physical function in oesophago-gastric cancer, some clear patterns of change in physical function, and associations with treatment outcomes were observed.

Firstly, both NAC and NCRT are associated with significant reductions in cardiorespiratory fitness (von Dobeln et al., 2016, Lund et al., 2015, Jack et al., 2014). Surgery is the treatment of choice for localised oesophageal cancer (Kidane et al., 2015) and is the only curative treatment for gastric cancer (Carcas, 2014). However, for locally advanced disease (Kidane et al., 2015, Carcas, 2014, Lordick et al., 2013, Cunningham et al., 2006), neoadjuvant treatment for oesophago-gastric cancer is standard of care, and this can lead to reduced physical function due to its effects on both the cardiovascular and respiratory systems, treatment-associated anaemia, increased oxidative stress, treatment related fatigue, reduced physical activity levels, and impaired nutritional status (von Dobeln et al., 2016, Lund et al., 2015, Jack et al., 2014). Although functional capacity as measured by the 6MWT appears to be unaffected during NAC (Tatematsu et al., 2013a), cardiorespiratory fitness as measured using the more sensitive measure of CPET, reduces significantly following both NAC and NCRT (von Dobeln et al., 2016, Lund et al., 2015, Jack et al., 2014, Liedman et al., 2001) in patients with oesophago-gastric cancer. Furthermore, a study with low risk of bias by Jack et al. (2014) reported that those with lower levels of fitness were actually less likely to complete NAC and that lower baseline fitness was associated with greater one year mortality, highlighting the need for high quality RCTs to examine the efficacy of exercise rehabilitation during NAC/NCRT to reduce physical decline (Xu et al., 2015)

Accordingly, rehabilitative interventions designed to maintain physical function during neoadjuvant treatment have considerable clinical potential. This review identified only one paper which prescribed a rehabilitative programme during neoadjuvant treatment for oesophageal cancer (Xu et al., 2015). There is emerging research, particularly in colorectal cancers that suggests that exercise during NAC/NCRT can prevent physical decline during treatment (Heldens et al., 2016, Morielli et al., 2016). In patients with oesophageal cancer, Xu et al. (2015) demonstrated that multidisciplinary rehabilitation involving exercise and dietary counselling has the potential to help minimize physical function deficits, and weight loss during NCRT. Weight loss, particularly sarcopenia is an important predictor of neoadjuvant treatment tolerance, and survival in

oesophago-gastric cancer (Awad et al., 2012), as weight loss has been associated with increased severity and incidence of chemotherapeutic toxicity (Yip et al., 2014, Awad et al., 2012). Therefore, there is clear justification for MDT rehabilitation programmes like the one implemented by Xu et al. (2015) during NAC/NCRT that aim to prevent both the weight loss and physical function deficits experienced during NAC/NCRT, in order to improve treatment completion rates and outcomes. However, the generalization of Xu et al. (2015) results to the global oesophago-gastric cancer population is limited as the majority of their participants were male with squamous cell oesophageal carcinoma, which is the more common pathology observed in the Asian population. Further high quality RCTs are required globally to determine the efficacy of multidisciplinary rehabilitation during neoadjuvant therapy for both squamous cell and adeno oesophago-gastric cancer.

Another point to highlight is the association between pre-operative physical function and outcomes post-operatively. Despite surgical advances, oesophago-gastric cancer surgery is still associated with a significant risk of post-operative morbidity and mortality (Moyes et al., 2013). CPET mimics the surgical stress conditions the cardiorespiratory unit experiences during surgery (Moyes et al., 2013), and is an established predictor of post-operative outcome following major thoracic and abdominal surgery (Moran et al., 2016). This review concurs with the findings of Moran et al. (2016) that the usefulness of CPET as a prognostic indicator in upper gastro-intestinal cancer remains unclear. The heterogeneity of the current literature base is perhaps a major contributing factor to this finding. Comparisons between studies were difficult due to the different exercise capacity outcomes reported e.g. VO_2max, maximum power etc. There was consistent evidence from three studies included in this review that lower cardiorespiratory fitness is associated with a higher risk of developing PPCs post oesophagectomy/gastrectomy (Moyes et al., 2013, Forshaw et al., 2008, Nagamatsu et al., 2001). However, the relationship between cardiorespiratory fitness and non-cardiopulmonary complications, unplanned ICU admissions, and mortality requires further investigation. Despite these conflicting findings, pre-habilitative exercise interventions which aim to improve pre-operative fitness and thus post-surgical outcome require exploration. A pilot study included in this review by Timmerman et al. (2011), examined the impact of a pre-operative exercise programme in 5 oesophageal cancer patients, and found significant improvements in cardiorespiratory fitness could be achieved pre-operatively. Preoperative inspiratory muscle training (IMT) to prevent PPCs post oesophago-gastric cancer surgery also seems to be a promising area of research (Valkenet et al., 2014).

A strength of this review is that synthesis was limited to studies measuring physical function objectively rather than subjectively. The strongest results with regards to using physical function as a predictor of surgical outcome were observed in the studies above that utilised the highly sensitive, gold standard of cardiorespiratory fitness assessment, CPET. The results of this review suggest that other measures of physical function such as the 6MWT, ISWT, HGS, and accelerometer measured activity levels have limited ability to predict outcome post-oesophagectomy/gastrectomy. While these tests are good indicators of functional capacity, that are easier, quicker, and more cost effective to implement in the clinical environment compared to CPET, they are unable to stress the cardiovascular system sufficiently to provide a valid and sensitive measure of true cardiorespiratory fitness (Sato et al., 2016, van Egmond et al., 2016, Wang et al., 2016, Chen et al., 2011, Feeney et al., 2011, Rawat et al., 2011, Murray et al., 2007). The results of this review indicate the usefulness of these more accessible means of physical function testing for patients with oesophago-gastric cancer to predict surgical outcome remains unclear.

Finally, this review examined the impact of oesophago-gastric surgery on physical function. Results demonstrate that significant reductions in physical function occur in the first three months post oesophago-gastric cancer surgery (Tatematsu et al., 2013b, Inouez et al., 2003, Taguchi et al., 2003), emphasising the need for early interventions to aid physical recovery. Enhanced recovery after surgery (ERAS) programmes aim to accelerate recovery and promote earlier discharge, and have been well established in the patients scheduled for colorectal surgery (Findlay et al., 2014). Although aspects of this multimodality approach still require validation, it is becoming a standard part of oesophago-gastric cancer surgery recovery. At present, despite low levels of evidence, the ERAS approach recommends day 1 post-op early mobilisation to promote return to physical function, and prevent delayed discharge following oesophagectomy/gastrectomy (Markar et al., 2015, Findlay et al., 2014, Mortensen et al., 2014). Structured early inpatient rehabilitation programmes have the potential to improve early post-operative physical function, aid recovery, and expedite discharge following oesophagectomy/gastrectomy. A pilot programme included in this review by Lococo et al. (2012) explored the feasibility of such programmes, and found a 4 week MDT led in-patient rehabilitation programme in 8 patients immediately post oesophagectomy could result in significant improvements in functional capacity as measured by 6MWT.

Clear conclusions regarding the longer term impact of oesophago-gastric cancer on physical function and the use of exercise interventions to aid recovery were difficult due to the sparsity of literature. Physical function is an area of QOL that patients report remains reduced at up to 1 year

post oesophago-gastric cancer resection (Scarpa et al., 2011). Often long term follow-up by objective measures is problematic due to the high disease mortality rate, and also difficulties in attempting to follow-up patients who are on continuing treatments. One study included in this review suggested a good physical recovery was possible (Fagevik Olsen et al., 2005), however a higher quality study by von Dobeln et al. (2016) reported that cardiorespiratory fitness remains reduced at 1-2 years following oesophageal cancer treatment. A recently published article by our research group concurs with the findings of von Dobeln et al. (2016). Gannon et al. (2017) reported exercise capacity was significantly lower in 25 patients >6 months post oesophagectomy compared to health age matched controls ($p<0.001$). Long term physical function deficits are likely due the high prevalence of malabsorption and malnutrition as a result of oesophagectomy/gastrectomy (Heneghan et al., 2015, Miller and Bozeman, 2012). Clinically significant weight loss (>10% loss in body weight) is prevalent in 48.9% of survivors of oesophago-gastric cancer at 24 months post-surgery (Heneghan et al., 2015).

Given the observed deterioration in physical function and nutrional deficits in oesophago-gastric cancer survivorship, there is considerable rationale for identifying strategies to address these impairments. Dietary and exercise interventions in cancer surviorship (predominanently breast and colorectal cancers) have been found to improve fitness, strength, diet quality, body composition, and also positively influence biomarkers associated with cancer and survival (Pekmezi and Demark-Wahnefried, 2011). There is a clear need for investigation of dietary and exercise interventions in oesophago-gastric cancer survivorship to target the long term weight and muscle loss, and physical function deficits experienced by survivors. Chasen and Bhargava (2010) highlighted the potential of such programmes, investigating the impact of an 8 week pilot programme of exercise, dietary counselling and MDT input in survivors of oesophago-gastric cancer. The intervention resulted in improved nutrition, functional capacity, and reduced global distress. However, the study had significant risk of bias, and accordingly the results should be considered with caution.

1.5.5 Limitations of systematic review

As discussed in section 1.5.3.2, the major limitation of the current body of evidence regarding physical functioning in oesophago-gastric cancer is the heterogeneity of the literature base, and, accordingly a meta-analysis is not possible at present. Sources of heterogeneity included; variations in cancer type, multiple measures of physical performance e.g. CPET, 6MWT etc., differences in reported outcomes for similar tests e.g. max power instead of maximum oxygen consumption, variance in timing of measurements, and differences in the type and timing of rehabilitative

interventions. The high risk of bias in some of the included studies should also be noted. Several prognostic studies ranked poorly in terms of bias due to confounding, with several studies failing to give consideration to confounders such as receiving NAC/NCRT or smoking and their impact on physical function and outcomes following surgery. Furthermore, with the exception of Xu et al. (2015) , the articles involving rehabilitative interventions to improve physical functioning exhibited high risk of bias, in particular in relation to blinding and randomisation. However, it is important to note when assessing the quality of exercise intervention studies that it is practically impossible to blind subjects to exercise interventions, but blinding of assessors should be routinely implemented.

1.5.6 Conclusion of systematic review

Neoadjuvant treatment (NAC/NCRT), although associated with increased survival, can result in deficits in cardiorespiratory fitness which may cause increased risk of morbidity and mortality post-operatively particularly in those with low baseline fitness. Pre-operative cardiorespiratory fitness is prognostic of development of PPCs post-oesophagectomy/gastrectomy but the association between cardiorespiratory fitness and other surgical outcomes requires further investigation. The evidence demonstrates significant deficits in physical function occur in the first three months post oesophagectomy/gastrectomy, however the long term impact of oesophago-gastric cancer on physical function remains unclear. Overall the effects of treatment for oesophago-gastric cancer on physical function require further investigation through high quality longitudinal studies. Given the increased focus on improving the quality of survivorship in oesophago-gastric cancer, there is clear rationale for multidisciplinary rehabilitation programmes which aim to improve physical function and quality of life, and therefore should be investigated by high quality randomised control trials.

1.6 Chapter 1 - Summary

Chapter 1 began with a complex overview of cancer of the oesophagus and stomach. Both are typical of more complex cancers, with each similarly presenting late, and cure may only be achieved with major surgery often in combination with difficult chemotherapy or chemo-radiation regimes (Reynolds et al., 2017). Curative treatment along with the effects of these diseases themselves may lead to a myriad of physical and nutritional side effects which may persist into survivorship.

Chapter 1 then examined physical functioning as an important target for rehabilitation in cancer survivorship. The systematic review (Section 1.5) provides consistent evidence that several domains of physical function including cardiorespiratory fitness, experience considerable decline throughout curative therapy for oesophago-gastric cancer, and this in turn may impact upon treatment response and the risk of treatment associated morbidity. Therefore, it follows that this deterioration may persist into survivorship. Preliminary publications in survival highlight considerable deficits in physical function (Gannon et al., 2017, von Dobeln et al., 2016). As previously discussed, physical function impairments can negatively impact on individuals, restricting their ability to perform their usual tasks of daily living. Patients with physical function impairments are less likely to engage in physical activity, further accelerating deficits in physical performance, which can have a devastating impact on HRQOL.

The systematic review (Section 1.5) also highlighted the dearth of rehabilitative research in oesophago-gastric cancer. Increasingly, emphasis is being placed in cancer research on strategies which aim to improve the quality of survivorship. This is addressed in the new 10 year National Cancer Strategy 2017-2026, which acknowledges the development of cancer survivorship programmes as a key area for cancer service improvement in Ireland (Healthy Ireland et al., 2017). Given this growing focus on quality of survivorship, there is a clear justification for interventions that aim to improve physical functioning in oesophago-gastric cancer survivorship.

To this end, this thesis explored the impact of a multidisciplinary rehabilitation programme in oesophago-gastric cancer survivorship. As aforementioned, survivors of oesophagogastric, experience significant nutritional compromise as a result of the cancer and its treatments, and issues with weight loss, sarcopenia, and malnutrition are highly prevalent among survivors. As unintentional weight loss is a significant concern for survivors of oesophago-gastric cancer, it is imperative when designing an exercise intervention, to utilise strategies to minimise the risk of

additional weight loss when patients increase their exercise participation. Accordingly, when designing the rehabilitation programme for this thesis, a supervised exercise intervention was combined with 1:1 dietary counselling, and group education sessions.

1.7 Thesis Aims and Objectives

Given the dearth of previous research regarding multidisciplinary rehabilitation in this cohort, the initial stage of this thesis involved a pilot study to establish the feasibility of the planned multidisciplinary rehabilitation programme (Study I), and the efficacy of the programme to improve cardiorespiratory fitness, the criterion measure of physical function, was then further explored in Study II. As little is known regarding the rehabilitative needs of patients in their first 6 months post-oesophago-gastric cancer surgery, Study III engaged qualitative methods to explore patient's perspectives of their early physical recovery. The overall aim of this thesis and the overall aims of each individual study are presented in Figure 1.10. Specific objectives of each study will be described in detail in the corresponding chapters.

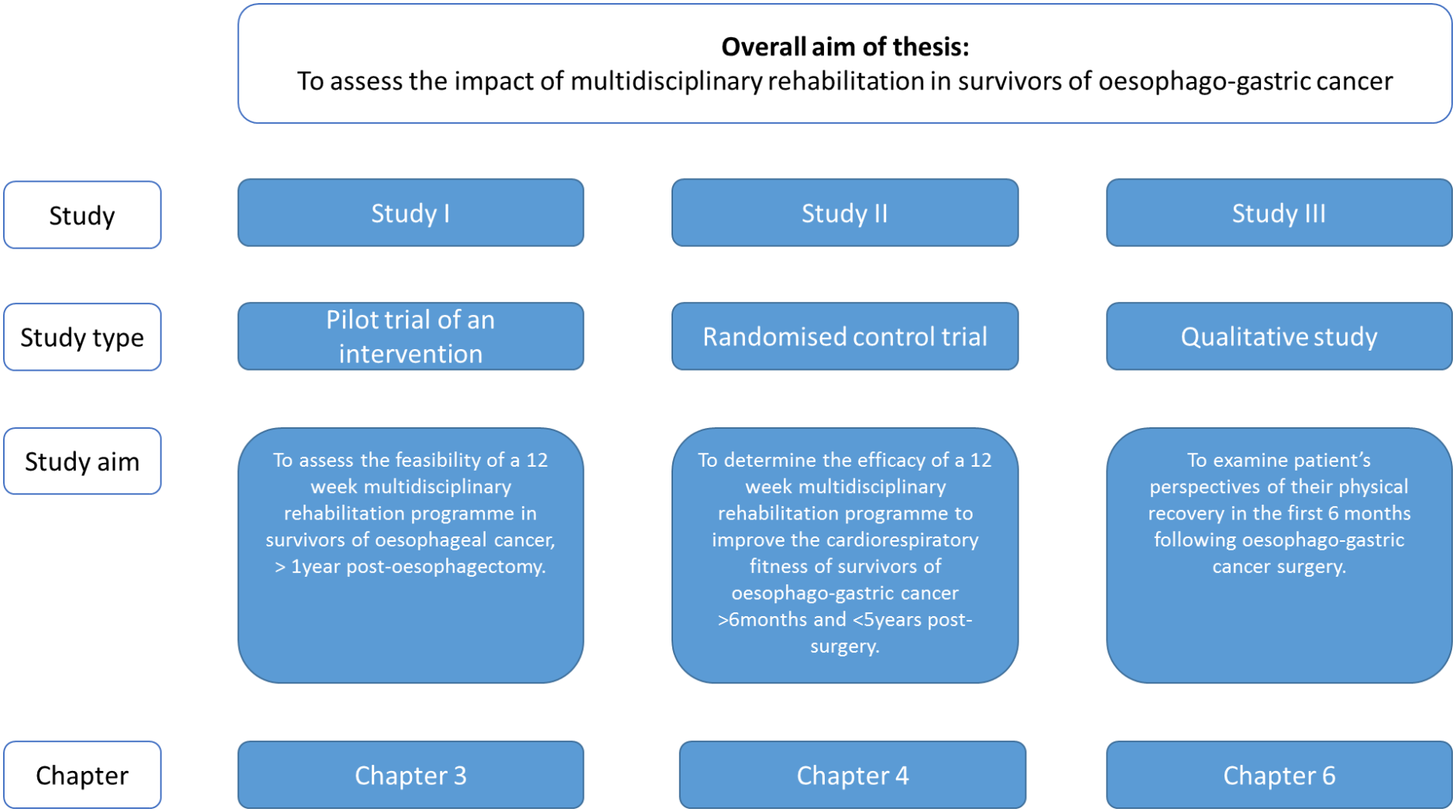

Figure 1.10 Thesis study designs and overall aims

Chapter 2 Quantitative Methods

2.1 Introduction

This chapter will describe the study designs, sampling methods, data analysis, and background to assessments used in the quantitative studies (Study I and Study II) of this thesis. A number of assessments are common to both Study I and Study II and subsequent chapters will refer back to the relevant sections in this chapter when describing individual study methodologies.

2.2 Background Research Methods

2.2.1 Study Designs

A variety of study designs may be utilised to examine clinical research questions. Studies may be observational or experimental in nature. The quantitative studies of this thesis (Study I and Study II) were experimental in nature, Study I was a pilot intervention study with a single-arm pre-post-test design, and Study II was a RCT. Both of these study approaches are discussed in the following sections.

Study I of this thesis was a pilot intervention study with a single-arm pre-post-test design. The purpose of a pilot study is to examine a study approach that is intended to be implemented in a larger scale study (Moore et al., 2011, Leon et al., 2011, Thabane et al., 2010). Van Teijlingen and Hundley (2001) identified several advantages of pilot studies. Pilot studies allow for preliminary testing of hypothesis, they facilitate a more precise testing of the hypothesis in the main study, they allow for identification of unforeseen issues that may arise in the implementation of the main trial, and they facilitate modification of the study protocol. Pilot studies also exhibit a number of limitations. Firstly, they are exploratory in nature, and, as such, power analyses are not used to calculate sample size, and instead it is acceptable for the sample size to be determined on pragmatics such as patient flow and budgetary constraints (Leon et al., 2011). Secondly, inaccurate predictions may be made on the basis of the pilot data. Pilot studies may give an indication that an intervention may be successful, but do not have the statistical power for assumptions to be made. Pilot studies may also be unable to predict issues that might arise in a larger, more heterozygous sample. Issues with contamination may also occur with pilot studies. Contamination can occur in two ways; i) pilot study data included in main study analysis,

and ii) pilot study participants are recruited again for the main study and new measurements taken. A further limitation of pilot studies is the risk of publication bias. Pilot studies are under-reported in published literature as publishers of journals exhibit preference for studies that demonstrate statistically significant results (Leon et al., 2011, Van Teijlingen and Hundley, 2001, Van Teijlingen et al., 2001).

Study II of this thesis implemented a RCT design, which is considered the gold standard of experimental study design (Stel et al., 2007, Wade, 1999). The RCT is the only type of study that can establish cause and effect, and, given the strength of the evidence from RCTs, a single good quality RCT can directly affect clinical decision making and patient care (Altman, 1996). Despite the clear strengths of the RCT study design, it is not without its' short-comings. Firstly, RCTs are inherently expensive to run. Secondly despite strong internal validity, RCTs may have poor external validity. Participants are required to meet a strict list of inclusion and exclusion criteria before acceptance onto a RCT, therefore this may limit the generalisability of the results to a wider population (Grimes and Schulz, 2002). Another limitation of RCTs is the risk of contamination between the experimental and control groups. For example in an exercise trial, participants in the control group might also increase their exercise participation, which may limit the effect size of results (Steins Bisschop et al., 2015). Other disadvantages of the RCT design include time constraints with regards to assessment of long term outcomes, and ethical issues. For example, it may be argued that it is unethical to deny a control group a treatment even if the efficacy of the treatment is unknown (Sanson-Fisher et al., 2007).

2.2.2 Sampling

An adequate sampling method and sufficient sample size are imperative in quantitative research. Statistical work in health research typically involves using a sample to draw conclusions from a larger population. With the exception of very rare conditions, it would be almost impossible or extremely expensive to test all patients with a particular condition (Carter and Lubinsky, 2016). To this end, it is necessary to utilise a means of reducing the number of participants in a study without increasing the risk of bias. Random or probability sampling is used to select a sample that is representative of the population that is under study without inducing bias (Bland, 2015, Riffenburgh, 2012). The probability that a member of the population will be chosen for the sample is purely by chance. The list from which the sample is to be drawn is referred to as the sampling frame (Bland, 2015, Carter and Lubinsky, 2016).

Although desirable, sometimes random sampling is not possible and non-probability sampling methods are used. Non-probability sampling methods cannot be fully reflective of a population and are intrinsically biased, however they can be useful in exploratory research such as pilot studies, and are widely used in rehabilitative research (Carter and Lubinsky, 2016). Examples of non-probability sampling methods include convenience sample, quota sampling, purposive sampling, and snowball sampling. Purposive and snow balling sampling are frequently used in qualitative research and as such will be discussed in Chapter 5, section 5.4.

Sample size calculation is a central issue when designing a study. Calculation of sample size is necessary to ensure sufficient data is collected to allow for the detection of statistically significant results, and it also helps prevent too many being recruited to a sample as this could lead to a waste of resources (Riffenburgh, 2012). The objective during sample size calculation is to find a balance between the risk of a type I or type II error occurring. A type I error (α) occurs when the null hypothesis is rejected when it is true. A type II error (β) occurs when the null hypothesis is accepted when it is in fact false (Bland, 2015).

Calculation of sample size involves specification of a number of parameters including:

- An estimate of the standard deviation is required to give indication of magnitude of chance variation.
- It must be specified whether a one or two-sided test is required.
- A significance level (α) i.e risk of type I error must be defined. Conventionally 0.05 and 0.01 are used.
- The minimal important difference (Δ) of the outcome of interest must be specified.
- The power (1- β) of the test must be determined. A powerful test is one which has a high probability of rejecting the null hypothesis when it is false. Most studies aim to have a power of 80% or higher (Riffenburgh, 2012, Mullins, 2003).

2.2.3 Reliability and Validity

2.2.3.1 Reliability

Reliability refers to the extent to which a scale produces consistent results, if the measurements are repeated a number of times. The reliability of a scale is defined as how free it is from random error (Pallant, 2016, Stokes, 2011). Errors in measurement may be random or systematic. Random errors are commonly a result of inattention or inaccuracy, whereas systematic errors are typically considered and minimised during the development of the measurement tool (Stokes, 2011). Several components of reliability may be examined including instrument, intra-rater, inter-rater, and intra-subject reliability.

Reliability can be quantified in terms of relative or absolute reliability (Carter and Lubinsky, 2016). Relative reliability can be reported as inter-rater reliability or intra-rater reliability, and internal consistency. Internal consistency is a measure of how well the items on a test measure the same construct or concept (Pallant, 2016). Relative reliability is measured with some form of correlation coefficient (Carter and Lubinsky, 2016). The relative reliability of categorical data can be analysed with percentage agreement and kappa coefficient. The kappa coefficient (κ) corrects for chance agreement between assessors, while the weighted kappa coefficient (κw) allows for partial agreement between raters. The relative reliability of continuous data can be determined using intra-class correlation coefficient (ICC), and is the most commonly reported reliability coefficient regarding the measures utilised in this thesis. The ICC is an indication of the variance due to error, and is usually presented along with κ and κw. ICCs are not without limitation. The ICC can be determined using different models, types, and measures which can result in different values, and lead to difficulty in selection of the appropriate method and also interpretation of ICCs. ICCs are also highly sensitive to subject variability which can lead to abnormally low or high ICC results (Lee et al., 2012).

Internal consistency can be determined using Pearson-product moment correlation coefficient (PPMCC). The PPMCC reflects the linear relationship between two sets of continuous data but not the agreement between the sets of data, therefore caution should be used when using the PPMCC to determine reliability. Crohnbach's alpha is a commonly used statistical expression of internal consistency, and is calculated from pairwise correlations between items to compare

individual items to the overall score (Stokes, 2011). Absolute reliability is defined as the standard error of the measurement (SEM)(Carter and Lubinsky, 2016). Absolute reliability indicates the degree to which a score varies on repeated measurements, and is used to calculate the minimal detectable change. The minimal detectable change is the smallest change that can occur in a measure that is not attributable to error (Stokes, 2011).

2.2.3.2 Validity

Validity of an outcome measure refers to how well the outcome measure, measures what it is designed to measure (Pallant, 2016). There are many different forms of validity including face, content, criterion, construct, and convergent. Validity coefficients are used to measure criterion validity and convergent validity (aspect of construct validity). Pearson-product moment correlation (PPMCC) is used for detection of a linear relationship between outcome measure data. Spearman's rank order correlation is used when there is no linear relationship. Construct and Content validity can be assessed using factor analysis. Factor analysis aims to simplify correlation matrices, and can be used to detect associations between outcome measures assessing similar constructs and highlight differences between outcome measures that assess different constructs (Stokes, 2011).

The reliability and validity of the methods used in the quantitative studies of this thesis will be presented and considered in terms of the coefficients and methods discussed above.

2.2.4 Principles of Data Analysis

The preliminary phase of data analysis involves the use of descriptive statistics and assessing the distributions of the data for normality. Categorical variables (derived from nominal or ordinal data) are analysed using frequencies or the percentage of frequencies and descriptive statistics for are presented in pie-charts and bar charts. Continuous variables (scale data) are described by a measure of central tendency (mean, median, mode) and a measure of variation around the mean/median (standard deviation/ inter-quartile range) and may be described graphically in histograms or boxplots. Descriptive statistics for continuous variables provide information regarding the distribution of scores. Skewness refers to the symmetry of the distribution about its mean, and kurtosis gives an indication of the peak of the distribution (Pallant, 2016).

The assumption of normality is a requirement of parametric statistical testing. A normal distribution refers to a distribution of scores that is symmetrical around the mean with a bell shaped curve. Visually normality can be assessed through analysis of the shape of distribution of histograms, and inspection of normal probability plots (Normal Q-Q plot). Statistically the Kolmogorov-Smirnov (K-S) test assesses for normality. A non-significant result ($p>0.05$) indicates a normal distribution. To facilitate parametric testing, distributions that are not normally distributed may be transformed. Common transformations include square root transformations, logarithm transformations, and inverse transformations. If the assumption of normality is still not achieved after transforming the data, an alternative, non-parametric test must be used. Normally distributed data is presented as mean (standard deviation) and non-normally distributed data is presented as median (inter-quartile range) (Pallant, 2016).

Statistical significance testing considers if an observed difference is sufficiently large enough to warrant concluding the existence of a systematic difference from a hypothesised value. With statistical testing, the hypothesis to be tested is referred to as the null hypothesis (H_0), it is assumed to be true unless the statistical test clearly demonstrates otherwise. The alternative hypothesis is labelled H_1. If H_0 is rejected the test is deemed to be statistically significant (Mullins, 2003). A p-value is an estimate of the probability of getting the observed results when the null hypothesis is true. The significance level of a test is referred to as alpha (α), and is the value below which the difference between groups is not likely due to chance. Alpha is most commonly set at 0.05. A p-value of >0.05 indicates a non-significant result and that the null hypothesis should not be rejected. A p-value of <0.05 indicates a statistically significant result and that the null hypothesis should be rejected. Alternatively, confidence intervals which represent the spread of the data can be used to determine statistical significance. Confidence limits are typically set at 0.95 (95% confidence interval). In statistical testing 95% confidence intervals which do not contain zero are deemed to be statistically significant at the 5% level (Gardner and Altman, 1986).

A number of statistical tests can be utilised to compare differences in continuous variables between groups. Parametric tests include the independent-samples t-test, the paired-samples t-test, and analysis of variance (ANOVA). The non-parametric alternatives to these tests are the

Mann-Whitney U Test, Wilcoxon Signed Rank Test, and the Kruskal-Wallis Test (Pallant, 2016, Bland, 2015, Riffenburgh, 2012). Study I of this thesis, presented in Chapter 3, utilised the paired-sample t-test, and the Wilcoxon Signed Rank Test to compare pre and post intervention measurements taken on the same group.

The statistical approach for Study II, presented in Chapter 4, involved the use of analysis of covariance (ANCOVA). ANCOVA is a useful tool in a two group study as it allows for control of pre-existing differences between the groups by using baseline scores as a covariate. There are a number of additional assumptions associated with ANCOVA. The assumptions of ANCOVA are normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariate (Pallant, 2016). Non-parametric data, was analysed using ranked Quade's test (Quade, 1967). Quade's test is not an inbuilt procedure in SPSS. However, it is easily performed in SPSS by following a three step approach, i) using the RANK procedure to rank the dependent variable and any covariates, ii) running a linear regression of the ranks of the dependent variables on the ranks of the covariate/s and saving the unstandardized residuals, and iii) performing a one way analysis of variance (ANOVA) on the residuals, using the grouping variable as a factor, the F test resulting is the Quade test statistic. Differences between groups at baseline in categorical variables were determined using the Chi-square test for independence and the Fisher's Exact Probability Test.

2.3 Measurement of Physical Functioning

Physical functioning refers to an individual's capacity to undertake tasks important in daily living (Brach, 2000). In this thesis, physical functioning was objectively assessed via measurements of physical fitness including tests of exercise capacity, muscle strength, and body composition, in Study I and Study II. Details of measures of exercise capacity, and muscle strength are discussed in the following section. The assessment of body composition is discussed separately in section 2.4.

2.3.1 Exercise capacity

Physical fitness is defined as "the ability to carry out daily tasks with vigour and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies"(Clarke, 1979). Physical fitness can be described in terms of health-related, and skill-related components (Caspersen et al., 1985). Health-related components of physical fitness include; cardiovascular endurance, body composition, muscular strength and endurance, and flexibility. Skill-related components of physical fitness include; agility, coordination, balance, power, reaction time, and speed (Caspersen et al., 1985). Exercise capacity is termed the maximal level of exertion an individual can sustain (Goldstein, 1990). Assessment of cardiorespiratory fitness is important as it has been found to be inversely proportional to risk of mortality, risk of cardiovascular disease, and health care costs (Weiss et al., 2004, Thompson et al., 2003, Myers et al., 2002). Furthermore, higher cardiorespiratory fitness is associated with greater functional capacity, glucose metabolism, bone health, psychological well-being, and health related quality of life (Thompson et al., 2003).

2.3.1.1 Measurement of exercise capacity

Exercise capacity is assessed for many clinical purposes. Clinically, exercise testing is primarily used as a diagnostic evaluation tool. For example it can be used to detect arrhythmias, and determine the severity of cardiovascular and respiratory diseases (Froelicher and Stahr, 2005, Weisman and Zeballos, 2001). Exercise testing is regularly used as a screening tool in advance of major surgery to determine suitability for surgery and predict risk of post-operative morbidity, mortality, length of hospital stay (Moran et al., 2016, ATS/ACCP, 2003). Assessment of exercise capacity also facilitates the formulation of exercise prescription based on a patient's true fitness (ATS/ACCP, 2003). Often exercise testing is used as an outcome measure to evaluate the success

of a treatment e.g. an exercise intervention (Froelicher and Stahr, 2005). Exercise testing also has a role in the education of patients regarding fitness status, and as a motivational tool to encourage greater participation in exercise (Hussey, 2005).

Measurement of maximal oxygen consumption (VO_2max) by a Cardiopulmonary Exercise Test (CPET) is the gold standard for measuring cardiorespiratory fitness (Moran et al., 2016, Hussey, 2005). VO_2max is the product of maximal cardiac output and arterial-venous oxygen difference (ACSM, 2010). VO_2max results can be expressed in litres per minute (l/min), however, clinically, interpretability is improved if VO_2max results are presented relative to the patient's body mass in millilitres per minute per kilogram (ml/min/kg)(Hussey, 2005). VO_2max is most accurately measured using open circuit spirometry which measures expired air composition and respiratory volume during an exercise test to exhaustion (ACSM, 2010, Hussey, 2005). Along with VO_2max open circuit spirometry also facilitates the calculation of the anaerobic threshold (AT). The AT has been defined as "during exercise, the level of oxygen consumption (VO_2) above which aerobic energy production is supplemented by anaerobic mechanisms causing a sustained increase in lactate and metabolic acidosis"(Wasserman, 1987).

Despite its' advantages, there is considerable cost involved in maximal exercise testing. Testing must take place in a suitable laboratory space, requires specialised testing equipment, and access to emergency-response equipment. Furthermore, maximal exercise testing can only be carried out by professional personnel highly educated in exercise science, and also may require supervision by medical personnel (ACSM, 2010, Hussey, 2005). In some circumstances maximal exercise testing might not be appropriate, for example in cancer research patients undergoing continuing treatments e.g. chemo/radiotherapy or those with advanced cancer undergoing palliative care (ACSM, 2010).

Alternatively, if maximal exercise testing is not feasible, a sub-maximal test can be used. Submaximal testing can be used to predict VO_2max and to assess functional performance (Noonan and Dean, 2000). Examples of predictive submaximal tests include the Modified Bruce Treadmill Test, the Astrand and Rhyming Cycle Ergometer Test, the Rockport Walking Test, and the incremental shuttle walk test (Hussey, 2005, Noonan and Dean, 2000). Submaximal functional performance tests include the six minute walking test (6MWT), 12 minute walking

Test (12MWT), and the timed up and go test (Hussey, 2005, Noonan and Dean, 2000). Although submaximal testing is less accurate in determining fitness than maximal testing, its' strengths include lower costs, it is quicker to perform, requires less equipment, it can be easily administered in a clinical setting, and is suitable for use with most clinical populations (ACSM, 2010, Hussey, 2005).

Study I and Study II of this thesis utilised both a maximal test of cardiorespiratory fitness (CPET) and a submaximal performance test (6MWT). Details of these methods will be discussed in the following section. A submaximal test was included in the protocol to allow for longer term follow-up analysis of physical functioning in participants that had previously enrolled in the RESTORE Phase I study at St James's Hospital. RESTORE Phase I aimed to longitudinally capture changes in physical functioning and nutritional status from the time of oesophageal cancer diagnosis until six months post-surgery.

2.3.1.2 Cardiopulmonary Exercise Testing

CPET is considered the most reliable and objective method of exercise testing (Agnew, 2010). CPET is generally considered a safe procedure with risk of death or life threatening complications reported as 2 to 5 per 100,000 tests (ATS/ACCP, 2003). In advance of a CPET, a number of aspects of testing must be determined including the equipment to be utilised and the test protocol. CPET testing is usually performed on either a cycle ergometer or a treadmill. Cycle ergometers typically require less space, and are less costly than treadmills. Cycle ergometers also facilitate easier monitoring of cardiovascular status as the recording of ECG and the monitoring of blood pressure is at less risk of disturbance due to movement or noise artefact (Hussey, 2005, ATS/ACCP, 2003). Cycling is also a safer form of exercise for participants that may have balance issues (Jones et al., 2008). The work performed (watts) during the CPET can be easier quantified with a cycle ergometer compared to treadmill test. However, during cycle ergometer testing the quadriceps are prone to discomfort and fatigue which can result in earlier test termination (Vanhees et al., 2005). Walking is for most people a more familiar and comfortable form of exercise, and therefore treadmill testing is often the preferred testing method (ACSM, 2010, Hussey, 2005, ATS/ACCP, 2003). However, VO_{2max} has also been found to be overestimated by 5-10% when assessed using a treadmill test (ATS/ACCP, 2003).

In terms of absolute reliability, a systematic review by Vickers (2003) established the standard error of measurement (SEM) for CPET as 2.58 ml/min/kg. Vickers (2003) reported that average SEM of a sample increases as the sample VO_{2max} increases, and that population and other protocol parameters such as exercise mode do not influence the SEM. The test re-test reliability of CPET by cycle ergometer in individuals with cardiac or respiratory disease was examined by Barron et al. (2014). A cycle ergometer CPET was found to have excellent test re-test ability at detecting peak VO_2 (ICC 0.95, 95% CI 0.94–0.97), and good test-test reliability at determining VO_2 at the anaerobic threshold (ICC 0.84, 95% CI 0.78–0.89). Age, gender, body mass index, disease aetiology, protocol change did not affect the test-retest reliability. The reliability of CPET specifically in cancer populations has been understudied. Scott et al. (2015) investigated the reliability of a treadmill CPET in men with prostate cancer, and found the test had excellent test-retest reliability for determining peak VO_2 (ICC 0.91, $r=0.92$, $p<0.001$). In contrast, Scott et al. (2015) also reported significant test-retest variability in peak VO_2, with significantly higher values achieved upon 2nd testing (27.0(5.6) vs 28.1 (5.3) ml/min/kg $p<0.05$), highlighting the need for caution with regards to interpretation of CPET data.

Protocols for CPET consist of the following; i) a low-intensity warm-up phase, ii) a continuous progressive exercise phase to maximum, and iii) a cool-down phase (Agnew, 2010, Hussey, 2005). The CPET protocol should be tailored for the individual participant (Jones et al., 2008). It is recommended that the intensity of the test is set such that the participant should reach their maximum in 6-10 minutes (Agnew, 2010). A single CPET generates approximately 5000 separate measurements, which provide a surplus of clinically meaningful data with regards to physical fitness. Cardiovascular measurements include heart rate, systolic and diastolic blood pressure, 12 lead ECG, and oxygen pulse (VO_2/HR). Respiratory parameters included respiratory rate, SPO_2, minute ventilation (VE), and tidal volume (VT). Metabolic gas exchange measurements include VO_2, VCO_2, respiratory exchange ratio (RER), and the anaerobic threshold (AT) (Agnew, 2010, Vanhees et al., 2005).

The use of CPET in oncology has to date largely been confined to the pre-operative assessment of lung cancer patients and cancer research. CPET has been found to be safe and feasible for most patients with cancer, even those with advanced disease (Jones et al., 2007). However, with

the growing importance of exercise interventions throughout the cancer continuum, CPET has been utilised more and more in cancer populations to aid development of, and assess the efficacy of rehabilitative exercise interventions (Jones et al., 2008). In oesophago-gastric cancer research CPET has been used to investigate the relationship between aerobic fitness and risk of post-operative complications (Moyes et al., 2013, Forshaw et al., 2008, Nagamatsu et al., 2001), and also to examine the effects of treatment (chemo/chemoradiotherapy/ surgery) on cardiorespiratory fitness (von Dobeln et al., 2016, Lund et al., 2015, Jack et al., 2014, Taguchi et al., 2003).

2.3.1.3 CPET measurement procedure

Safety Considerations

Patients with cancer may be considered a higher risk population with regard to CPET, due to the pathophysiological effects of the cancer and its treatment on the body's systems (Jones et al., 2008). For example, in oesophageal cancer, patients undergoing neoadjuvant chemotherapy experience systemic side effects including; immunosuppression, anaemia, and physiological toxicity, which can lead to skeletal muscle wasting, increased oxidative stress, and mitochondrial death (Jack et al., 2014). Therefore, it is important that patients with cancer undergo a thorough screening process in advance of a CPET. Prior to recruitment participant's in Study I and Study II were i) screened for contraindications to exercise testing and prescription, and ii) approval was also sought from the Upper Gastrointestinal Surgical team at St James's Hospital (SJH) regarding study suitability. At the start of their screening assessments participants were required to answer a battery of questions pertaining to their medical history. The battery included questions with regard to cardiovascular disease, respiratory disease, cancer history, diabetes, neurological conditions, orthopaedic conditions, and any other medical conditions that may impact on their ability to exercise safely. Participant's current medications were also recorded. Past medical history was also evaluated through review of the patient's electronic and paper-chart medical records.

All CPETs took place in the Wellcome Trust HRB Clinical Research Facility (CRF) at St James's Hospital (SJH). The CRF is a dedicated research centre within SJH which is staffed by highly skilled research nurses. Crash trolley facilities are available within the CRF, and the CRF is serviced by

the SJH crash team. All researchers working on this project were required to undergo basic life support (BLS) training in advance of commencing work in the CRF. All researchers were also required to complete a structured induction to the CRF which included instructions in the event of an emergency.

Prior to the CPET assessment of participant's cardiovascular status included measurement of resting blood pressure (BP)(sitting and supine), heart rate, and oxygen saturation levels. In the event of measurements which were deemed outside normal limits (resting systolic BP >200mmHg, and/or diastolic BP >110 mmHg, tachydysrhythmia or bradydysrhytmia (ACSM, 2010), and room air desaturation at rest <85% (ATS/ACCP, 2003)), the CPET was not performed and patients were referred on to appropriate follow-up services. Cardiovascular status was monitored throughout the test and in the immediate post test period until variables had returned to resting values. A cycle ergometer test was chosen as the method of testing as it facilitated more accurate monitoring of cardiovascular status during the exercise test.

There was a minimum of two researchers present for all CPETs. Each CPET was administered by a physiotherapist or exercise physiologist experienced in exercise testing. All CPETs were supervised by a physician from the Upper Gastrointestinal Surgical team at SJH. Participants also had a resting 12- Lead ECG (Philips PageWriter TC70 Cardiograph, USA) in advance of all CPETs. The CPET was not performed if any ECG abnormalities which are contraindications to exercise testing were observed and participants were referred on to appropriate follow-up services. The ECG was monitored throughout the test and an abnormal ECG reading e.g. ST or QRS changes, arrhythmias etc., would have resulted in test termination. The ECG was removed only once the participant was deemed to have returned to their pre-test status. Accordingly, any abnormalities occurring during or post-test would have resulted in patient referral to appropriate follow-up services.

Equipment Preparation

The measurement of oxygen consumption during all CPETs in Study I and Study II was performed using the $K4B^2$ equipment ($K4B^2$ User Manual, Cosmed, Italy). Prior to testing both the turbine and the gas analyser (sampling line) were calibrated. The turbine was calibrated using a 3 litre

calibration syringe, this was to update the gain of the flowmeter. Calibration of the gas analyser involved 3 separate tests:

1. Room Air Calibration. Room air was sampled and the baseline CO_2 analyser was updated to the gain of the O_2 analyser to match predicted atmospheric values.
2. Reference Gas Calibration. A gas of known composition (5% CO_2, 16% O_2,) was sampled from a cylinder and updated baseline and gain of analysers to match predicted values of gases.
3. Delay Calibration. Requires the tester to breath in and out of the device. This measures accurately the time necessary for gas to pass through the sampling line.

Participant Preparation

Participants were instructed to wear light clothing suitable for exercise for their assessment. Heart rate was monitored using the 12 lead ECG during the CPET. Leads were secured using easy tear medical tape. The K4B^2 was secured to the participant using a harness. Participants were sized for correct mask and strap size. The height of the cycle ergometer (COSMED ergoline GMbH, Germany) was adjusted to a suitable height for each participant. The testing protocol was explained to participants prior to commencing the test. The protocol for Study II initially included blood lactate measurement at rest, 4 minutes into the test, and test completion, using a lactate monitor (Lactate Plus, Lactate Meter, NovaBiomedical, UK), however due to equipment failure and inaccuracies, this data was not used in the analysis.

Testing Procedures

Testing commenced with a 3 minute warm-up/ familiarisation period during which participants cycled without resistance on the cycle ergometer. Following the warm-up period, the main test began. The test increments were determined using the formula implemented by Agnew (2010) (Figure 2.1). Tests began at a power of 10-20 Watts and increased by 10-20 Watts per minute. Heart rate was recorded every minute from the ECG. Blood pressure was assessed every 4 minutes manually using a sphygmomanometer (Welch Allyn) and stethoscope. The test was terminated when participants had reached their max (VO_2 plateau, HR_{max} exceeded, RER >1.2), or when participants requested to stop due to physical difficulties such as dizziness, shortness of breath, leg fatigue, or musculoskeletal pain. Following termination of the test participants

were required to complete a 3 minute cool-down cycle without resistance. Participants were then allowed to rest and cardiovascular status was monitored until measures returned to resting levels.

$$Work\ rate\ increment\ (Watts.min^{-1}) = \frac{peak\ VO2 - VO2\ unloaded}{100}$$

Peak VO_2 ($ml.min^{-1}$) men = height (cm) - age (years) x 20

Peak VO_2 ($ml.min^{-1}$) women = height (cm) –age (years) x 14

VO_2 unloaded ($ml.min^{-1}$) =150 + [6 x weight (kg)]

Figure 2.1 Formula used to determine work rate increments (Agnew, 2010)

Data Analysis

Data analysis was performed using the COSMED K4B^2 software. The software utilises programme algorithims and presents measured data to the specifications of the American Thoracic Society (ATS) and European Respiratory Society (ERS) (COSMED, 2003). The software also allows for detection of the anaerobic threshold (AT) via the 'Modified V-Slope Method'. During an incremental exercise test the net increase in lactic acid production results in an increase in the rate of VCO_2 relative to VO_2. Calculation of the AT by the 'Modified V-Slope' method involves the plotting of VCO_2 vs VO_2. The point at which VCO_2 begins to increase more rapidly than VO_2 is identified as the anaerobic threshold (Sue et al., 1988, Beaver et al., 1986).

2.3.1.4 The Six Minute Walk Test (6MWT)

The 6MWT is a submaximal exercise performance test. It is a simple, self-paced test, which calculates how far an individual can walk on a hard, flat surface in 6 minutes (O'Neill et al., 2005). The test was initially developed in the 1960's by Balke (1963) to assess functional capacity.

Unlike CPET the results of the 6MWT do not identify the nature of exercise limitation, however as most activities of daily living are performed at submaximal levels it does give a good indication of functional capacity. It should therefore not be seen as an alternative to CPET but rather a complement to it (ATS, 2002). As discussed in Chapter 1 (section 1.5) the literature has identified that there may be a poor correlation between assessment of maximal exercise capacity and functional performance as measured by 6MWT in oesophageal cancer, particularly during neoadjuvant treatment where significant reductions in cardiorespiratory fitness as measured by CPET have been observed (von Dobeln et al., 2016, Lund et al., 2015, Jack et al., 2014), however no studies have reported significant reductions in 6MWT distance during this time-period (Tatematsu et al., 2013a). Accordingly, the 6MWT was used in conjunction with CPET, in order to examine the effect of the intervention on functional performance.

Clinically the 6MWT is used in chronic lung disease to assess for exercise induced desaturation, and across many medical conditions to quantify exercise capacity and to analyse the effects of treatment (medical or exercise interventions) on functional capacity (O'Neill et al., 2005, ATS, 2002). The 6MWT has developed from a tool that was used primarily in lung and cardiac disease, to a tool that has been validated for use in many clinical populations including older adults (Rikli and Jones, 1998), Alzheimer's disease (Ries et al., 2009), neurological conditions including stroke and muscular dystrophy (McDonald et al., 2013, Billinger et al., 2012), and type II diabetes (Alfonso-Rosa et al., 2014). More recently Schmidt et al. (2013) found the 6MWT, to not only be safe and feasible, but a reliable and valid measure of functional capacity in patients with cancer. They reported the intraclass-correlation coefficient (ICC) for the test-retest reliability of walking distance in the 6MWT for cancer patients as r=0.93 (95%CI 0.86-0.97, p<0.001) and the coefficient of variation (CV) was 3%. The validity of the 6MWT was investigated by comparing distance walked to different objective and subjective measures of exercise or functional capacity. Schmidt et al. (2013) reported significant correlations between 6MWT distance and exercise capacity (VO_2peak r=0.67), maximum workload (W_{max} r=0.70), perceived physical function (r=0.55), and age (r= − 0.52), (all p<0.001). In oesophago-gastric cancer research, the 6MWT has been used to determine the efficacy of pilot rehabilitative interventions (Xu et al., 2015, Chasen and Bhargava, 2010), and also to evaluate the effects of curative treatment (neoadjuvant chemotherapy and surgery) on functional capacity (Tatematsu et al., 2013a, Tatematsu et al., 2013b).

2.3.1.5 6MWT measurement procedure

Safety Procedures

All participants in Study I and Study II completed the baseline medical screening and successfully completed a CPET prior to completing the 6MWT. Resting heart rate, blood pressure, oxygen saturation along with the rate of perceived exertion (RPE) (BORG Scale) (Appendix V) were assessed in sitting prior to commencement of the 6MWT. All pre-screening outcomes were considered contraindications to the 6MWT in the presence of an abnormal value.

Equipment and Participant Preparation

The 30 metre course was mapped out on a hospital corridor within the CRF using 10 cones placed at 3 metre intervals. A portable non-invasive oximeter (Fingertip Pulse Oximeter, ChoiceMed, Beijing, China) was placed on participants fingers to monitor heart rate and oxygen saturation levels during the 6MWT.

Testing Procedures

All 6MWT were performed in line with the ATS Guidelines (ATS, 2002). Participants were required to walk up and down the 30m course for 6 minutes. Prior to starting the test standardised instructions were given as per the ATS (2002) as follows: *'The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway, Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop and to rest a necessary. You may lean against the wall while resting but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I am going to show you. Please watch the way I turn without hesitation'.* The tester then demonstrated one lap. The tester than delivered the final standardised instructions; *'Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now or whenever you are ready. '*

The following standardized instructions were delivered during the test;

Time remaining	Instruction to patient
5 minutes	*You are doing well. You have 5 minutes to go*
4 minutes	*Keep up the good work. You have 4 minutes to go*
3 minutes	*You are doing well. You are halfway done*
2 minutes	*Keep up the good work. You have only 2 minutes left*
1 minutes	*You are doing well. You have only 1 minute to go*
15 seconds	*In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you.* *Stop.*

In the event of a participant stopping for a rest during the test the following instruction was given;
'*You can lean against the wall if you would like; then continue walking whenever you feel able.'*

During the test the number of laps completed were recorded on the case report form. Heart rate, oxygen saturation, and RPE were recorded at each minute. The test was terminated when the 6 minutes were complete or if the patient stopped the test due to physical symptoms such as shortness of breath, dizziness or fatigue, or if patients had abnormal heart rate or oxygen saturation levels during the test. Blood pressure, heart rate, and oxygen saturation levels were then monitored until they returned to resting levels. The primary outcome was distance travelled in 6 minutes.

2.3.2 Muscle strength

Muscle strength refers to the amount of force a muscle can exert during a contraction (Taylor and Fletcher, 2013). Muscle strength can be assessed statically or dynamically. Static strength is referred to as isometric strength. During an isometric contraction the muscle contracts but the joint angle or muscle length do not change. Dynamic muscle strength can be measured through assessment of isotonic or isokinetic contractions. In an isotonic contraction, the tension of the muscle is kept constant, as the muscle length changes. There are two types of isotonic contractions, concentric and eccentric. During a concentric contraction, the muscle actively shortens whereas during an eccentric contraction, the muscle actively lengthens. Isokinetic

contractions differ to isotonic contractions in that the muscle contracts through its full range, as velocity changes (ACSM, 2010).

Measurement of muscle strength is particularly important in patients with cancer, as both the cancer and its' treatments can result in significant loss of body weight including a loss of skeletal muscle mass (Santilli et al., 2014). In cancer, muscle loss is likely due to a combination of sarcopenia and cancer cachexia. Loss of skeletal muscle mass and strength is termed sarcopenia (Stene et al., 2013, Muscaritoli et al., 2010). Cancer cachexia has been defined as 'a multifactorial syndrome characterized by severe body weight, fat and muscle loss and increased protein catabolism due to underlying disease' (Muscaritoli et al., 2010). Low muscle mass is a significant prognostic indicator of chemotherapeutic toxicity, and survival in breast, colorectal, and non-Hodgkin lymphoma cancers (Rier et al., 2016). Loss of muscle mass is particularly pertinent in cancers of the oesophagus and stomach, as nutritional compromise can further accelerate weight loss. In oesophageal cancer loss of muscle mass has been identified as prognostic of survival (Harada et al., 2016). As loss of muscle mass is closely associated with muscle strength and functional capacity, muscle strength has become an important assessment in oesophago-gastric cancer.

2.3.2.1 Measurement of muscle strength

Isokinetic testing is a valid and reliable method of muscle strength testing and is considered the reference standard for other methods of strength testing. Isokinetic testing measures peak muscle force using computerised equipment that allows for control of the velocity of joint rotation. However, as isokinetic testing is expensive, and consequently equipment is not widely available, alternative methods of strength testing are employed frequently in research (Stark et al., 2011, ACSM, 2010). In non-laboratory settings the one-repetition maximum (1RM) is considered the gold standard of dynamic strength testing (Seo et al., 2012). 1RM refers to the greatest force that can be generated in one contraction and is determined by the maximum weight (resistance) that can be moved through the full range of motion (ACSM, 2010). Often 1RM testing is not feasible due to the size of the equipment involved. Alternatively, in both the clinical and research setting, isometric muscle strength is determined using hand held dynamometry. Hand held dynamometers are low cost, portable and convenient devices, which

have been found to have strong reliability and validity in determining muscle strength (Mentiplay et al., 2015).

Isokinetic muscle testing was not available in the CRF at SJH, so in this thesis muscle strength was determined using isometric and isotonic methods. Isometric hand grip strength (HGS) was determined using hand held dynamometry in Study I and Study II. Isotonic strength was assessed in Study II using a 1RM leg press test. These methods will be discussed in the following sections.

2.3.2.2 Hand grip strength (HGS)

HGS is a widely-used method of assessing strength as it is a convenient and robust tool which gives a good indication of overall muscle strength (Chen et al., 2011). Clinically HGS is used to characterise muscle strength and results may be quantified by comparing to age and sex defined normative values (Spruit et al., 2013). HGS is a useful tool as it has been found to correlate strongly with other outcomes of clinical interest including muscle mass, physical function, bone density, frailty risk, and nutritional status (Bohannon, 2015, Chen et al., 2011). Furthermore, weak HGS has been found to be a strong predictor of cause specific (cardiovascular disease and respiratory disease) mortality and total mortality (Bohannon, 2015, Rantanen et al., 2003, Rantanen et al., 2000). Low HGS is also associated with increased length of hospital stay (Bohannon, 2015).

Due to the strong association between HGS, body composition, and nutritional status, HGS is a well suited outcome tool for the assessment of patients with oesophago-gastric cancer who are often nutritionally compromised. Clinically, HGS is used as part of a screening battery for sarcopenia in oesophago-gastric cancer (Bohannon, 2015). In oesophago-gastric cancer research HGS has been used to predict surgical outcomes (Wang et al., 2016, Sato et al., 2016, van Egmond et al., 2016), to assess the effectiveness of rehabilitative interventions (Bowrey et al., 2015), and assessment of muscle strength across the cancer continuum (Fagevik Olsen et al., 2005) (Chapter 1, section 1.5).

HGS was assessed in this thesis using a Jamar plus digital hydraulic hand held dynamometer. The Jamar dynamometer is the most widely cited in the literature, and is the gold standard to which other dynamometers are compared to. Once calibrated correctly, and performed using the standardised positioning and instructions recommended by the American Association of Hand Therapists (Fess, 1992), the Jamar is considered to have good to excellent test-retest reliability ($r>0.80$) and excellent inter-rater reliability ($r=0.98$) (Kim and Shinkai, 2017, Roberts et al., 2011, Mathiowetz, 2002). Trutschnigg et al. (2008) investigated the precision and reliability of the Jamar in determining HGS in individuals with lung and gastrointestinal cancer, and reported the Spearman's rank correlation coefficient as 0.966, and percent of coefficient of variation (%CV) as 6.30. A further strength of the JAMAR dynamometer is that there is an abundance of normative data that results may be compared to, for example healthy Caucasians (Gunther et al., 2008), Irish adults (Kenny et al., 2013), British adults (Spruit et al., 2013), and German adults (Steiber, 2016).

2.3.2.3 HGS measurement procedure

HGS was measured in Study I and Study II using a hand-held dynamometer (Jamar plus digital dynamometer, China) (Figure 2.2). This dynamometer is calibrated annually. The Jamar dynamometer weighs approximately 600g. It has a screen display which can be set to display results in either kilograms or pounds. The handle position of the Jamar can be adjusted. There are a choice of five handle positions, but the second position is considered the most reliable (Roberts et al., 2011). Accordingly, all HGS measurements for this thesis were taken at the second handle position.

Figure 2.2 Jamar plus digital dynamometer

HGS testing was performed as per the American Society of Hand Therapists recommendations (Fess, 1992). Participants were required to sit-upright in a chair, both feet touching the ground with hips and knees at 90^{o}. Shoulders were adducted and neutrally rotated, elbows were flexed at 90^{o}, forearm was held in a neutral position, and the wrist was held in slight extension (0^{o}-30^{o}). Participants were instructed to squeeze the dynamometer as hard as possible using one brief maximal contraction avoiding extraneous body movement. Participants repeated the test three times in each hand. One minutes rest was held between each attempt. All trials were recorded in the case report form and the best score was utilised for data analysis.

2.3.2.4 1RM

As previously stated 1RM testing is considered the gold standard of assessing muscle strength in the non-laboratory setting. It is well utilised by both fitness and health professionals, and is used to quantify muscle strength and determine the effectiveness of resistance training interventions (Seo et al., 2012). The reliability and validity of 1RM testing was initially established in young participants, experienced in resistance training, however it has since been found to be a reliable and valid measure in middle aged adults with no resistance training experience. In inexperienced participants the results are considered valid once participants have been given a sufficient familiarisation period before testing (Levinger et al., 2009). 1RM has been used to determine muscle strength in individuals with breast (Winters-Stone et al., 2012, Schmitz et al., 2009), prostate (Martin et al., 2015b), and lung cancer (Edvardsen et al., 2015). To the author's

knowledge, Study II in this thesis is the first study to incorporate 1RM testing in a study of patients with oesophago-gastric cancer. 1RM testing is considered a safe procedure for survivors of cancer, with low potential for injury (Winters-Stone et al., 2012). 1RM has been validated for testing of upper limb strength (bench press or military press), and lower limb (leg press and leg extension). A strength of 1RM testing is normative data based on age and body mass are available to compare results to reference populations (ACSM, 2010). In Study II, a horizontal leg press strength test was utilised to assess lower limb hip (gluteus maximus) and knee (quadriceps femoris) extensor strength. The leg press 1RM test has been found to be a reliable method of determining lower limb strength in both males (CV = 0.235, ICC =0.997, $p<0.05$), and females (CV=0.315, ICC= 0.997, $p<0.05$) (Seo et al., 2012).

2.3.2.5 1RM measurement procedure

Safety Procedures

Participants were screened for co-morbidities which would prohibit resistance training prior to attempting the 1RM. Uncontrolled hypertension (>180/110 mmHg) indicated an absolute contraindication to 1RM testing. An aerobic warm-up is essential prior to maximal strength testing. The 6MWT was always performed before the 1RM to ensure leg muscles were adequately warmed-up. Participants were also further warm-up/familiarised with the equipment by completing a series of submaximal contractions on the leg press machine.

Testing Procedures

1RM testing was conducted in line with the ACSM (2010) Guidelines. Participants were instructed to sit in the horizontal leg press machine (Impulse Fitness, United Kingdom,) with their lower back firmly supported against back rest, and feet positioned on the metal plate with back of heels in line with bottom grip, feet shoulder width apart, knees positioned at 90^{o}. Participants were required to hold onto side grip, brace core muscles and push plate until legs extended and return slowly to the 90^{o} position. The warm-up/familiarisation phase consisted of 6 repetitions at approximately 60% of 1RM with 2 minutes rest followed by 3 repetitions at approximately 80% of 1RM with 2 minutes rest. A maximum of 5 trials were then allowed to determine the 1RM, however during each test the aim was to achieve the 1RM in three attempts to avoid unnecessary fatigue. A rest period of two minutes was allowed between each trial. All

attempts were recorded in the case report form. The final successful 1RM attempt was used for the purpose of data analysis.

2.4 Body Composition

Body composition is a component of health related physical fitness, and is the term used to describe the relative percentage of fat to fat-free mass (ACSM, 2010, Lee and Gallagher, 2008). Measurement of body composition is an important outcome in cancer research, particularly in cancers of the upper gastrointestinal tract, as fat mass and lean soft tissue have been associated with both cancer risk and outcomes. Obesity is a known risk factor for development of both oesophageal cancer (Falk, 2009), and cancer of the gastric cardia (Karimi et al., 2014). Sarcopenia is also a strong predictor of dose limited toxicity in patients undergoing neoadjuvant treatment for oesophago-gastric cancer (Tan et al., 2015), and also short and long term surgical outcomes for patients undergoing oesophagectomy or gastrectomy (Wagner et al., 2016).

2.4.1 Measurement of body composition

Clinically, body composition may be assessed using anthropometric methods such as height, weight, body mass index, circumferential measurements, skinfolds, and bioelectrical impedance analysis (BIA) (ACSM, 2010). In laboratory settings body composition may be determined by a number of methods. These include; Dual-energy X-Ray Absorptiometry (DXA), dilution techniques, air displacement plethysmography, three-dimensional photonic scanning, CT, and MRI. These laboratory measures deliver accurate measures of body composition, however they are very expensive and require technical expertise (Lee et al., 2014).

Body composition was measured in Study I and Study II of this thesis. The following section will discuss the assessment of body composition through anthropometric methods (weight, standing height, and circumferential measurements), and also BIA.

2.4.2 Anthropometry

Anthropometry involves the measurement of body dimensions including length, width, circumference and skinfold thickness. Anthropometric methods are widely used in field research as they are relatively inexpensive and are well tolerated by participants (Fosbol and Zerahn, 2015). Body mass index (BMI) is calculated by dividing body weight in kilograms by height in

metres squared, and is reported in kilograms per metre squared (kg/m^2). It provides an estimate of the ideal weight in relation to a person's height, and is used to classify bodyweight as i) underweight (BMI <18.5), ii) normal weight (BMI 18.5 -24.9), iii) overweight (BMI 25 -29.9), iv) class I obesity (BMI 30 -34.9), v) class II obesity (BMI 35.0 -39.9), or vi) class III obesity (BMI 40-59) (ACSM, 2010). However, a major limitation of BMI is that it is unable to distinguish between fat and fat free mass (Wells and Fewtrell, 2006). Circumferential measures such as waist circumference are recommended for use in conjunction with BMI to assess those at increased risk of chronic disease. Waist circumference measurements give a good indication of central fatness, which is an important health outcome as abdominal obesity is associated with morbidity (Wells and Fewtrell, 2006). Waist circumference has been validated as a surrogate measure of visceral fat compared to CT in healthy adults ($r=0.85$; $p<0.001$) (Gradmark et al., 2010). Mid arm circumference measurements have been found to correlate well with BMI (kg/m^2) (Pearsons $r=0.78$; $p<0.001$) (Benítez Brito et al., 2016). Furthermore, mid arm circumference measurements are also considered a good indicator of nutritional status, and reductions in mid-arm circumference have been associated with increased mortality risk in elderly populations (de Hollander et al., 2013).

2.4.3 Anthropometry measurement procedures

Body Weight and Standing Height

Body weight and standing height was measured, on a SECA digital medical scales and stadiometer. Participants were measured in one layer of light clothes, without shoes. Participants were required to stand, without shoes, on the footplate, with their back against the stadiometer, legs together, arms down by the their sides, and mid-axillary line in parallel to the stadiometer. The head was positioned in the Frankfort horizontal plane established by a line passing through the tragion (front of the ear) and the lowest point of the eye socket (Figure 2.3). The headboard was lowered until it touched the crown of the head, compressing the hair. Measurements were recorded to the nearest 0.1kg and 0.1cm respectively.

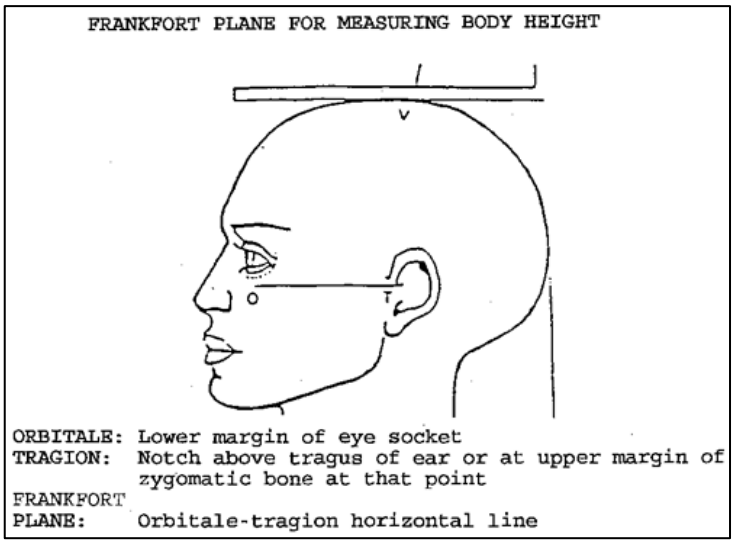

Figure 2.3 Frankfurt horizontal plane

Body mass index

BMI was calculated by dividing weight in kilograms by height in metres squared (kg/m^2).

Waist Circumference

Waist circumference was measured using a non-stretch flexible measuring tape placed over one layer of clothing at the mid-point between the superior border of the iliac crest and the bottom rib, following normal expiration (WHO, 2011). Participants were asked to identify the anatomical landmarks on their own body and estimate the mid-point. Participants held the tip of the measuring tape in place while they turned on the spot, allowing the tape to wrap around them. The tape was positioned perpendicular to the long axis of the body and parallel to the floor. Measurements were taken in duplicate, to the nearest millimetre and averaged for data entry.

Mid-Arm Circumference

Mid-arm circumference was measured on the left arm. Participants were required to stand with the arm hanging down loosely. The measurement was taken with a non-stretch flexible measuring tape at the point half way between the olecranon process of the ulna and the acromion process of the scapula (Figure 2.4). Measurements were taken in duplicate, to the nearest millimetre, and averaged for data entry.

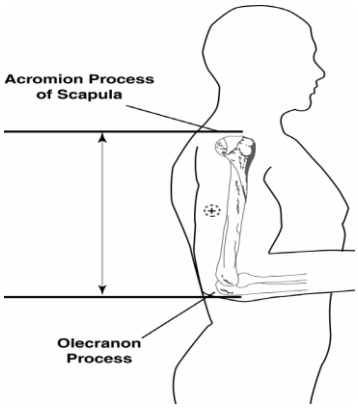

Figure 2.4 Anatomical land marks for mid-arm circumference measurement

2.4.4 Bioelectrical impedance analysis (BIA)

BIA measures the impedance of the body to a low voltage electrical current, and is used to predict fat free mass (FFM) (Lee and Gallagher, 2008). BIA works on the assumption that 73% of the bodies FFM is water. The impedance results of resistance (R) and reactance (Xc), are used in empirical equations by the BIA analyser software to give an estimate of total body water (TBW) and FFM (Raeder et al., 2017). The predictive equations give consideration to population, age, and ethnic group parameters (Khalil et al., 2014). A number of modalities of BIA are available. BIA may be single frequency or multi-frequency. Single frequency BIA typically utilises a frequency of 50Hz, however it is only able to calculate TBW and FFM. Multi-frequency BIA utilises a number of frequencies, and has an advantage over single frequency BIA in that it can break down TBW into intracellular water (ICW) and extracellular water (ECW). BIA machines may be whole body or segmental. In whole body BIA the whole body is analysed as one cylinder, whereas in segmental BIA the body is broken down into several compartments for analysis and this accounts for variability in the distribution of body fluid. Segmental BIA gives a more accurate estimation of skeletal muscle mass (SMM) (Raeder et al., 2017, Lee and Gallagher, 2008, Wells and Fewtrell, 2006). Verney et al. (2015) examined the validity of multi-frequency segmental BIA and reported its' ability to calculate fat mass (FM) and fat free mass (FFM) compared well to DXA. DXA-FM% and BIA-FM% were correlated ($p<0.001$; $r= 0.852$; ICC [IC95%]: 0.84 [0.75 – 0.90]; concordance coefficient: 0.844), and DXA-FFM and BIA-FFM were correlated ($p<0.001$; $r=0.976$; ICC [IC95%]: 0.95 [0.93 – 0.97].

The strengths of BIA are that it is relatively low cost, portable, has a low patient burden, safe, and can be easily used clinically (Raeder et al., 2017, Lee and Gallagher, 2008). It is particularly useful in cancer populations, such as oesophago-gastric cancer where fat free mass is an important prognostic indicator (Yip et al., 2015, Ryan et al., 2009). However, the main limitation of BIA is that it is a predictive method of determining body composition, and lacks the accuracy of imaging techniques such as CT and MRI. However, its' huge practicality in both clinical and research settings outweighs this lack of accuracy (Ward, 2012).

BIA was performed in Study I and Study II of this thesis using the SECA mBCA 515 (Seca, Hamburg, Germany) body composition analyser (Figure 2.5). The SECA mBCA 515 is a segmental, multi-frequency bioelectrical impedance analyser. The device has an integrated scale, and has four pairs of stainless steel electrodes positioned at each hand and foot. The device segments the body into six compartments: left and right upper limb, left and right lower limb, and left and right trunk (Raeder et al., 2017, Bosy-Westphal et al., 2017). The seca mBCA is very reliable and has been validated against a four-compartment model in healthy adults. Bosy-Westphal et al. (2013) reported the coefficient of determination for all prediction equations was high (0.94 for ECW, 0.98 for FFM and 0.98 for TBW).

Figure 2.5 The SECA mBCA 515

2.4.5 BIA measurement procedure

Patient Preparation

Participants were screened for contraindications to BIA which include electronic implants (pacemaker/ implantable cardioverter defibrillator), and metallic joint replacements e.g. total hip replacement, total knee replacement. Participants were asked to remove outer layers of clothing, chunky jewellery, and to empty their pockets. Participants were also instructed to remove their shoes and socks/tights.

Measurement Procedure

All measurements were performed as per the manufacturer's instructions. Participants stood on the SECA mBCA 515 in bare feet ensuring their heels and balls of their feet were in contact with the metal electrodes at the base of the machine. Participants were instructed to keep still and look ahead whilst body weight was calculated. The tester inputted the participant's standing height. The analyser then sought confirmation that the participants had no contraindication to BIA prior to BIA analysis. Participants were required to stand still and ensure both hands and feet were in contact with the electrodes. Following completion of the measurement participants could release their grip on electrodes. The SECA mBCA then required input of estimated daily energy expenditure, date of birth, sex, and ethnicity prior to calculation of results. The following details were then recorded: body weight, BMI, fat mass (kg), fat free mass(kg), % fat mass, % fat free mass, segmental fat and muscle, skeletal muscle index, hydration (total, intracellular and extracellular) and phase angle.

2.5 Physical activity

Physical activity is defined as 'any bodily movement produced by skeletal muscles that results in energy expenditure'(Caspersen et al., 1985). The energy expenditure associated with physical activity (AEE) is part of total energy expenditure (TEE). TEE consists of three components; i) resting metabolic rate (RMR), this accounts for 60-70% of TEE and is influenced by gender, body composition and age, ii) diet induced energy expenditure (DEE), this accounts for approximately 10% of TEE, and iii) AEE, this is the most variable component of TEE and can range from 20-30% of TEE (Vanhees et al., 2005). Physical activity includes activities undertaken as part of work, leisure, sport or household activities. Exercise is a subcategory of physical activity which is

planned, repetitive, and structured, and aims to improve one or more aspects of physical fitness (Vanhees et al., 2005, Caspersen et al., 1985).

Physical activity can be classified in a number of ways. Metabolic equivalent (MET) is a useful and easily interpretable means of describing the energy involved in different physical activities. One MET is defined as the ratio of metabolic rate to RMR and is equivalent to 3.5mlO_2/min/kg (Ainsworth et al., 2011, ACSM, 2010). Ainsworth et al. (2011) categorised the intensity of physical activities according to MET level in the Compendium of Physical Activities. Sedentary behaviour is classified as 1-1.5 METs, light intensity physical activities utilise 1.6-2.9 METs, moderate intensity activity requires 3-5.9 METs, and vigorous intensity activity involves >6 METs. Internationally the recommended level of physical activity for a healthy lifestyle is considered to be 150 minutes of moderate intensity activity or 75 minutes of vigorous intensity per week (ACSM, 2010, O'Donovan et al., 2010).

The quantification of physical activity has become an important health outcome. Inactivity is considered one of the biggest threats to global health. A sedentary lifestyles is associated with greater risk of chronic diseases including cardiovascular disease, type II diabetes, and increased mortality risk (Vanhees et al., 2005). Furthermore, greater engagement in physical activity is associated with multiple health benefits including improvement in cardiovascular and respiratory function, enhanced well-being, reduced feelings of anxiety and depression, reduced risk of osteoporosis, and reduced risk of falls and functional disability in older people (ACSM, 2010, Freedson and Miller, 2000). There is strong evidence that physical inactivity is an independent risk factor for developing colon cancer, postmenopausal breast cancer and endometrial cancer, and emerging evidence that increasing physical activity can improve survival in colon, postmenopausal breast and prostate cancer (Kruk and Czerniak, 2013). There is less evidence regarding the relationship between physical activity and other cancers (Demark-Wahnefried et al., 2015, Schmitz et al., 2010). In recent years a systematic review and meta-analysis by Behrens et al. (2014) found an inverse relationship between physical activity and risk of developing oesophago-gastric cancer. A dose response analysis found that the risk of oesophago-gastric cancer was most reduced if patients engaged in moderate-vigorous activity 5 times per week (RR = 0.67, 95% CI = 0.58-0.79).

2.5.1 Measurement of physical activity

The assessment of physical activity can be described as; i) criterion assessment, ii) subjective assessment, and iii) objective assessment of physical activity. The gold standard for quantifying physical activity is by calculating energy expenditure via direct calorimetry (Vanhees et al., 2005). This method however lacks practicality as it is cumbersome, expensive and unpleasant for patients. Instead indirect calorimetry, is used to calculate energy expenditure by measurement of oxygen consumptions and/or CO_2 production and is considered the criterion to which other measures of physical activity should be validated against. The subjective assessment of physical activity involves the completion of self-report measures such as questionnaires and activity diaries, whereas objective assessment of physical activity involves the use of activity and heart rate monitors (Vanhees et al., 2005).

The criterion method of physical activity measurement, indirect calorimetry, is considered expensive and impractical for use in field studies. The doubly labelled water (DLW) technique is a variation of indirect calorimetry which has been utilised in both field and laboratory studies. (Westerterp, 2009). DLW uses isotopes to calculate TEE. However it is unable to distinguish between RMR, DEE, and AEE, and is also very expensive (Vanhees et al., 2005). Therefore, the use of DLW and indirect calorimetry is mainly for validation studies of other measures in the laboratory setting.

Subjective methods include behavioural observation, self-report questionnaires, and physical activity diaries. Behavioural observation was one of the earliest methods of assessing physical activity, and is used frequently in paediatric research (Welk et al., 2000). This method has the advantage that it allows for collection of contextual information about activity. However it is has not been validated against the criterion DLW, is time consuming, and the presence of the observer may influence the activity of the individual under investigation (Vanhees et al., 2005). Self-report measures including activity diaries and questionnaires are widely used in research. They are cheap, highly accepted by participants due to the low participant burden, and may be used in large scale population research (Prince et al., 2008, Vanhees et al., 2005). Activity diaries when maintained accurately can give useful information regarding frequency, intensity, type and duration of physical activity. A major limitation of activity diaries is that they may motivate participants to become more active during their period of recording their activity.

Questionnaires are a useful method of quantifying physical activity in large epidemiological studies. Commonly used questionnaires of physical activity include the International Physical Activity Questionnaire (IPAQ), the Baecke Questionnaire of Habitual Physical Activity, the Minnesota Leisure Time Physical Activity Questionnaire, and the Global Physical Activity Questionnaire. However, questionnaires exhibit issues with recall of activity and response bias, and are unable to quantify accurately the levels of physical activity achieved (Prince et al., 2008). Furthermore, physical activity questionnaires have been found to have limited reliability and validity. When compared to DLW, activity questionnaires either over or underestimate physical activity (Shephard, 2003).

The objective assessment of physical activity involves the use of devices such as pedometers, accelerometers, heart rate monitors, and activity trackers. Pedometers are low cost, small, lightweight devices which are typically worn at the waist and are used to quantify locomotion by calculating the total number of steps. Pedometers are relatively inexpensive and are useful for large epidemiological studies, and health campaigns which involve goal setting e.g. achieving 10,000 steps a day (Freedson and Miller, 2000). The data output is number of steps, but they can also be used to calculate distance travelled if stride length is known. Pedometers only detect movement in the vertical plane, therefore they are not sensitive to non-walking activities. Pedometers are also not as accurate at detecting at high and low speeds, and do not store data, therefore do not facilitate the tracking of activity over time (Vanhees et al., 2005, Freedson and Miller, 2000).

Accelerometers are more complex instruments than pedometers, and measure the acceleration and deceleration of movement. Accelerometers may be uniaxial (detects movement in vertical plane only), or triaxial (measures movement in the vertical, horizontal, and sagittal plane simultaneously) (Freedson and Miller, 2000). Triaxial accelerometers are the preferred field method of quantifying physical activity (Westerterp, 1999). Advantages of accelerometers are they are small, unobtrusive devices to wear, they have a large memory, can record the amount and intensity of activity (Freedson and Miller, 2000, Westerterp, 2009). Disadvantages of accelerometers include an under estimation of energy expenditure, and inability to quantify water based activities (Vanhees et al., 2005).

Heart rate monitors are sometimes used to quantify physical activity. The relationship between heart rate and oxygen (VO_2) consumption is known to be linear, and as such heart rate can be considered an acceptable marker of physical activity (Freedson and Miller, 2000). Heart rate monitors are relatively inexpensive and involve a chest strap and monitor which is worn as a watch at the wrist. Heart rate monitors allow for the storage of large amounts of data, and give a good indication of the intensity of activity. However, heart rate is susceptible to other non-activity factors such as emotional stress, temperature, and humidity, so heart rate results should be analysed with caution. Furthermore, less fit individuals will exhibit higher heart rate responses to activity than trained individuals, making comparisons between participants difficult. Heart rate monitoring may be used in combination with accelerometry to give more information about intensity of physical activity (Westerterp, 2009, Vanhees et al., 2005).

In recent years there has been huge surge in the popularity of consumer activity trackers, e.g. FitBit, GarminVivoSmart etc. These devices are accelerometer based and have been used primarily by consumers to monitor their physical activity (Lee et al., 2014). Most devices are linked to a computer application which can be used by consumers to track their physical activity over time. More recently consumer activity trackers have been used in field research, and have been shown to have good potential as objective measures of physical activity. Evenson et al. (2015) investigated the inter-device reliability of the Fitbit and found consistently high inter-device reliability for steps (Pearson and ICC 0.76–1.00), distance (ICC 0.90–0.99), and energy expenditure (Pearson and ICC 0.71–0.97). However, more research is required to determine the reliability and validity of such devices for research purposes (An et al., 2017, Lee et al., 2014).

Given the advantages and disadvantages of each physical activity assessment method discussed above, a triaxial accelerometer was chosen as the most appropriate measure of quantifying physical activity levels for this thesis. In Study I and Study II, physical activity levels were assessed using the Actigraph GT3X+ accelerometer. Its use will be discussed in the following sections.

2.5.2 Actigraph accelerometer

The ActiGraph wGT3X$^+$ (Actigraph, LLC, Pensacola, Florida) activity monitor is a small (4.6 x 3.3 x 1.5cm, 19g) device (Figure 2.6). The wGT3X$^+$ has a battery life of 31 days, 2GB of data storage, and is charged via USB. The device is water resistant to a depth of 1 metre for 30 mins. The device may be worn on the wrist, waist, ankle or thigh. The Actigraph monitor generates data

every minute, and reports motion across 3 axis: axis 1 (activity in the vertical plane), axis 2 (activity in the horizontal plane), and axis 3 (activity in the perpendicular plane). Vector magnitudes (VM)s is calculated by calculating the square root of the sum of the square of each of the axis counts (VM=√(axis 1)^2 +(axis 2)^2 + (axis 3)^2. The vector magnitude indicates the intensity of physical activity. The Actigraph wGT3X$^+$ accelerometer is considered a reliable and valid measure of intensity specific physical activity and sedentary behaviour in healthy adults. Aadland and Ylvisåker (2015) investigated the inter-instrument reliability of the Actigraph wGT3X$^+$ and reported there were no significant differences between two devices worn on contralateral hips (effect size ≤0.042; p ≥.213) in 87 healthy adults. The validity of the Actigraph wGT3X$^+$ in healthy adults was investigated by Kelly et al. (2013) The accuracy of the Actigraph wGT3X$^+$ in quantifying physical activity was found to be high when compared to oxygen consumption (r=0.810, p<0.001).

Figure 2.6 The Actigraph wGT3X$^+$

2.5.3 Actigraph accelerometer measurement procedure

The Actigraph wGT3X$^+$ was initialised using the Actilife 6 Data Analysis Software (Version 6.13.3). The device was always scheduled to start recording data from midnight of the day of the assessment day. A sample rate of 30 hz (30 accelerations per second) was selected when initialising each monitor. Participant details including study ID + time point, gender, height, weight, date of birth, race, limb and side of placement were inputted using the Actilife software and the device was then initialised.

Participants in Study I and Study II were provided with the activity monitor at the end of each of their assessments. They were asked to wear the monitor for 7 days on the right side of the waist

secured with an adjustable elastic belt. Participants were provided with verbal instructions and a written information leaflet with instructions about the device and a diary to record the times the device was taken on and off each day (Appendix VI). The device was to be worn during waking hours only. The device was to be removed only for sleeping/ showering/ bathing and going for a swim. After 7 days of wearing the monitor participants returned the monitor to the research team in the provided stamped addressed envelope. Data from the returned monitor was then downloaded using the Actilife 6 Software. Two files were generated from each download, a *GT3x file containing the raw data and a *AGD file containing epoch level data (an epoch length of 60 seconds was used).

2.5.4 Actigraph accelerometer data analysis

All data analysis was completed using the Actilife 6 software. Wear-time validation was performed using the Choi et al. (2011) technique which is a built in algorithm in Actilife 6. It uses a forward and backward looking windowing technique to categorize non-wear times. Non-wear times were then eliminated from the analysis. Activity intensity was defined from previously validated cut-points (Freedson Adult (1998): sedentary activity 0-99 counts per minute (CPM), light 100-759 CPM, moderate 1952 -5724 CPM, vigorous 5725-9498 CPM, and very vigorous ≥9499 CPM. Bouts of moderate-vigorous intensity physical activity of 10 minutes duration were also defined using Freedson et al. (1998) Adult cut-points. The GT3X+ can also measure energy expenditure, and metabolic rate but that data was not used for analysis in the studies presented.

2.6 Health related quality of life and well-being

Traditionally morbidity and mortality were reported as the key indicators of population health. However, with increased life expectancy, the evaluation of the quality of years lived has become an important health outcome, particularly as there are growing numbers of people living with chronic diseases and disability (Chen, 1995). Aspects of quality of life pertaining to health are termed health related quality of life (HRQOL). The assessment of HRQOL typically encompasses domains of mental, emotional, social, and physical functioning (Ferrans, 2005). Well-being is another aspect of HRQOL. The term subjective well-being refers to an individual's positive evaluation of psychological function and life experience. Subjective well-being is divided into three categories; i) evaluative well-being refers to how satisfied one is with life, ii) hedonic well-being pertains to feelings and moods including happiness and sadness, and iii) eudemonic well-

being investigates the meaning and purpose of life (Lukaschek et al., 2017, Steptoe et al., 2015). The assessment of HRQOL and well-being is particularly useful in both cancer research and clinical care. HRQOL at diagnosis has been found to be prognostic of survival in cancer. Furthermore, assessment of HRQOL in patients with cancer is useful for elucidating the effects of treatment on well-being, and also identifying unexpected side-effects of cancer treatment (Jensen et al., 2012, Chen, 1995).

2.6.1 Measurement of HRQOL and well-being

HRQOL is usually determined by interview or questionnaire. Patient reported outcome measures (PROM) are considered the gold standard for evaluating HRQOL. The purpose of PROMs may be either evaluative or discriminative. Evaluative measures calculate the 'within person change' over time whereas discriminative measures are used to distinguish between groups or individuals at a particular time-point. Most PROMs are designed to do both. PROMs may be generic or condition specific (Feeny et al., 2013). Condition specific PROMs are designed for use with particular conditions and are more sensitive to change. However they do not allow for comparisons between different populations. Examples of generic PROMs which have been well utilised in the literature are the MOS Short Form-36 (SF-36) and the Duke Health Profile (Perret-Guillaume et al., 2010, Ware and Sherbourne, 1992). Examples of condition specific HRQOL of life questionnaires include the European Organisation for the Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30) and the Functional Assessment of Cancer Therapy–General (Fact-G) questionnaire (Scarpa et al., 2011). These questionnaires also have cancer specific subscales to measure disease specific issues for example the EORTC oesophageal cancer subscale, the EORTC-QLQ-OES18 (Blazeby et al., 2003), and the Functional Assessment of Cancer Therapy-oesophageal cancer subscale (FACT-E) (Darling et al., 2006).

Assessment of well-being is dependent on the aspect of subjective well-being under analysis. Evaluative well-being is typically determined using scales such as the Cantril ladder, whereas in depth interviewing is typically required for analysis of eudemonic well-being (Steptoe et al., 2015). Hedonic well-being can be assessed using likert scale questionnaires. A large number of instruments to record hedonic well-being have been reported in the literature. The gold standard of determining well-being has yet to be determined (Linton et al., 2016).

In this thesis HRQOL was determined in Study I and Study II using the EORTC-QLQ-C30 (version 3.0) and the oesophageal site specific EORTC-QLQ-OES18 (Appendix VII). In Study II well-being was also assessed using the perceived well-being questionnaire.

2.6.2 EORTC-QLQ-C30 and EORTC-QLQ-OES18

The EORTC-QLQ-C30 was used for this thesis as it is a valid and reliable measure of HRQOL for patients with cancer, and is also the most well documented instrument in studies examining HRQOL in oesophago-gastric cancer (Pullmer et al., 2014, Aaronson et al., 1993). Barman et al. (2012) examined the reliability and validity of the EORTC-QLQ-C30 in oesophageal cancer, and reported that all scales demonstrated good internal consistency reliability (Cronbach's Alpha Coefficient (α) range 0.650-0.934), and convergent validity (the coefficient of correlation of all scales >0.40). The EORTC-QLQ-C30 consists of five functional scales (physical, social, role, emotional and cognitive function), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/ QOL scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). All of the scales and single item results are transformed to a score ranging from 0 to 100. In functional scales, a higher functional score indicates greater function, whereas in symptom scales, a higher symptom score indicates higher symptom burden. A high score in the global health status/ QOL scale represents a high HRQOL (Fayers PM and Group, 2001). The EORTC-QLQ-OES18 has four symptom scales (dysphagia, eating problems, reflux, and pain) and six single items (trouble with swallowing saliva, choking, dry mouth and taste, coughing, and speech problems).

2.6.3 EORTC data analysis

The numerical responses for each question were entered into a Microsoft excel spreadsheet. Scoring of the data was completed as per the EORTC Scoring Manual (Fayers PM and Group, 2001). A raw score for each scale was calculated, which is an average score of the items that contribute to the scale. Linear transformations were used to standardise raw score results so that scores ranged from 0 to 100. The scoring procedure is outlined in Appendix VIII.

2.6.4 Perceived well-being questionnaire

Hedonic well-being was determined in Study II using the perceived well-being questionnaire (McLean et al., 2010). The perceived well-being questionnaire assesses sleep quality, fatigue, muscle soreness, stress and mood on a five point likert scale (Appendix IX). Reliability of this measure has been established (Roe, 2016). In the absence of a recommended measure of well-being, the perceived well-being questionnaire was selected for use in Study II as it has previously been used to assess well-being in exercising populations (Roe, 2016, McLean et al., 2010).

2.6.5 Perceived well-being questionnaire data analysis

The numerical responses to each question were entered into a Microsoft Excel spreadsheet. The score for each item was recorded and an overall well-being score was determined by adding all 5 scores.

2.7 Chapter 2 - Summary

Chapter 2 began by outlining the background research methods underlying this thesis, providing rationale regarding the choices of study design, statistical methods, and outlining the research principles of reliability and validity that required due consideration in selection of measures for this thesis.

The Chapter then outlined the reliability, validity, and procedures for the quantitative measures utilised in this thesis. Quantitatively, this thesis focused on measures of physical function, body composition and HRQOL. Measures of physical function included; cardiorespiratory fitness (CPET), physical performance (6MWT), accelerometer measured physical activity levels, and tests of muscle strength (1RM and HGS). Body composition measures included; anthropometric measures and bioimpedance analysis. Quality of life was determined via questionnaire (EORTC-QLQ-C30).

The forthcoming two chapters detailing Study I and Study II, will reference back to this chapter in the descriptions of their methodologies.

Chapter 3 Study I: The feasibility of a multidisciplinary rehabilitation programme in oesophageal cancer survivorship

Abstract

Aims

Study I aimed to establish the feasibility of a multi-disciplinary programme to improve functional performance and QOL for oesophageal cancer survivors.

Methods

This study was a single-arm feasibility study. Patients who were greater than 12 months post completion of curative treatment for oesophageal cancer including oesophagectomy and who had node-negative post-surgical pathology received a letter of invitation to participate. The programme consisted of 12 weeks supervised and home-based exercise, dietetic counselling and education sessions from the multi-disciplinary team. Feasibility outcomes included recruitment rates, adherence, adverse events and retention. Other outcomes, including cardiopulmonary fitness (maximal cardiopulmonary exercise test and six minute walk test (6MWT)), QOL (EORTC questionnaire) and body composition (bioimpedence analysis), were assessed pre- and post-intervention.

Results

Twelve participants (mean, standard deviation (SD) age 61.4 (7.29) years, 8 male) consented to participate, representing a recruitment rate of 55%. Mean class attendance was 82 (13)% and adherence to the home exercise programme was 78(32)%. No adverse events occurred and all participants completed the programme. Aerobic fitness improved by 3.99 (2.7) ml/kg/min (20.08 ml/kg/min pre-intervention, 24.08 ml/kg/min post-intervention, $p<0.004$). 6MWT distance improved by 56.3 (35.3) m ($p<0.003$). Global and functional QOL scores increased while symptom scores decreased. Body composition remained stable.

Conclusion

This pilot work demonstrated high feasibility and acceptability of the proposed intervention in this complex cohort. Clinically significant improvements in functional performance and QOL were evident without compromise to body composition. While current results are limited due

to the selected population and single-arm design they will guided the design of Study II, a randomised controlled trial.

This study has been published in Diseases of the Esophagus (Appendix X)

L. O'Neill, E. Guinan, S. L. Doyle, J. A. Elliott, J. O'Sullivan, J. V. Reynolds, J. Hussey; Rehabilitation strategies following esophageal cancer (the ReStOre trial): a feasibility study. Dis Esophagus 2017; 30 (5): 1-8. doi: 10.1093/dote/dow012

Citations: 2 (11.12.2017)

3.1 Introduction

This chapter outlines the methods, results, and discussion of the first study undertaken as part of this thesis. Study I describes a pilot programme designed to examine the feasibility of a 12 week multidisciplinary rehabilitation programme consisting of supervised and unsupervised exercise sessions, dietary counselling, and education sessions for survivors of oesophageal cancer. As described in the introductory chapter of this thesis, oesophageal cancer survivors experience long term complications including fatigue, reflux, dysphagia, pain, and diarrhoea (Chang et al., 2014), which may lead to nutritional and functional compromise resulting in impaired quality of life (QOL)(Xu et al., 2015, Chang et al., 2014, Schmitz et al., 2010). It is well acknowledged that there is a need for development of research into rehabilitation programmes in lesser studied cancers, such as oesophageal cancer, to help address the multifaceted rehabilitative needs survivors may experience (Chapter 1, section 1.5). Study I describes the development of a multidisciplinary rehabilitation programme to help address the specific issues faced by survivors of oesophageal cancer.

3.2 Study aims and objectives

The overall aim of Study I was to examine the feasibility of a 12 week multidisciplinary led rehabilitation programme consisting of supervised exercise sessions, dietary counselling, and education sessions for survivors of oesophageal cancer who are greater than one year post completion of curative treatment.

The specific objectives of Study I were:

- To examine the feasibility of the 12 week multidisciplinary rehabilitation programme as determined by recruitment rate, adherence, acceptability, and adverse events.
- To investigate the effect of the 12 week multidisciplinary programme on cardiorespiratory fitness (VO_2max), physical performance (6MWT), and physical activity levels.
- To investigate the impact of the 12 week multidisciplinary programme on health related quality of life (HRQOL).

3.3 Methods and measures

3.3.1 Study design

Study I was designed as a single arm pilot intervention study with a single-arm pre-post-test design. The characteristics of a pilot study have been discussed in Chapter 2, section 2.2.1.

3.3.2 Funding

This study was part of a Health Research Board funded project (Award number: HRA-POR-2014-535).

3.3.3 Ethical Approval

Ethical approval was granted by the joint SJH-Tallaght Hospital Research Ethics Committee (Appendix XII). Hospital approval was granted by the Research and Development Hub at St James's Hospital. All procedures performed in Study I were in accordance with the 1964 Helsinki declaration and its later amendments. All researchers involved in Study I had successfully completed Good Clinical Practice training. All participants provided written, informed consent (Appendix XI).

3.3.4 Sampling and Recruitment

Suitable participants were identified from the Upper Gastrointestinal Cancer Registry of St James's Hospital (SJH), Dublin and contacted via letter which contained a copy of the patient information leaflet (PIL) (Appendix XI) and invited to express an interest in participation. Recruitment was completed by the main investigator (Linda O'Neill). Inclusion criteria included;

>6 months post successful completion of curative treatment for histologically confirmed oesophageal cancer that included oesophagectomy +/- neoadjuvant/ adjuvant chemo/radiotherapy, medical approval to participate, living within one hour travel radius of the research facility, and willing to attend the scheduled programme of appointments. Exclusion criteria included; unsuccessful treatment outcome, co-morbidities that would preclude safe exercise participation, and evidence of metastatic or recurrent disease.

3.3.5 Measures and Testing Protocol

All study appointments including assessments and the multidisciplinary rehabilitation programme were completed in the Wellcome Trust HRB Clinical Research Facility (CRF) at SJH, Dublin. This setting was chosen as it is a dedicated space for research activities, has a fully equipped gymnasium, and also to ensure maximum safety, as the CRF has direct access to the hospital emergency services (crash team) in the event of an emergency. Testing was completed at pre-rehabilitation (T1) and immediately post-intervention (T2) (Figure 3.1).

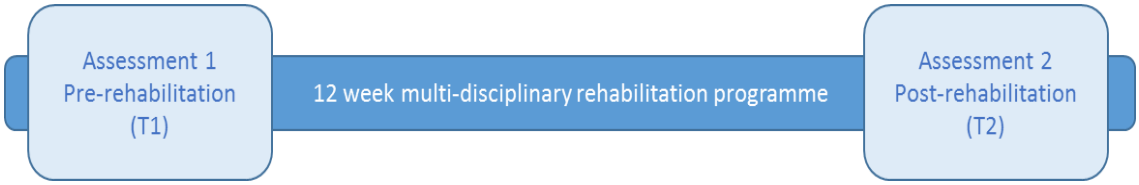

Figure 3-1 Study I assessment time-points

Multidisciplinary Research Team

The author (Linda O'Neill) was the lead investigator on Study I, with responsibility for protocol development, recruitment, data collection, management of all study visits, data collection, and implementation of the supervised and unsupervised exercise sessions, data analysis, and dissemination of results. Due to the multidisciplinary nature of the study, the lead investigator was supported by a multidisciplinary team of researchers. All assessments were performed by the same research team (Linda O'Neill, Dr Emer Guinan, and Dr Suzanne Doyle). The exercise intervention was delivered by Linda O'Neill and the dietary intervention was delivered by Dr Suzanne Doyle. The education sessions were organised by Linda O'Neill and Dr Suzanne Doyle.

The background, validity, and reliability of all measures performed have been described in Chapter 2.

The following measurements were completed in the listed order:

- **Standing height** and **weight** was measured according to the procedures outlined in section 2.4.3.
- Participants completed medical screening, including resting blood pressure and ECG. Participants that successfully completed screening proceeded on to the **CPET**, as per the protocol in section 2.3.1.3.

Following a recovery period:

- **Waist circumference** and **mid-arm circumference** were measured according to the procedures outlined in section 2.4.3.
- **Body composition** was analysed using BIA according to the procedures in section 2.4.5.
- **Hand grip strength** was determined using hand grip dynamometer as per the procedure in section 2.3.2.3.
- Physical performance was analysed using the **6MWT** as per the protocol in section 2.3.1.5.
- Participants were provided with an **Actigraph GT3-X** accelerometer to wear for one week when leaving the centre (measurement procedure outlined in section 2.5.3). The monitor was then returned in a stamped addressed envelope to the research team.
- Participants were provided with the **EORTC-QLQ-C30** and **OES18** (described in section 2.6.2) to be completed within one week of their study assessment.

Demographic information and past medical history details were gathered from hospital medical records including medical charts, the Powerchart electronic patient record system at SJH, the Upper Gastrointestinal Cancer Registry database at SJH, and from participant interviews.

Feasibility

Feasibility was determined through analysis of recruitment rates (percentage of eligible study population that consented to participation), programme adherence (number of prescribed supervised and unsupervised sessions completed), retention, acceptability of the intervention and assessments (participant feedback), improvement of outcomes, and adverse events.

3.3.6 Multidisciplinary Rehabilitation Programme

Following completion of baseline (T1) assessments, participants commenced a 12 week multidisciplinary rehabilitation programme. The multidisciplinary rehabilitation programme consisted of supervised and homebased exercise sessions, 1:1 dietary counselling, and group education sessions.

The multidisciplinary rehabilitation schedule is illustrated in Figure 3.2.

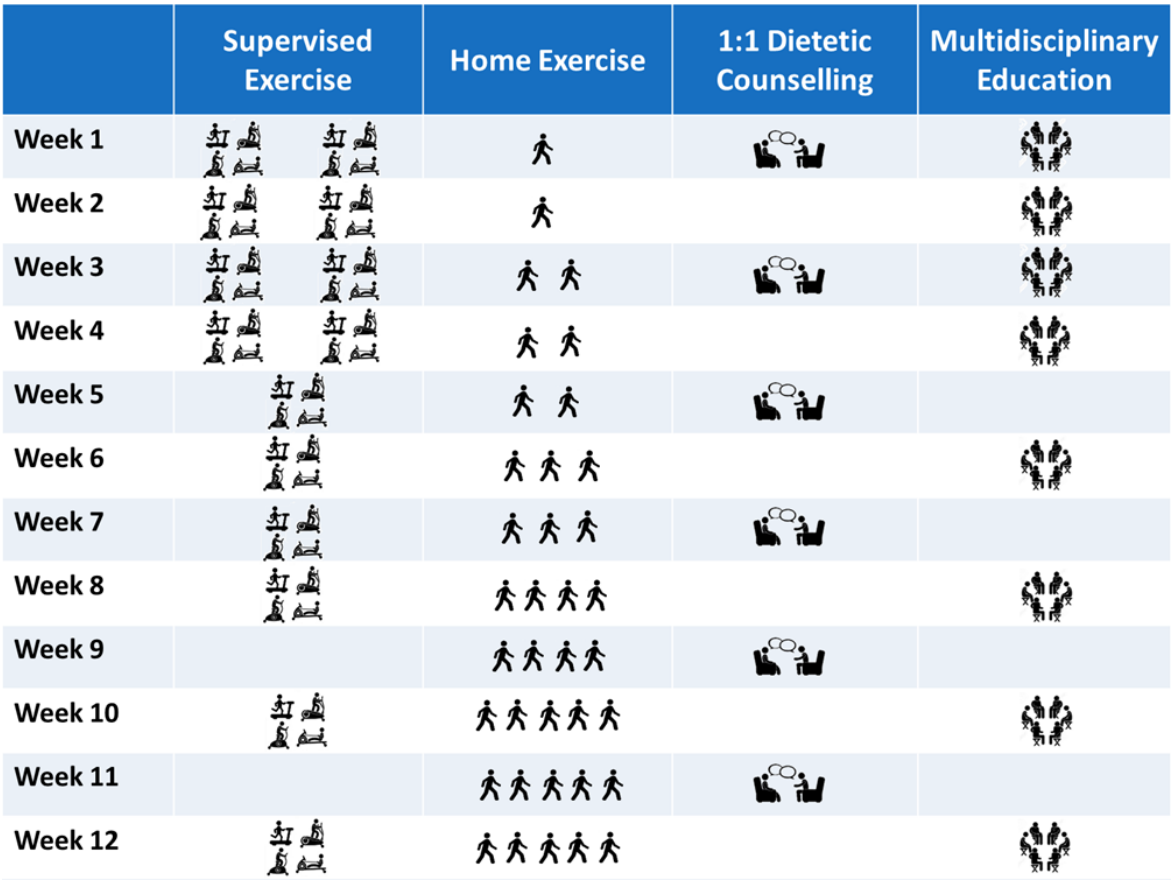

Figure 3.2 RESTORE rehabilitation programme

3.3.6.1 Theoretical Framework

This 12 week programme of multidisciplinary rehabilitation aimed to give participants a greater sense of self-efficacy over their recovery from oesophageal cancer. Self-efficacy has been described as 'ones beliefs in one's capabilities to successfully execute courses of action', and is

considered a strong predictor of behaviour (McAuley et al., 2011). With this in mind the programme was based on the Social Cognitive Theory (SCT) theoretical foundation (Bandura, 1977, Bandura, 2004) as it includes perceived self-efficacy as a key determinant of health behaviour change. Other core determinants of the model include; knowledge of health risks, outcome expectations, and perceived facilitators and impediments of behaviour (Bandura, 2004).

The design of this multidisciplinary programme incorporated each of these core determinants. It was an important goal of the programme to enhance self-efficacy amongst participants, to give them the belief that they could safely return to physical activity following their cancer journey, and promote lasting lifestyle changes. This goal was targeted through enhancing patient knowledge across the three components of the programme (exercise, dietary counselling, group education sessions), providing participants with education on the benefits of exercise, exercise safety, maintaining a stable body weight, and managing other symptoms such as fatigue. Outcome expectations were derived through the setting of individualised exercise and dietary goals throughout the programme. The programme was also developed with perceived facilitators and impediments of physical activity in mind. Key facilitators of the programme were the clear structure, dedicated exercise space, and a motivated rehabilitation team. The multidisciplinary nature of the programme also helped address barriers to activity e.g. fear of weight loss, fatigue etc. to maximise adherence to the programme.

3.3.6.2 Exercise Programme

Supervised exercise sessions were delivered by the lead investigator, a physiotherapist (Linda O'Neill). The maximum patient instructor ratio was 1:6. The class commenced with a 5 to 10 minute warm-up which consisted of progressive aerobic exercises including marching on the spot and arm swinging. The exercise session concluded with a 5 minute cool-down, light resistance work, and a stretching period. The main aerobic exercise programme was completed on a treadmill, stationary bike, or cross trainer.

Weekly exercise goals were agreed between participants and the physiotherapist (LON). Intensity was prescribed by percentage heart rate reserve (HRR) using the Karvonen formula:

[Target Heart Rate =((maximum heart rate – resting heart rate) x % exercise intensity) + resting heart rate] (ACSM, 2010). Subjects commenced exercising at 30-45% HRR. This was based on participants' baseline CPET results which indicated that participants had mostly either very poor or poor exercise tolerance (Figure 3.4). Intensity was monitored during supervised sessions using polar heart rate monitors (Polar FT7, China) (Figure 3.3). The FT7 consists of a monitor worn as a watch on the wrist, and a chest strap. Participants were educated on how to use the polar heart rate monitor during the exercise class and were provided with a personal one to wear during their supervised and unsupervised sessions for the duration of the programme. Participants also received written instructions on how to use their monitor (Appendix XIII).

Figure 3.3 Polar FT7 watch and chest strap

Home exercise sessions were recorded in an exercise diary (Appendix XIV). Participants were free to complete any aerobic activity they preferred e.g. walking, cycling. The intensity of the home exercise programme was progressed in the same manner as the supervised class. Duration, frequency, and intensity of exercise were increased as the programme progressed by the study physiotherapist in line with ACSM guidelines for exercise testing and prescription (ACSM, 2010) (Table 3.1). By the end of the programme participants were prescribed 150 mins of moderate intensity exercise (60% HRR) per week. As the programme progressed there was a gradual switch on emphasis from supervised to home based sessions to help improve participants sense of self-efficacy with regards to their rehabilitation.

Table 3.1 RESTORE exercise programme prescription

	Frequency*		Intensity†	Time
	Supervised Exercise Sessions	**Home Exercise Sessions**		
Week 1	2	1	30-45% HRR	20
Week 2	2	1	30-45% HRR	20
Week 3	2	2	35-50% HRR	20
Week 4	2	2	35-50% HRR	25
Week 5	1	2	35-50% HRR	25
Week 6	1	3	40-55% HRR	25
Week 7	1	3	40-55% HRR	30
Week 8	1	4	40-55% HRR	30
Week 9	0	4	45-60% HRR	30
Week 10	1	5	45-60% HRR	35
Week 11	0	5	45-60% HRR	35
Week 12	1	5	45-60% HRR	35

**Indicates frequency of exercise sessions in days per week.* † *Based on pilot data from our research group it was anticipated that baseline fitness levels would be 'very poor' and 'poor'. Exercise prescription was commenced at 30-45% Heart Rate Reserve (HRR) and progressed gradually over the course of the intervention to 45-60% HRR (moderate intensity activity).*

Safety Precautions

All supervised exercise sessions took place in the Clinical Research Facility at SJH. As described in section 2.3.1.3 the CRF is staffed by highly skilled research nurses. Crash trolley facilities are available within the CRF, and the CRF is serviced by the SJH crash team. All researchers working on this project were trained in Basic Life Support.

All participants had their blood pressure, heart rate, and oxygen saturation levels taken in advance of each session to ensure suitability for exercise participation. In the event of a value indicating emergency medical attention required, participants would be admitted immediately

to SJH via the Accident and Emergency department. Abnormal values requiring non-urgent medical review would be referred to the participant's GP for follow-up. Participants would not be allowed continue on the programme until they were medically cleared to do so.

Safety throughout the session was monitored through the use of polar heart rate monitors as described above. Following completion of the session measurements of blood pressure, heart rate and oxygen saturation levels were taken to ensure participants were recovering normally from their exercise session.

Given the age profile of the study population, musculoskeletal difficulties including arthritic changes were common amongst participants with several having history of joint replacement. The physiotherapist was cognisant regarding patients existing musculoskeletal issues and modified exercise prescription accordingly for participants to minimise discomfort. Musculoskeletal discomfort was monitored in at risk patients using the numerical rating scale and individual advice was given regarding symptom management.

Fatigue is also a prevailing symptom in this population. The physiotherapist was also cognisant of this in delivery of the sessions and modified sessions when needed (e.g. prescribed shorter bursts of activity) for participants.

3.3.6.3 Dietary Counselling

Nutritional assessments were carried out in a 1:1 setting by the study dietitian (Dr Suzanne Doyle). Dietary intakes were assessed by diet history and 24-hour recall, through which multiple considerations affecting usual diet were documented, to include: food groups, variety of foods consumed, portion sizes, meal frequency, cooking methods, food preparation facilities at home, food preparation abilities, food security, known food allergies, personal likes and dislikes, cultural beliefs, appetite, and GI symptoms on eating. These considerations were documented in line with best practice (Thomas and Bishop, 2007) to enable the dietitian to gauge participant capacity and willingness to address dietary challenges. Using this information, the dietitian worked with each participant to collaboratively devise dietary goals which were evidence-based

and tailored to participant need. Motivational interviewing and cognitive behavioural therapy techniques (Thomas and Bishop, 2007) were used to help participants to accomplish the goals set. Diet-related goals were devised and revised as the intervention progressed, with the number of sessions with the dietitian determined by a participant's weight status, number and type of dietary challenges, progress with dietary goals, and willingness to engage.

Safety Considerations

To manage the potential adverse outcome of excess weight loss, the dietitian regularly assessed each participant's weight to ensure that participants did not exceed established, evidence-based thresholds indicative of significant weight loss. The dietitian weighed participants every 1-2 weeks to keep a record of weight patterns over the course of the intervention. To determine percentage weight change, the dietitian used the following calculation: [((baseline weight - current weight) / baseline weight) * 100]. Blackburn et al. (1977) thresholds for the categorisation of weight loss were then applied, where relevant, and weight loss was deemed significant if it exceeded: 2% in 1/52; 5% in 1/12; and 7.5% in 3/12. Were a participant to exceed any of these thresholds, nutrition support would have increased, and the nutrition support measures implemented would have taken into account the physiotherapist's current and short-term exercise goals for the participant. No participant exceeded the thresholds for safe weight loss.

3.3.6.4 Education Intervention

Group education sessions focused on topics that were of specific relevance to oesophageal cancer survivors. Education sessions were delivered by a range of members of the multidisciplinary team and representatives of organisations that support people with oesophageal cancer, including a representative of the surgical team, cancer nurse specialist, dietitian (Dr Suzanne Doyle), physiotherapist (Linda O'Neill), psycho-oncology, a mindfulness practitioner, and representatives from local cancer charities. Details of the education sessions are presented in Table 3.2 below.

Table 3.2 Study I education talks

	Presenter	Role	Topic
1	Ms Linda O'Neill	Research Physiotherapist	Benefits of Physical Activity in Cancer Survivorship
2	Dr Suzanne Doyle	Research Dietitian	Nutrition in oesophageal cancer survivorship
3	Dr Helen Heneghen	Upper GI Surgical Team	Medical issues following oesophagectomy
4	Ms Noelle Ryan	Chairperson Oesophageal Cancer Fund	Introduction to the work of the Oesophageal cancer fund
5	Dr Sonya Collier	Psycho-oncology	Managing fatigue in survivorship
6	Ms Deirdre Murphy	Irish Cancer Society Representative	Irish Cancer Society peer support programme and general services
7	Ms Patricia Pugh	ARC Cancer Support Representative	Mindfulness
8	Ms Linda O'Neill/ Dr Suzanne Doyle/ Dr Emer Guinan	Research team	Informal feedback discussion with participants

3.3.7 Statistical Analysis

Statistical analyses were performed using SPSS 22 (SPSS Inc.; Chicago, IL, USA). Prior to analysis variables were tested for normality of distribution using the Kolomogorov-Smirnov test. Normally distributed continuous variables are presented as mean (standard deviation), non-parametric continuous variables are presented as median (inter quartile range). Normally distributed data was analysed using a paired t-test. Non-parametric data was analysed using the Wilcoxon Signed Rank test. A p-value of <0.05 was considered as statistically significant.

3.4 Results

3.4.1 Participant Characteristics

Recruitment for Study I took place in April 2015. 22 patients who met the inclusion criteria and were known to live in a commutable distance to the research facility were invited to participate. 10 declined participation and 12 consented. Descriptive characteristics for the 12 participants are presented in Table 3.3.

Table 3.3 Demographic characteristics of participants

Characteristic	Mean (Standard Deviation)/ Frequency (Percentage %)
Sex	
Male	8 (66.67%)
Female	4 (33.33%)
Age (years)	61.41(7.29)
Height (cm)	171.11 (9.37)
Weight (kg)	70.93 (19.95)
BMI (kg/m^2)	24.04 (8.54)
Time post-surgery at programme commencement (months)	22.16(8.54)
Histological type of tumour	
Adenocarcinoma	8 (66.67%)
Squamous Cell Carcinoma	4 (33.33%)
Type of Surgery	
Transhiatal Oesophagectomy	2 (16.67%)
2-Stage Oesophagectomy	5 (41.67%)
3-Stage Oesophagectomy	5 (41.67%)
Neoadjuvant Treatment	
Yes	10 (88.33%)
No	2 (16.67%)
Adjuvant Treatment	
Yes	1 (8.33%)
No	11 (91.67%)

Data are presented as the mean (standard deviation) for continuous variable and as frequency (percentage) for categorical variables.

3.4.2 Data Normality

Physical performance was assessed using CPET, the 6MWT, HGS, and accelerometer measured physical activity levels. The following physical performance measures were normally distributed; 6MWT (T1), HGS (T1), VO_2 at AT (T1, T2), VO_{2max} (T2), number of Freedson (1998) bouts (T1, T2),

minutes spent in Freedson (1998) bouts (T1,T2), total time sedentary (T1,T2), total time in light activity (T1,T2), total time in moderate activity (T2), and total time in moderate-vigorous activity (T2). The following were not normally distributed; 6MWT (T2), VO_2max (T1), total time in moderate activity (T1), total time in vigorous activity (T1, T2), and total time in moderate-vigorous activity (T1). Paired t-tests were used to analyse variables normally distributed at both time-points (VO_2 at AT, number of Freedson bouts, minutes spent in Freedson bouts, total time sedentary, total time in light activity), and the non-parametric Wilcoxon Signed Rank test was used to analyse 6MWT, and VO_2max, total time in moderate activity, total time in vigorous activity, and total time in moderate-vigorous activity.

All body composition variables with the exception of extra-cellular water (T1), fat free mass index (T2), and R (T2) were normally distributed. These variables were analysed with the non-parametric Wilcoxon Signed Rank Test. Quality of life was assessed with the EORTC-QLQ-C30 and EORTC-QLQ-OES18. The functional scales of Global health status, and cognitive function, and the symptom scale of fatigue were normally distributed at both time points and were analysed using a paired t-test. All other functional and symptom scales were not normally distributed at both time-points and were analysed with the non-parametric Wilcoxon Signed Rank Test.

3.4.3 Feasibility Outcomes

Twelve participants out of a potential study population of 22 consented to participate, representing a recruitment rate of 55%. The programme was well accepted by all participants with 100% completing the programme. The total number of supervised exercise sessions was 14. Participants attended a mean 11.5(1.88) sessions representing an adherence rate to the supervised rehabilitation programme of 82(13) %. Adherence to the home exercise programme was assessed using exercise diaries. The total number of prescribed home exercise sessions was 37. Some participants greatly exceeded the number of prescribed sessions whereas others struggled to comply (range 7-92). When all completed home exercise sessions were considered participants completed a mean 43.67 session which was 118(76) % of the prescribed sessions. When only prescribed home sessions are considered for analysis the mean number of home exercise sessions was 28.91 (11.93) which represents an adherence rate of 78.15(32.36)%. No adverse events were recorded during the intervention or assessments.

3.4.4 Physical Performance Results

As per the ACSM reference values (ACSM, 2010) based on age and gender, at T1 6 participants (50%) cardiorespiratory fitness was categorised as very poor, 5 were categorised as poor (41.7%) and one was classified as excellent (8.3%).This had improved at T2 to 3 participants being classified as very poor, 5 participants poor (41.7%), 1 fair (8.3%), 2 good (16.7%), and 1 excellent (8.3%) (Figure 3.4).

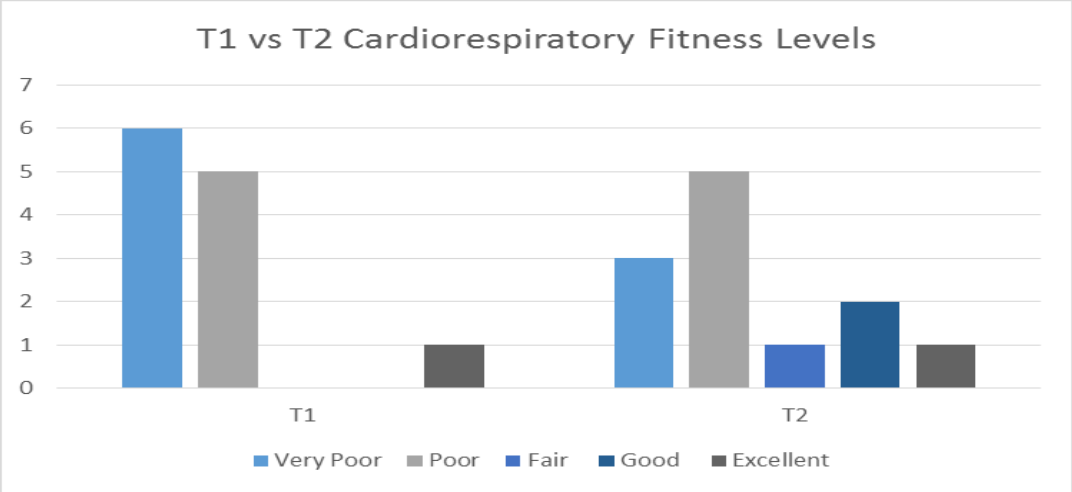

Figure 3-4 Pre-habilitation (T1) vs Post-rehabilitation (T2) cardiorespiratory fitness categories

Number of participants in each cardiorespiratory fitness category at pre-intervention (T1) and post-intervention (T2)

At T1 participant's average VO_2 at Anaerobic Threshold (AT) was 12.94 (3.87)ml/min/kg. Post-intervention this increased by 2.39(1.70) ml/min/kg to 15.33(4.03) ml/min/kg (95% CI -3.70 to -1.08) (p=0.003) (Figure 3.5). VO_2max also improved from 20.08 (5.2)ml/min/kg at T1 to 24.08 (4.99)ml/min/kg at T2 (mean increase 3.99 (2.7)ml/min/kg (95% CI -5.71 to -2.28) (p=0.004)) (Figure 3.6). Distance walked in the 6MWT improved from 532.17(78.25) m at T1 to 588.5(73.14)m (mean increase 56.3(35.33)m) at T2 (95% CI-78.78 to -33.88) (p=0.003) (Figure 3.7). At T1 mean HGS was 35.04(10.40) kg. At the time of T2 assessments however problems with the hand grip dynamometer resulted in inaccurate data collection and invalid results. Consequently, HGS data was not analysed.

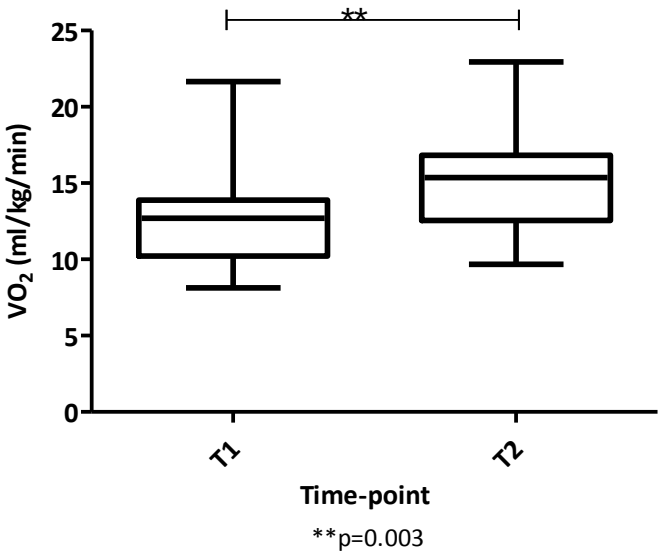

Figure 3-5 VO_2 (ml/min/kg) at Anaerobic Threshold

VO_2 at Anaerobic Threshold (AT) improved from 12.94 (3.87)ml/min/kg at T1 to 15.33(4.03) ml/min/kg at T2 (mean increase 2.39(1.70) ml/min/kg (95% CI -3.70 to -1.08) (p=0.003)).

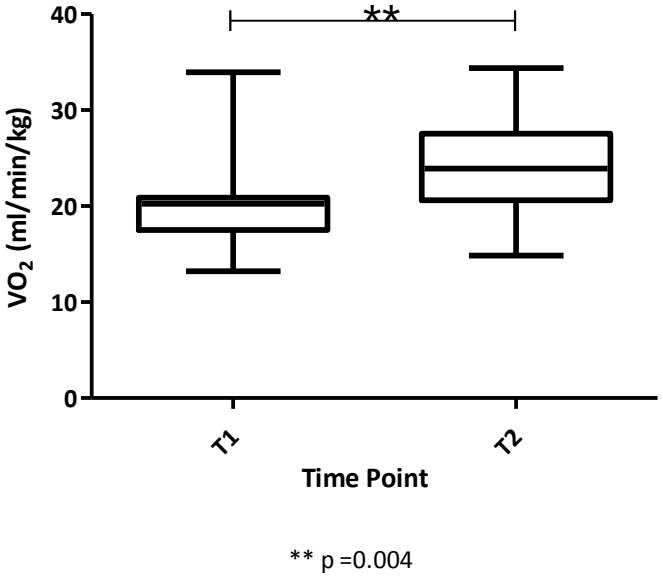

Figure 3-6 Maximum oxygen consumption (VO_2max (ml/min/kg))

VO_2max improved from 20.08 (5.2)ml/min/kg at T1 to 24.08 (4.99)ml/min/kg at T2 (mean increase 3.99 (2.7)ml/min/kg (95% CI -5.71 to -2.28) (p=0.004)).

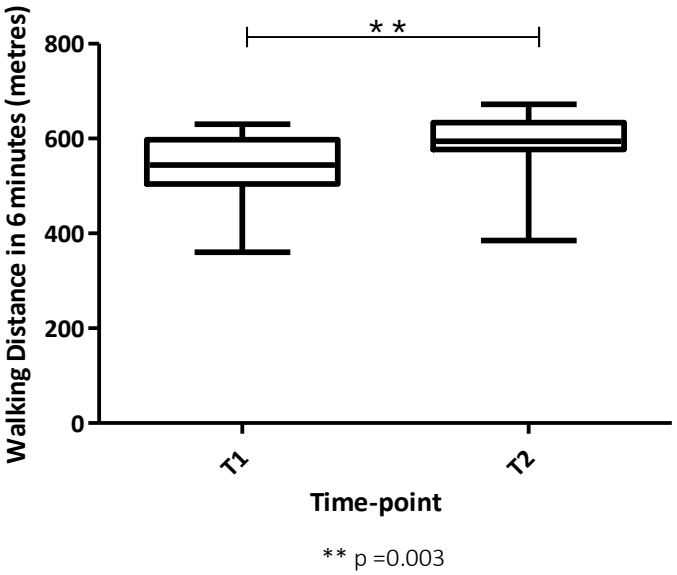

Figure 3-7 Six minute walking test (6MWT) distance (metres)

6MWT distance improved from 532.17(78.25) m at T1 to 588.5(73.14)m at T2 (mean increase 56.3(35.33)m) (95% CI-78.78 to -33.88) (p=0.003)).

3.4.5 Physical activity results

Physical activity results are presented in Table 3.4. No significant changes were observed in activity levels as measured by the Actigraph accelerometers.

Table 3.4 Actigraph activity monitor results

Variable	Pre-intervention (T1)	Post-intervention (T2)	Difference (T1-T2)	p-value
	Mean (SD)/ Median (IQR)	**Mean (SD)/ Median (IQR)**	**Mean (95% CI)**	
Number of Freedson (1998) Bouts	6.75 (4.33)	7.91 (5.07)	1.16(-4.12 to 1.78)	0.403[a]
Time spent in Freedson (1998) bouts (minutes)	181.08 (157.43)	207.67 (138.55)	26.58 (-129.88 to 76.72)	0.583[a]
Total time per activity level				
Total sedentary (minutes per week)	3587.00 (623.21)	3309.42 (582.21)	-277.58 (-62.24 to 617.41)	0.100[a]
Total light (minutes per week)	1871.91 (542.05)	1690.91 (415.88)	-181.00 (-34.82 to 396.82)	0.092[a]
Total moderate (minutes per week)	194 (312.25)	269.00 (31.75)	22.41 (-78.23 to 33.39)	0.396[b]
Total vigorous (minutes per week)	0.00 (21.50)	0.00 (31.75)	1.33 (-10.58 to 7.91)	0.893[b]
Total very vigorous (minutes per week)	0.00 (0.00)	1.16 (3.74)	1.16 (-3.54 to 1.21)	0.180[a]
Total moderate and vigorous activity (MVPA)(minutes per week)	194.00 (326.75)	287 (235.25)	24.91 (-82.69 to 32.85)	0.363[b]

Data expressed as mean (standard deviation) for normally distributed data and as median (interquartile range) for non-normally distribute data (total moderate, vigorous, and MVPA activity (minutes per week)).

[a] P-value for paired t-test comparing changes from T1 to T2.

[b] P-value for Wilcoxon signed rank test for non-normally distributed values.

3.4.6 Quality of Life

QOL scores from the EORTC QLQ-C30 are presented in Table 3.5, and QLQ-OES18 subscale results are detailed in Table 3.6. Clinically important difference in the EORTC are defined as an increase of 10% or more in a function scale, or reduction of 10% in a symptom scale (Nafteux et al., 2013). At baseline, global QOL was 70.83 (20.26), increasing to 81.25 (11.85) post-intervention (p=0.006). This increase of 10.42% was both statistically significant and clinically meaningful. The role function scale, and symptom scales of sleep, diarrhoea, financial issues, and cough, all showed clinically significant improvements, however these results did not achieve statistical significance (Table 3.5 and 3.6).

3.4.7 Body Composition

Body composition results are presented in Table 3.7. Bio-impedance analysis was completed on 9 of the 12 participants. Three participants were unable to be assessed secondary to joint replacements and compression socks. Skeletal muscle mass results are reported for 8 of these participants. Muscle mass was too low for the bio-impedance analyser to detect in one participant. Significant reductions in lean soft tissue in the left arm and total body water were observed from T1-T2. No significant changes were observed in any other body composition variable.

Table 3.5 European Organisation for Research and Treatment of Cancer (EORTC), core quality of life questionnaire, the QLQ-C30 results

Variable		Pre-intervention (T1)	Post-intervention (T2)	Difference (T1-T2)	P-value
	Scale abbreviation	Mean (SD)/ Median (IQR)	Mean (SD)/ Median (IQR)	Mean (95% CI)	
Global Health Status (QOL)	GL2	70.83 (20.26)	81.25 (11.85)	10.42 (-17.24 to -3.59)[c]	0.006[a*]
Function Scales					
Physical function	PF2	86.67 (33.33)	90.00 (18.33)	5.55 (-12.51 to 1.40)	0.083[b]
Role function	RF	91.67 (58.33)	100.00 (16.67)	15.27 (-30.56 to 0.01)[c]	0.160 [b]
Emotional function	EF	87.50 (25.00)	83.33 (25.00)	-0.69 (-.83 to 2.22)	0.317 [b]
Cognitive function	CF	77.77 (21.71)	80.56 (18.58)	2.77 (-14.58 to 9.02)	0.588 [a]
Social function	SF	100.00 (58.33)	91.67 (29.17)	8.33 (-21.49 to 4.83)	0.167 [b]
Symptom Scales					
Fatigue	FA	28.70 (21.94)	28.70 (26.14)	0.00 (-9.51 to 9.51)	1.000 [a]
Nausea/ vomiting	NV	00.00 (00.00)	00.00 (12.50)	1.83 (-4.44 to 1.66)	0.317 [b]
Pain	PA	00.00 (00.00)	00.00 (00.00)	-8.33 (-.11 to 16.78)	0.063 [b]
Dyspnoea	DY	33.33 (33.33)	16.67 (33.33)	-2.78 (-3.34 to 8.89)	0.317 [b]
Insomnia	SL	16.67 (66.67)	16.67 (33.33)	-13.89 (-7.21 to 34.99)[c]	0.102 [b]
Appetite loss	AL	16.67 (33.33)	00.00 (33.33)	0.00 (-15.64 to 15.64)	1.000 [b]
Constipation	CO	00.00 (33.33)	00.00 (33.33)	-5.55 (-6.67 to 17.78)	0.317 [b]
Diarrhoea	DI	16.67 (33.33)	00.00 (33.33)	-13.89 (-5.17 to 32.96)[c]	0.109 [b]
Financial difficulties	FI	00.00 (58.33)	00.00 (25.00)	-13.89 (-7.21 to 34.98)[c]	0.180[b]

*Data expressed as mean (standard deviation) for normally distributed data (Global Health Status, Cognitive function and Fatigue). The remaining not normally distributed scales are presented as median (interquartile range). *Statistically significant difference.*

[a] *P-value for paired t-test examining changes from T1 to T2.*

[b] *P-value for Wilcoxon Signed Rank Test examining changes from T1 to T2.*

[c] *Signifies a clinically significant change in a variable from T1 to T2.*

Table 3.6 European Organisation for Research and Treatment of Cancer (EORTC), oesophageal cancer subscale the QLQ-OES18 results

Variable		Pre-intervention (T1)	Post-intervention (T2)	Difference (T1-T2)	P-value
	Scale Abbreviation	Mean (SD)/ Median (IQR)	Mean (SD)/ Median (IQR)	Mean (95% CI)	
Dysphagia	OESDYS	5.55 (19.45)	0.00 (19.45)	-1.85 (-8.06 to 11.76)	0.854[b]
Eating Problems	OESEAT	8.33 (14.59)	8.33 (8.34)	-3.47 (-0.73 to 7.66)	0.084[b]
Reflux	OESRFX	0.00 (16.67)	0.00 (16.67)	-2.78 (-3.34 to 8.89)	0.492[b]
Pain	OESPA	11.11 (19.44)	0.00 (19.44)	-2.78 (-2.54 to 8.09)	0.257[b]
Trouble when swallowing saliva	OESSV	0.00 (00.00)	0.00 (00.00)	-2.78 (-3.33 to 8.89)	0.317[b]
Choked when swallowing	OESCH	0.00 (00.00)	0.00 (33.33)	5.56 (-13.80 to 2.69)	0.157[b]
Dry mouth	OESDM	0.00 (33.33)	0.00 (25.00)	-8.33 (-1.25 to 17.91)	0.083[b]
Trouble with taste	OESTA	0.00 (25.00)	0.00 (25.00)	0.00	1.000[b]
Trouble with coughing	OESCO	16.67 (33.33)	0.00 (0.00)	-11.11 (-5.37 to 27.59)[c]	0.157[b]
Trouble talking	OESSP	0.00 (00.00)	0.00 (0.00)	0.00	1.000[b]

Data not normally distributed. Data expressed as median (interquartile range) for all scales.

[b] *P-value for Wilcoxon Signed Rank Test for differences between T1 and T2.*

[c] *Signifies a clinically significant change in a variable from T1 to T2.*

Table 3.7 Body composition results

Variable	Pre-intervention (T1)	Post-intervention (T2)	Difference (T1-T2)	p-value
	Mean (SD)/ Median (IQR)	**Mean (SD)/ Median (IQR)**	**Mean (95% CI)**	
Weight (kg)	70.93 (19.95)	70.29 (19.47)	-0.65 (-0.32 to 1.61)	0.169[a]
BMI (kg/m^2)	24.04 (05.02)	23.79 (04.82)	-0.25 (-0.08 to 0.57)	0.121[a]
Waist circumference (cm)	84.68 (17.55)	83.39 (17.89)	-1.29 (-0.13 to 2.71)	0.071[a]
Mid arm circumference (cm)	26.43 (3.99)	26.54 (3.48)	0.11 (-0.92 to 0.71)	0.777[a]
Bioimpedance Analysis (n=9)				
Fat mass (kg)	19.48 (08.40)	19.74 (08.04)	0.26 (-1.35 to 0.83)	0.596[a]
Fat mass percentage (%)	27.11 (05.86)	28.22 (05.38)	1.11 (-2.35 to 0.13)	0.073[a]
Fat free mass (kg)	50.67 (14.99)	49.94 (15.02)	-0.73 (-0.12 to 1.58)	0.139[a]
Fat mass index (kg/m^2)	06.47 (02.45)	06.62 (02.31)	0.16 (-0.45 to 0.13)	0.252[a]
Fat free mass index (kg/m^2)*	18.60 (06.05)	18.60 (06.05)	-0.23 (-0.05 to .0.52)	0.093[b]
Skeletal muscle mass (kg)	25.44 (08.72)	24.86 (08.97)	-0.58 (-0.14 to 1.30)	0.093[a]
Lean soft tissue left arm (kg)	2.76 (01.17)	2.63 (01.13)	-0.13 (.041 to 0.22)	0.011 [a]*
Lean soft tissue right arm (kg)	2.86 (01.23)	2.74 (01.23)	-0.11 (-.02 to 0.25)	0.088[a]
Lean soft tissue left leg (kg)	8.23 (02.43)	8.08 (02.54)	-0.14 (-0.06 to 0.35)	0.140[a]
Lean soft tissue right leg (kg)	8.50 (02.68)	8.38 (02.81)	- 0.11 (-0.17 to 0.38)	0.378[a]
Total body water (litres)	37.31 (11.13)	36.62 (11.19)	-0.69 (0.02 to 1.35)	0.044[a]*
Extra cellular water (litres)*	19.1 (8.55)	18.60 (08.85)	-0.24 (-1.45 to 0.63)	0.182[b]
Hydration (%)	79.67 (6.34)	79.88 (5.77)	0.22 (-1.93 to 1.49)	0.772[a]
Xc (Ω)	56.04 (8.90)	50.48 (19.55)	-5.55 (-10.14 to 21.26)	0.438[a]
R (Ω)*	542.00 (240.35)	561.50 (217.80)	83.37 (-240.86 to 74.11)	0.257[b]
Phase Angle (Ψ)	5.11 (0.63)	5.08 (0.61)	-0.03 (-0.13 to 2.71)	0.397[a]

*Data expressed as mean (standard deviation) for normally distributed data and as median (interquartile range) for non-normally distribute data (Fat free mass index, extra cellular water, and R). *Statistically significant result. Abbreviation: BMI = Body mass Index.*

[a] P-value for paired t-test comparing changes from T1 to T2.

[b] P-value for Wilcoxon signed rank test for non-normally distributed values.

3.5 Discussion

Study I established that a 12 week multidisciplinary rehabilitation programme is safe and feasible for survivors of oesophageal cancer. Feasibility was demonstrated through recruitment rates, adherence, acceptability, and lack of adverse events. Participants also showed significant improvements in physical performance measures and QOL following the intervention. The results of Study I suggested the efficacy of this programme warranted further investigation and validation, ideally within a randomised control trial (RCT).

The feasibility of the Study I intervention was assessed through analysis of recruitment rates, adherence, and adverse events. A recruitment rate of 55%, was achieved through a mail-drop to potential participants. There is limited literature regarding the expected rate of recruitment in cancer survivor exercise trials, however studies suggest <40% is typical (Daley et al., 2007). Good feasibility was also demonstrated by a high adherence rate of 82(13)% to the supervised sessions. A previous review by Kampshoff et al. (2014) examined exercise adherence in breast or colorectal cancer survivors who in contrast to the complex needs of the cohort recruited to Study I, typically experience less treatment-related morbidity, and therefore may present fewer barriers to exercise. Kampshoff et al. (2014) reported that adherence ranged from 62-78%, therefore emphasising the particularly high acceptability of the Study I intervention. Participants in Study I reported work, family commitments and travel to the research centre as being barriers to attending supervised sessions.

Compliance with the home exercise sessions was monitored using exercise diaries. The number of completed home exercise sessions ranged from 7 to 92. The large range perhaps highlights the different levels of motivation among participants. The results show that several participants greatly exceeded the prescribed amount of home sessions whereas some participants struggled to comply. When considering only prescribed sessions, adherence was 78.15 (32.36)%. Participants reported lack of time, lack of motivation, aversion to instruction, other illness, and work and family commitments as reasons which prevented them from achieving the prescribed number of exercise sessions. Study I implemented a number of recommended methods to promote habitual exercise in cancer survivors (Bourke et al., 2014). These included goal setting, self-monitoring (using Polar heart rate monitors), and encouraging participants to repeat the same level of exercise achieved in their rehabilitation class in an unsupervised capacity. The

large variance in compliance with the unsupervised sessions in this study concurs with the review by (Bourke et al., 2013) that it is difficult to get sedentary cancer survivors to adhere to the recommended 150 mins of moderate intensity activity per week. All 12 participants completed the intervention signalling high acceptability. In terms of safety, no adverse events occurred during any assessments or treatment sessions.

Clinically meaningful and statistically significant improvements in cardiorespiratory fitness were demonstrated through increases in VO_2 at AT, and VO_2max. As highlighted in the systematic review in Chapter 1, the use of CPET to measure cardiorespiratory fitness in patients with oesophageal cancer has largely been confined to the preoperative setting (Moran et al., 2016, Forshaw et al., 2008, Nagamatsu et al., 2001). Little is known about the cardiorespiratory fitness of oesophageal cancer survivors as previous work has used subjective measures to determine physical function (Chang et al., 2014, Barbour et al., 2008). The results of the Study I T1 assessments demonstrate that survivors of oesophageal cancer have very poor or poor levels of aerobic fitness. Post-intervention, participants achieved an improvement in VO_2max of 3.99(2.7)ml/min/kg which is an improvement of greater than one metabolic equivalent of oxygen (MET) (1MET = 3.5ml/min/kg). In a systematic review and meta-analysis of exercise interventions in breast cancer survivors, McNeely et al. (2006) pooled data from 3 studies that assessed change in fitness using CPET and deemed an increase in exercise capacity of 3.39ml/min/kg to be clinically meaningful. An improvement in 1 MET corresponds with a 12% (men) and 17% (women) reduction in mortality (Gulati et al., 2003, Myers et al., 2002). Therefore, the improvement in VO_2max achieved by this feasibility study's participants may be considered a meaningful result. Improvement in physical function was also demonstrated by increased distance walked during the 6MWT. In patients with cancer, a change of 54m is deemed a clinically meaningful difference (Tatematsu et al., 2013a), and therefore the improvement observed in this study, 56.3(35.3)m, may be considered clinically meaningful for the participants. Large variance was seen in the physical activity scores as measured by the Actigraph activity monitor, and no statistically significant improvements were observed. A small increase of 24.92(95%CI -82.69 to 32.85) minutes per week in moderate-vigorous physical activity (MVPA), may have contributed to the improvements observed in aerobic fitness. MVPA is an important outcome for cancer survivors as it has been shown to correlate highly with HRQOL and overall survival in breast and colon cancer survivors (Boyle et al., 2015, Phillips et al., 2015).

Several domains of HRQOL improved following the Study I intervention. At baseline, participants had global health scores that were slightly lower than normative values (T1 average = 70, normative data = 81) (Scott NW, 2008). At follow-up, global health scores exceeded the normative data (T2 average =81). As survivors of cancer often experience psychosocial issues which may impair their ability to optimally engage in society (Aaronson et al., 2014), it is important to see that participants felt that their HRQOL had improved as a result of the rehabilitation programme. However, none of the symptom scales showed statistically significant improvements. This may have been due to the small sample size, and large variation in the symptoms experienced by participants. The subsequent RCT (Study II) will aim to detect improvements in symptom scores as previous research has documented the long-term symptom burden survivors of oesophageal cancer experience (Chang et al., 2014).

Body composition did not change with the intervention. Malnutrition is a serious long-term issue for patients post-oesophagectomy (Elliott et al., 2017). Other symptoms like dysphagia and reflux can also impair patient's ability to ingest adequate amounts of food (D'Journo et al., 2012, Ouattara et al., 2012). Weight loss post-surgery consists of loss of fat mass and depletion of skeletal muscle mass, termed sarcopenia (Anandavadivelan and Lagergren, 2016, Harada et al., 2016). Post-operative weight loss has been associated with reduced disease free survival (D'Journo et al., 2012). Therefore, it is an important outcome achieved by this feasibility study that the nutritionally compromised study population, under the guidance of a physiotherapist and dietitian, were able to increase their exercise participation without any compromise to body composition. The severity of the loss of skeletal muscle mass that may occur in oesophageal cancer survivors was highlighted by the results of one participant whose skeletal muscle mass was too low to be detected by BIA. Sarcopenia has been identified as a potential biomarker for poor prognosis in oesophageal carcinoma (Harada et al., 2016). The protocol for Study II of this thesis was amended following Study I to incorporate a resistance training component to attempt to counteract the devastating consequences of sarcopenia.

3.6 Study Limitations

Study I had several limitations that warrant discussion. Firstly, as a pilot study, it had a small sample size and a single arm. The primary aim of this study design was to assess feasibility, and a larger adequately powered RCT (Study II) has been implemented to examine the efficacy of

the intervention. Other lessons learned which informed the design of Study II, included the need for a resistance training component to combat the loss of muscle mass described in oesophageal cancer survivors, and also the need for a wellness measure. Post-intervention feedback highlighted that there was a great sense of improved confidence and well-being among participants as a result of participation in the multi-disciplinary programme. As positive psychological well-being has been associated with a favourable effect on survival in both healthy and disease populations (Chida and Steptoe, 2008), in the subsequent RCT (Study II) an outcome that captures that 'wellness' factor was included in the assessment battery. Finally, the cohort of survivors included in this feasibility study were known to have node negative pathology, and lived within a manageable commute of the research centre. Accordingly, the generalisability of the results to a wider cohort of cancer survivors is unclear.

3.7 Conclusion

Study I found that a 12 week multidisciplinary rehabilitation programme consisting of exercise, dietary counselling, and education was feasible for survivors of oesophageal cancer who were greater than one year post treatment completion. Clinically significant improvements in functional performance (VO_2 at AT, VO_2max, and 6MWT distance) and HRQOL were evident without compromise to body composition. As results of this pilot study were limited due to its' nature, the efficacy of this programme was further investigated by RCT in Study II.

Chapter 4 Study II: The impact of a multidisciplinary rehabilitation programme on cardiorespiratory fitness in oesophagogastric cancer survivorship – A Randomised Controlled Trial

Abstract

Aims:

The feasibility of a multidisciplinary rehabilitation programme was established in Study I. Study II evaluated the efficacy of the intervention on increasing cardiorespiratory fitness and quality of life (QOL) in oesophago-gastric cancer survivorship by RCT.

Methods

Study II randomized 43 disease-free patients at a median (range) of 30(6-62) months following treatment with curative intent, and without contraindications to exercise participation. Participants were randomized to receive either usual care, or the 12-week multidisciplinary rehabilitation programme. The primary outcome was maximal cardiopulmonary exercise testing (VO_2max). Secondary outcomes included physical function (6MWT), accelerometer measured activity levels, muscle strength (HGS and 1-RM), body composition (bio-impedance analysis), and QOL (EORTC-QLQ-C30). Outcomes were assessed at baseline (T0), post-intervention (T1), and at three-month follow-up (T2).

Results

Twenty-two participants were randomized to the control group (mean (standard deviation) age 64.14(10.46) years, BMI 25.67(4.83) kg/m^2, time post-surgery 33.68(19.56) months), and 21 to the intervention group (age 67.19(7.49) years, BMI 25.69(4.02) kg/m^2, time post-surgery 23.52(15.23) months). Three participants withdrew due to disease recurrence and one control participant dropped-out. Mean adherence to the exercise sessions were 94(12)% (supervised) and 78(27)% (home-based). Compared to T0, the intervention arm experienced a mean improvement in VO_2max of 3.47(2.58)ml/min/kg at T1, and 2.99(3.37)ml/min/kg at T2. In significant contrast, the control group VO_2max declined by 0.86(2.50)ml/min/kg at T1, and by 1.64(2.73)ml/min/kg at T2. Correcting for baseline VO_2max, the intervention arm had significantly higher VO_2max at both T1, 22.20(4.35) vs 21.41(4.49)ml/min/kg, $p<0.001$, and T2, 21.75(4.27) vs 20.74(4.65)ml/min/kg, $p=0.001$, compared with the control group. Correcting for baseline values, no significant changes in secondary measures were observed.

Conclusion

A 12 week multidisciplinary rehabilitation programme significantly improved the cardiorespiratory fitness of disease-free patients after oesophagogastric cancer surgery, without compromise in body composition. This RCT provides proof of principle for rehabilitation programs in survivorship of upper gastrointestinal cancer.

4.1 Introduction

The systematic review in Chapter 1, described the problem of physical decline in survivors of oesophago-gastric cancer, and identified that there is a paucity of literature regarding rehabilitative measures that aim to improve physical functioning in oesophago-gastric cancer survivorship. Furthermore, Chapter 1 highlighted the ongoing difficulties faced by oesophago-gastric cancer survivors with regards to nutrition, weight loss, and sarcopenia. Consequently, Study I, described in Chapter 3 of this thesis, investigated the feasibility of a multidisciplinary rehabilitation programme consisting of supervised and unsupervised exercise, dietary counselling, and education sessions in 12 survivors of oesophageal cancer. Study I established the feasibility of this intervention, and therefore the efficacy of that rehabilitative programme required further investigation by randomised control trial (RCT).

Consequently an RCT design was implemented in Study II to investigate the ability of the programme described in Study I to improve the cardiorespiratory fitness of survivors of oesophago-gastric cancer. A number of protocol amendments were made for Study II following the experience of Study I. Firstly, the recruitment timeframe was expanded to include participants from at least 6 months up to 5 years of survivorship to ensure study accrual targets were met within the planned study timeframe. Second, inclusion criteria were expanded to include those with gastric cancer, as given the similarities described in Chapter 1 between oesophageal and gastric cancer, gastric cancer survivors were considered an equally suited target population for this specific intervention. The inclusion of patients with gastric cancer also helped ensure recruitment targets were met. Finally, as discussed in Chapter 3, results of Study I highlighted the need for a well-being assessment, and also the addition of a resistance training component to target cancer related sarcopenia. Accordingly these were added to the Study II protocol.

The following sections outline the methods, results, and discussion of Study II.

4.2 Study aims and objectives

The overall aim of Study II was to examine the efficacy of a 12 week multidisciplinary led rehabilitation programme consisting of supervised and unsupervised exercise sessions, dietary counselling, and education sessions to improve the cardiorespiratory fitness of survivors of oesophago-gastric cancer who were >6 months and $\leq$5years post oesophago-gastric cancer surgery.

Specific objectives of Study II were to determine:

- The impact of a 12 week multidisciplinary rehabilitation programme on cardiorespiratory fitness as measured by CPET (VO_2max).
- The impact of the 12 week multidisciplinary rehabilitation programme on functional capacity as measured by 6MWT.
- The impact of the 12 week multidisciplinary programme on muscle strength as determined by HGS, and 1RM leg press strength.
- The impact of the 12 week multidisciplinary rehabilitation programme on accelerometer measured physical activity levels.
- The effects of the 12 week multidisciplinary rehabilitation programme on body composition.
- The impact of the 12 week multidisciplinary rehabilitation programme on HRQOL and well-being.

4.3 Methods and measures

4.3.1 Study design

Study II was a randomised controlled trial (RCT) of an intervention (12 week multidisciplinary rehabilitation programme). The methodological characteristics of a RCT have been described previously in Chapter 2, section 2.2.1.

4.3.2 Funding

This study was part of a Health Research Board funded project (Award number: HRA-POR-2014-535).

4.3.3 Ethical Approval

Ethical approval was granted by the joint St James's Hospital-Tallaght Hospital Research Ethics Committee (REC Reference: 2014-11 Chairman's Action (2)) (Appendix XII). Hospital approval was granted by the Research and Development Hub at St James's Hospital. As per Study I all procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments. All Study II researchers completed Good Clinical Practice training in advance of the study commencing. All participants were required to provide written, informed consent (Appendix XV).

4.3.4 Sampling and Recruitment

The lead investigator (Linda O'Neill (LON)) identified potential participants from the Upper Gastrointestinal Cancer Registry at St James's Hospital (SJH) Dublin database. When a patient's medical records indicated that he/she met all inclusion criteria, LON liaised with the Upper Gastrointestinal Surgery Team at SJH to confirm the patient's suitability for baseline testing and final eligibility screening. Once the surgical team had approved potential participation, LON contacted suitable candidates via a letter. The letter contained a copy of the patient information leaflet (PIL) (Appendix XV), and invited patients to express an interest in participation. Patients that did not reply received one follow-up phone call to find out i) did they receive the invitation letter, and ii) were they considering participation in the study.

Following on from Study I the inclusion criteria for Study II was expanded to include patients with oesophageal, oesophageal junction, and gastric cancer, and the timeframe for recruitment was expanded to include those from 6 months to 5 years post curative surgery, to ensure study accrual targets were met in the planned study time-frame. Accordingly, the inclusion criteria for Study II were; >6months and ≤5years post either oesophagectomy or gastrectomy +/- neo-adjuvant/adjuvant/perioperative chemo/chemoradiotherapy with curative intent for oesophageal/oesophageal junction/gastric cancer, and medical approval to complete CPET and the prescribed exercise intervention. Patients were deemed ineligible for participation if; i) treatment outcome was unsuccessful, ii) there was evidence of metastatic or recurrent disease, iii) lack of medical consent, or iv) presence of co-morbidities that would preclude safe exercise participation including; ECG abnormalities at rest or during CPET, congestive heart failure (New York Heart Association Class II, III or IV), uncontrolled hypertension (systolic blood pressure >180mm Hg and/or diastolic blood pressure >100 mm Hg at rest), recent serious cardiovascular

events (within 12 months) including, but not limited to, transient ischemic attack, cerebrovascular accident, or myocardial infarction, unstable cardiac, renal, lung, liver, or other severe chronic disease, uncontrolled atrial fibrillation, left ventricular function <50% (as per most recent MUGA/ECHO), or Chronic Obstructive Pulmonary Disease (COPD) GOLD Stages III/IV (FEV_1<50%, FEV_1/ FVC<70).

4.3.5 Measures and Testing Protocol

As per Study I, all study appointments for Study II were completed in the Wellcome Trust HRB Clinical Research Facility (CRF) at SJH, Dublin. Testing was completed at baseline (T0), immediately post-intervention (T1), and at three-month follow-up (T2) (Figure 4.1).

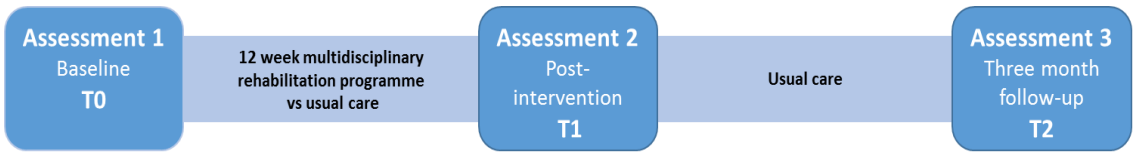

Figure 4-1 Study II assessment time-points

Multidisciplinary Research Team

Due to the multidisciplinary nature of Study II, the lead investigator (LON) coordinated the delivery of the programme with the support of a multidisciplinary research team for the duration of the study. Similar to Study I LON had responsibility for protocol development, recruitment, data collection, management of all study visits, implementation of the supervised and unsupervised exercise sessions, coordination of the education sessions, data analysis, and dissemination of results. The dietary intervention for Study II was delivered by Dr Annemarie Bennett (AMB).

The assessment battery for Study II was carried out by a team of researchers, led by the lead investigator (LON). The primary outcome, CPET, was performed by an assessor blinded to the participant's study group allocation. Over the 14 months of Study II assessments, there were four blinded assessors; Kate Devenney, Andrew Brooks, Louise O'Connor, and Philip O'Gorman. All assessors received the same training to ensure standardisation of CPET delivery. The CPETs were supervised by Dr Conor Murphy (CM) of the Upper Gastrointestinal surgery team at SJH.

In the case of CM being unavailable, another member of the surgical team supervised the CPET. LON had responsibility for consenting participants and interviewing them regarding their medical history. LON also took measures of height and weight prior to the CPET, conducted the 6MWT, 1RM test, and was responsible for the initialisation of the Actigraph activity monitors, and for providing participants with their questionnaire packs. AMB was responsible for the assessment of BIA and circumferential measurements, HGS, and the dietary assessment of participants. The background, validity, and reliability of all measures performed in Study II have been described previously in Chapter 2.

The following measurements were completed in the listed order:

- **Standing height** and **weight** were measured as described in section 2.4.3.
- Pre-CPET screening included resting blood pressure and ECG. Participants that successfully completed screening proceeded on to the **CPET**, which was performed by a blinded assessor as per the protocol in section 2.3.1.3.

Following a recovery period:

- **Waist circumference** and **mid-arm circumference** were measured as per section 2.4.3.
- **Body composition** was analysed using BIA according to the procedures in section 2.4.5.
- **Hand grip strength** was quantified using hand grip dynamometry as per the procedure in section 2.3.2.3.
- Physical performance was analysed using the **6MWT** as per the protocol in section 2.3.1.5.
- Leg strength was determined by a leg press **1-RM** test as outlined in section 2.3.2.5.
- Participants were provided with an **Actigraph GT3-X** accelerometer to wear for one week when leaving the centre (measurement procedure outlined in section 2.5.3). The monitor was then returned in a stamped addressed envelope to the research team.
- Participants were provided with the **EORTC-QLQ-C30** and **OES18,** along with a **Perceived well-being questionnaire** to be completed within one week of their study assessment (measurement procedure described in section 2.6.2 and 2.6.4).

Information pertaining to patient's past medical history and demographic characteristics was retrieved from hospital medical records including medical charts, the Powerchart electronic

patient record system at SJH, the Upper Gastrointestinal Cancer Registry database at SJH, and from participant interviews.

4.3.6 Randomisation

Following successful completion of baseline assessments, participants were then randomised to one of two groups. A control group that received usual care, or an intervention group that were required to take part in the 12 week multidisciplinary rehabilitation programme. Methods of randomisation were previously described in Chapter 2, section 2.2. Randomisation for Study II was performed by a research physiotherapist independent to the study (Grainne Sheill (GS)). GS used GraphPad software to generate a table of random numbers to determine study group allocation. Group allocation was concealed in a sealed envelope. Once participants had successfully completed their baseline assessments, LON opened the sealed envelope corresponding to their study identification number and notified participants of their study group allocation.

4.3.7 Multidisciplinary Rehabilitation Programme

Following completion of baseline (T0) assessments, participants randomised to the intervention group commenced the 12 week multidisciplinary rehabilitation programme. The number of rehabilitation sessions was unchanged from Study I and the rehabilitation schedule is described in Chapter 3, Figure 3.2.

4.3.7.1 Exercise Programme

Supervised exercise sessions were delivered by the lead investigator, a physiotherapist (LON). The maximum patient instructor ratio was 1:5. The aerobic component of the exercise programme was unchanged from Study I, and the frequency, intensity, type and time of exercise is described in section 3.3.5.1. As per Study I, intensity was monitored using polar heart rate monitors (Polar FT7, China).

As survivors of oesophago-gastric cancer are at significant risk of muscle atrophy and sarcopenia, a resistance training component was added on to the exercise programme for Study II. The

ACSM (2010) recommends that in addition to 150 minutes of moderate intensity physical activity per week, survivors of cancer should complete two to three sessions of resistance training a week with at least 48 hours between sessions, at an intensity of 40-60% of 1RM, with one to three sets of 8 to 12 repetitions per exercise involving all major muscle groups. Recently a meta-analysis by Strasser et al. (2013) reported that low/moderate intensity resistance training (<75% 1RM) achieved greater improvements in upper limb muscle strength in cancer survivors compared to moderate/high intensity resistance training (>75%) ($p=0.042$). Therefore, low-load high-repetition training may be more appropriate for cancer survivors who may be unable to sustain high intensity training due to sarcopenia related comorbidities. Accordingly, the resistance training component of the Study II exercise intervention was based on the recommendations of Strasser et al. (2013). The resistance training programme is presented in Table 4.1. Supervised resistance training sessions occurred immediately following supervised aerobic sessions to ensure muscles were adequately warmed-up. The resistance training programme targeted major upper and lower limb muscle groups. Examples of exercises completed by participants included bicep curls, overhead press, and leg press. Participants were supplied with Theraband elastic resistance bands to complete their prescribed unsupervised resistance training sessions at home.

As with Study I participants in the Study II intervention group were requested to record their home aerobic and resistance training sessions in an exercise diary (Appendix XVI). Additional methods of monitoring adherence were also included in the Study II protocol. Firstly, participants were required to record their aerobic sessions on their polar heart rate monitors. Secondly, Study II participants were given the opportunity to use Salaso, a web and smartphone based application, to record their adherence to unsupervised aerobic and resistance training sessions in conjunction with the exercise diary. The Salaso application was developed by physiotherapists to enhance the delivery of home exercise programmes, and includes a library of high definition exercise videos and the ability for patients to log adherence to exercise, and set personalised goals. A Health Research Board (HRB) Knowledge Exchange and Dissemination (KEDs) award was attained to develop and adapt the app. The application was customised especially for the Study II intervention both in terms of content and branding. This was facilitated through several consultation meetings between the Salaso app developers and the multidisciplinary rehabilitation team. A research assistant (Jonathan Moran (JM)) was employed through the KEDs funding to provide training and support to participants that wished to trial the use of the Salaso app. Each week LON informed JM of participant's weekly exercise prescription

and he updated the exercise information on participant's Salaso profiles accordingly. Salaso is registered with the UK and Ireland Data Protection Commissioner, and all data was secured in a password protected environment. Ethical approval was obtained for this amendment to the protocol (Amendment III, REC Reference:2016-01 List 1 (9), Appendix XII).

Table 4.1 Study II resistance training programme

Week	Frequency (days/week)		Intensity	Sets (S/MG/W)
	Supervised	Unsupervised		
1	2	0	12RM	2
2	2	0	12RM	2
3	2	0	13RM	3
4	2	0	13RM	3
5	1	1	14RM	4
6	1	1	14RM	4
7	1	1	15RM	5
8	1	1	15RM	5
9	0	2	16RM	6
10	1	1	16RM	6
11	0	2	17RM	6
12	1	1	17RM	6

S/MG/W = sets per muscle group per week

4.3.7.2 Dietary Counselling

As per Study I, dietary counselling was held in a 1:1 setting with the study dietitian (AMB). AMB delivered tailored dietary advice and education to the participants and specific dietary goals were set at the end of each session. AMB determined the number of dietary counselling sessions received by each participant based on clinical need. Weight was monitored consistently throughout the 12 week rehabilitation programme to ensure that participants were maintaining weight or were losing weight safely.

4.3.7.3 Education Sessions

Group education sessions were delivered by a range of members of the multidisciplinary team, focusing on topics that were of specific relevance to survivors of oesophago-gastric cancer. Following feedback from participants in Study I, the talks from the Irish Cancer Society and Oesophageal Cancer Fund were removed from the schedule, and were replaced with an initial introductory lecture, and an additional dietary talk. A representative from pyscho-oncology at SJH was unavailable, instead colleagues from the Discipline of Occupational Therapy in Trinity College Dublin facilitated the fatigue management talk in Study II. Details of the education sessions are presented in Table 4.2 below.

Table 4.2 Study II education talks

	Presenter	Role	Topic
1	Ms Linda O'Neill	Research Physiotherapist	Introduction to programme
2	Dr Annemarie Bennett	Research Dietitian	Nutrition in oesophago-gastric cancer survivorship
3	Dr Jessie Elliot	Upper GI Surgical Team	Medical issues in oesophago-gastric cancer survivorship
4	Ms Linda O'Neill	Research Physiotherapist	Physical activity in cancer survivorship
5	Ms Patricia Pugh	ARC Cancer Support Representative	Mindfulness
6	Dr Deirdre Connolly/ Ms Lauren Boland	Research Occupational Therapists	Fatigue management
7	Dr Annemarie Bennett	Research Dietitian	Making the best food choices for a healthy weight

4.3.8 Statistical Analysis

The primary outcome of Study II was cardiorespiratory fitness (VO_2max). As previously discussed an increase of 1 MET (3.5ml/min/kg) is considered a clinically important increase in cardiorespiratory fitness, as it has been associated with a significant reduction in all-cause mortality risk (Gulati et al., 2003, Myers et al., 2002). In order to achieve a 3.5ml/min/kg increase in cardiorespiratory fitness, standard deviation 3.81 ml/min/kg with 5% significance and 80% power, a total sample size of 19 participants per arm was required. To allow for drop-outs during the rehabilitation programme, 44 participants (22 per arm) were recruited.

Statistical analyses were performed using SPSS 22 (SPSS Inc.; Chicago, IL, USA). Prior to analysis variables were tested for normality of distribution using the Kolomogorov-Smirnov test. Normally distributed continuous variables are presented as mean (standard deviation), non-parametric continuous variables are presented as median (inter quartile range). Normally distributed data was analysed using Analysis of Covariance (ANCOVA), using baseline values as the covariate. Attempts were made to transform non-normally distributed variables using $\log_{10}$ or square root transformations. When normality could not be achieved the non-parametric Quade's test (Quade, 1967) was used instead of ANCOVA, again using baseline values as covariate. These statistical tests have been described previously in Chapter 2, section 2.2.4. A p-value of <0.05 was considered statistically significant. Interpretation of effect sizes was performed according to the original scales described by Cohen, 0.2 -0.5 (small to moderate effect), 0.51 -0.80 (moderate to large effect), and >0.80 large effect (Pallant, 2016). LON developed and implemented the analysis plan. The statistical approach was discussed and verified with the Centre for Support and Training in Analysis and Research (C-Star) at University College Dublin during a one hour consultation.

4.4 Results

4.4.1 Participant characteristics

Screening of both the Upper Gastrointestinal Cancer registry at SJH and the RESTORE trial databases identified 264 patients that had undergone curative surgery from 2011 to 2016, and that were known to be free from disease at their last follow-up (Figure 4.2). Between April 2016 and December 2016, 109 patients who had completed curative treatment for oesophageal or gastric cancer and met all other inclusion criteria were invited to participate in the study. Four patients had developed disease recurrence since their last follow-up and therefore no longer met the inclusion criteria, three had passed away, and 58 patients declined participation. The reasons for non-participation were family commitments (n=4), work commitments (n=9), travel too arduous (n=15), unable for time commitment (n=3), unwell (n=3), other health problems (n=2), or unknown (n=22). Forty-four patients consented to participation and were recruited over four enrolment phases. Phase I commenced in April 2016 (n=14), Phase II in June 2016 (n=11), Phase III in September 2016 (n=17), and Phase IV in December/January 2016/17 (n=2) (Figure 4.3).

Of the 44 patients that consented to participate, one participant did not complete baseline assessments due to previously undiagnosed atrial fibrillation, which was identified during ECG testing. Forty-three participants successfully completed baseline assessments and progressed to randomisation. Twenty-two participants were randomly assigned to the control group and 21 to the intervention group. Three participants were withdrawn from the study due to disease recurrence (two withdrawals from the control group after T0, and one withdrawal in the intervention group following T1). One drop-out occurred following T0 in the control group. Therefore, 43 participants completed T0 testing, 40 completed T1 testing, and 39 completed T2 testing.

Demographic characteristics of participants are presented in Table 4.3. Between group baseline characteristics were compared using independent t-tests, the Fisher's exact test, and the Chi-squared test were applicable. At baseline participants in both groups were comparable on most characteristics, with the exception of baseline cardiorespiratory fitness which was significantly higher in the control group ($p=0.026$).

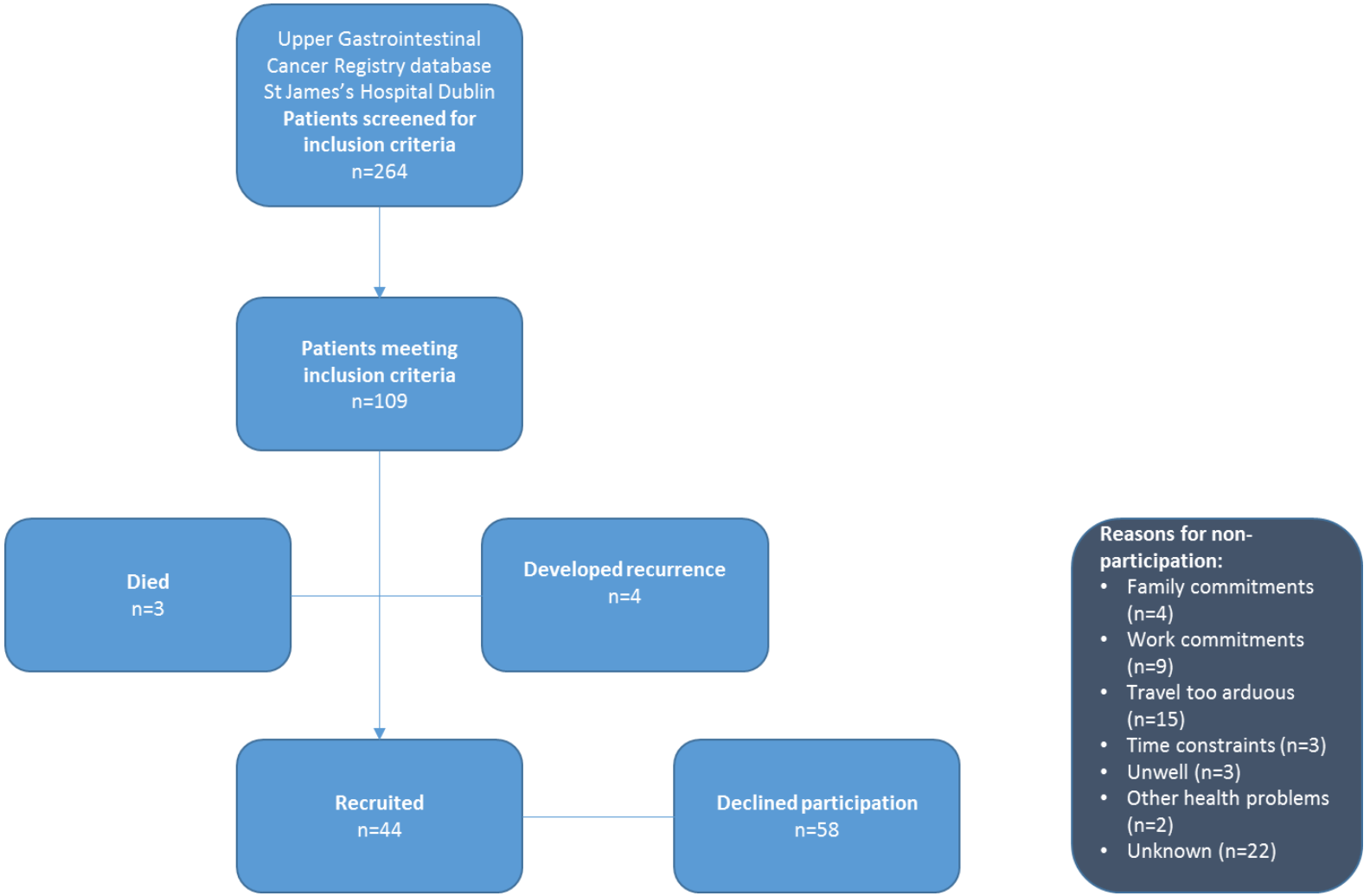

Figure 4-2 Study II Recruitment

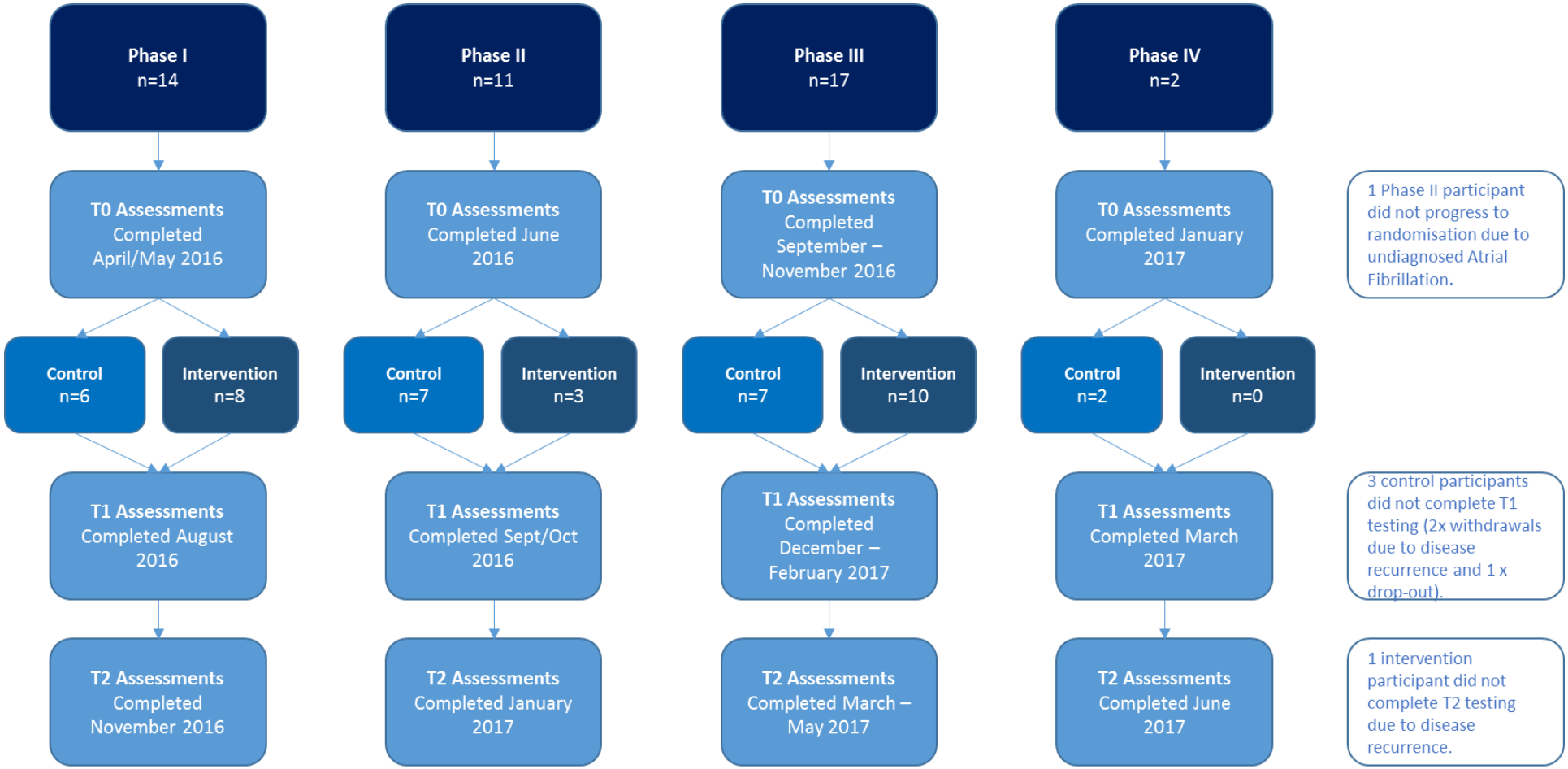

Figure 4-3 Study II details of enrolment phases

Recruitment for Study II, took place over a 10 month period from April 2016 to January 2017, in four enrolment phases. Phase I commenced in April 2016 (n=14), Phase II in June 2016 (n=11), Phase III in September 2016 (n=17), and Phase IV in December/January 2016/17 (n=2)

Table 4.3 Demographic characteristics of Study II participants

	Control (N=22)		Intervention (N=21)		
	Mean/ Frequency	**(Standard deviation)/(%)**	**Mean / Frequency**	**(Standard deviation)/(%)**	**p-value**
Sex					
Male	18	(81.8)	17	(81.0)	1.000
Female	4	(18.2)	4	(19.0)	
Age (years)	64.14	(10.46)	67.19	(7.49)	0.280
BMI (kg/m^2)	25.67	(4.83)	25.69	(4.02)	0.989
Baseline VO_{2max} (ml/min/kg)	21.75	(4.49)	18.73	(4.07)	0.026*
Baseline Fitness Category					
Very Poor	13	(59.1)	14	(66.7)	0.843
Poor/Fair	9	(40.9)	7	(33.3)	
Time post-surgery (months)	33.68	(19.56)	23.52	(15.23)	0.065
Histological type of tumour					
Adenocarcinoma	19	(86.4)	14	(66.7)	N/A
Squamous Cell Carcinoma	2	(9.1)	6	(28.6)	
Associated Barrett's	1	(4.5)	1	(4.8)	
Tumour Location					
Oesophagus	4	(18.2)	8	(38.1)	N/A
OG Junction	15	(68.2)	12	(57.1)	
Stomach	3	(13.6)	1	(4.8)	
Tumour Classification					
(T) Tis	2	(9.1)	2	(9.5)	N/A
T1	4	(18.2)	7	(33.3)	
T2	4	(18.2)	2	(9.5)	
T3	12	(54.5)	10	(47.6)	
T4	0	(0.0)	0	(0.0)	
(N) N0	14	(63.6)	12	(57.1)	
N1	3	(13.6)	8	(38.1)	
N2	5	(22.7)	1	(4.8)	

(M)	M0	22	(100)	21	(100)	
Type of Surgery						
	Transhiatal Oesophagectomy	5	(22.72)	8	(38.10)	N/A
	Transthoracic Oesophagectomy	11	(50.00)	11	(52.40)	
	Gastrectomy	6	(27.27)	2	(9.52)	
Neoadjuvant Treatment						
	Yes	16	(72.7)	11	(52.4)	0.287
	No	6	(27.3)	10	(47.6)	
Adjuvant Treatment						
	Yes	5	(22.7)	4	(19.0)	1.000
	No	17	(77.3)	17	(81.0)	
Barrett's Oesophagus						
	Yes	14	(63.6)	12	(57.1)	0.902
	No	8	(36.4)	9	(42.9)	

Data are presented as the mean (standard deviation) for continuous variable and as frequency (percentage) for categorical variables. N/A – unable to run a statistical test to compare between groups on some categorical variables as some variables do not meet minimum criteria of 5 in a category for the Chi-squared test and Fisher's exact test is only applicable for a 2 x 2 table.

**Statistically significant difference*

Abb: BMI = Body Mass index, T= Tumour, N=Nodes, M=Metastases

4.4.2 Data normality

At all three time-points the physical performance and activity variables of VO_2max, VO_2 at AT, 6MWT distance, HGS, 1RM, and time spent in light physical activity were normally distributed, and the number of Freedson (1998) bouts, total time in Freedson (1998) bouts, and vigorous activity were not normally distributed. Sedentary activity was normally distributed at T0 and T2, but was not normally distributed at T1. Moderate activity, and total moderate and vigorous activity (MVPA) were not normally distributed at T0 and T1, but were normally distributed at T2. Attempts were made to transform non-normally distributed physical activity level variables using square root transformations (log transformations were not applicable as some participants spent zero time in some categories of activity (log0 is undefined)), however normality was not achieved, and therefore, non-parametric tests were used for the analysis of all physical activity level variables with the exception of light activity.

At all three time points the body composition variables of waist circumference, fat free mass index (FFMI), lean soft tissue left leg (LSTLLEG), and extracellular water (ECW) were normally distributed. All other body compositions were transformed using log transformations to achieve the assumption of normality required for ANCOVA. None of the EORTC-QLQ-C30 or EORTC-QLQ-OES18 results were normally distributed. Attempts were made to transform the scale data using square root transformations (log transformations not applicable as some scale scores equal to zero (log0 is undefined)), however normality was not achieved, and the non-parametric, Quade's test was used for analysis.

4.4.3 Adverse events

No serious adverse events occurred during assessments or in the intervention period. During the rehabilitation programme, five participants reported an increase in musculoskeletal pain from pre-existing musculoskeletal conditions as a result of participation in the exercise programme. However, this was anticipated and accordingly the study physiotherapist (LON) delivered 1:1 tailored advice on pain management and modified their exercise prescription to minimise further musculoskeletal discomfort**.**

4.4.4 Adherence to exercise sessions

4.4.4.1 Adherence to supervised exercise sessions

Participants randomised to the intervention group (n=21) attended a mean 13.14(1.62) of the 14 scheduled supervised exercise sessions representing an adherence rate of 93.88(11.58)%.

4.4.4.2 Adherence to unsupervised exercise sessions

Adherence to the unsupervised, home-based exercise sessions was recorded using both self-reported measures (exercise diary or online Salaso application (app)) and polar heart rate monitors. All 21 participants were offered the opportunity to use the Salaso app in addition to an exercise diary to record their adherence. Only 5/21 participants randomised to the intervention group attempted to use the Salaso app. Following familiarisation with the app, 3/5 then expressed a preference to use the exercise diary and discontinued use of the app. Therefore, only two participants reported their adherence using the app for the duration of the rehabilitation programme.

Participants were prescribed a total of 37 unsupervised aerobic sessions and 10 resistance training sessions during the 12 week rehabilitation programme. Self-reported adherence to aerobic home exercise sessions was 77.99(27.31)%, and the total number of completed unsupervised aerobic sessions recorded by participants ranged from 5 to 64. Self-reported adherence to the unsupervised resistance training programme was 60.48(34.42)%, with the total number of sessions recorded by participants ranging from 0 to 10. Polar heart rate data was available on 20 participants. Data was missing on one participant due to a technical error. Adherence to the aerobic home exercise sessions as measured by the polar heart rate monitors was 65.95(32.60)%, and the total number of unsupervised aerobic sessions recorded ranged from 4 to 44.

Adherence to the unsupervised aerobic sessions as measured by self-report vs polar hear rate monitor was compared using a paired t-test. Self-reported adherence was significantly higher by 14.32(26.73)% (95% CI, 1.81-26.84 p=0.033). From the analysis of the polar data some participants appeared to have difficulty following the instructions for recording exercise sessions with the monitor. 14/20 participants for whom polar heart data was available, failed to stop the monitor after their prescribed session and the monitor continued to record from >4to<99 hours on a

minimum 1 occasion up to a max of 25 occasions. The mean number of times the polar heart rate monitor was not stopped was 6.45(7.23) per participant.

4.4.5 Physical function outcomes

4.4.5.1 Changes in cardiorespiratory fitness

Cardiorespiratory fitness was determined by CPET. Baseline (T0) CPETs were completed on 43 participants. At T1 40 CPETs were performed (1 drop-out and 2 withdrawals due to disease recurrence), and at T2 38 CPETS were performed (1 withdrawal due to disease recurrence and 1 participant declined to take part in the CPET due to an arthritic flare-up). Results for VO_2max, and VO_2 at AT at each time-point are detailed in Table 4.4. An independent t-test showed that the control group had a significantly higher VO_2max at baseline (21.75(4.49) ml/min/kg) when compared to the intervention group (18.73(4.07) ml/min/kg) (95% CI, 0.38-5.67, p=0.026). Baseline differences in VO_2 at AT where not statistically significant, 95% CI, -4.9 to 2.53, p=.180 (control =12.96(2.68)ml/min/kg vs intervention 11.94(2.19)ml/min/kg).

Compared to T0, the intervention arm experienced a mean improvement in VO_2max of 3.47(2.58)ml/min/kg at T1, and 2.99(3.37)ml/min/kg at T2. In significant contrast, the control group VO_2max declined by 0.86(2.50)ml/min/kg at T1, and by 1.64(2.73)ml/min/kg at T2. ANCOVA was used to analysis changes between the groups in cardiorespiratory fitness measures using the baseline values as the covariate. Correcting for baseline VO_2max, the intervention arm had significantly higher VO_2max at both T1, 22.20(4.35) vs 21.41(4.49)ml/min/kg, $F(1,37)=19.67$, $p<0.001$, partial eta squared (η_p^2) =0.35 (small effect size), and at T2, 21.75(4.27) vs 20.74(4.65)ml/min/kg, $F(1,35)=13.29$, $p=0.001$, η_p^2 =0.28 (small effect size) compared with the control group (Figure 4.4). There was no significant difference in VO_2 at AT (ml/min/kg) between the two groups at T1 after adjusting for T0 VO_2 at AT (ml/min/kg) , $F(1,37)=2.675$, $p=0.110$, η_p^2 = 0.07, but there was a significant difference between the groups in VO_2 at AT (ml/min/kg) at T2, $F(1,35)=5.085$, $p=0.030$, $\eta_p^2=0.13$ (very small effect size) (Figure 4.5).

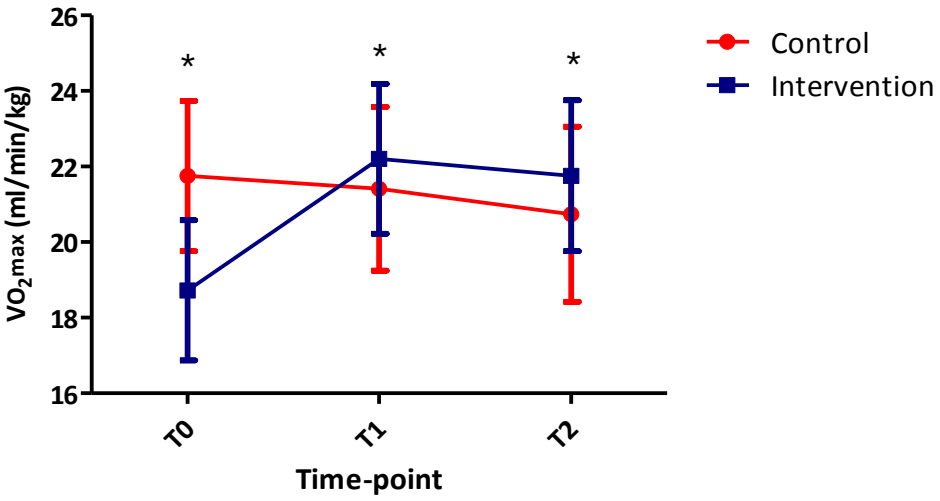

Figure 4-4 Changes in VO_2max (ml/min/kg) from T0 to T2

An independent t-test showed that the control group had a significantly higher VO_2max at baseline (21.75(4.49) ml/min/kg) when compared to the intervention group (18.73(4.07) ml/min/kg) (95% CI, 0.38 -5.67, p=0.026). ANCOVA results are corrected for baseline values. Significant differences in VO_2max (ml/min/kg) between the control and intervention group at T1, F(1,37)=19.67, p=0.000, partial eta squared (η_p^2) =0.35, and at T2, F(1,35)=13.29, p=0.001*, η_p^2 =0.28 were observed.*

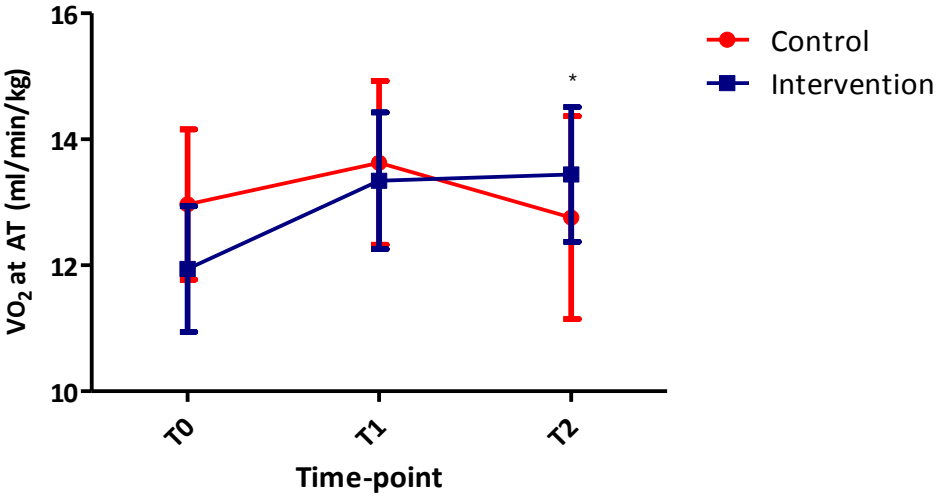

Figure 4-5 Changes in VO_2 at Anaerobic Threshold (ml/min/kg) from T0 to T2

The between group difference at baseline was not statistically significant (p=.180). ANCOVA results are corrected for baseline values. No significant between group differences in VO_2 at AT (ml/min/kg) were observed at T1, F(1,37)=2.675, p=0.110, η_p^2 = 0.07, but there was a significant difference between the groups at T2, F(1,35)=5.085, p=0.030, η_p^2=0.13.*

VO_2max results were compared to ACSM reference values (ACSM, 2010), which take into consideration both age and gender (Figure 4.6)**.** At baseline (T0) 27 participants (13 controls, 14 intervention) had very poor cardiorespiratory fitness, 12 had poor fitness (5 controls, 7 intervention) and 4 had fair level of fitness (all controls). At T1 the number of participants with very poor fitness reduced to 19 (11 controls, and 8 intervention), the number with poor fitness was 13 (6 controls and 7 intervention), and 8 participants had fair fitness (2 control and 6 intervention). At T2 there were 21 participants with very poor fitness (14 controls and 7 intervention), 14 with poor fitness (2 controls and 12 intervention) and 3 with fair level fitness (2 control and 1 intervention). Between group changes in cardiorespiratory fitness categories were analysed with the non-parametric Quade's test, using baseline fitness category as the covariate. After adjusting for baseline fitness categories significant differences between the control and intervention group in fitness categories were observed at both T1, F (1,38)=6.793, p=0.013 , η^2 =0.15 (small effect size), and T2, F(1,36)=13.659, p=0.001, η^2= 0.27 (small effect size).

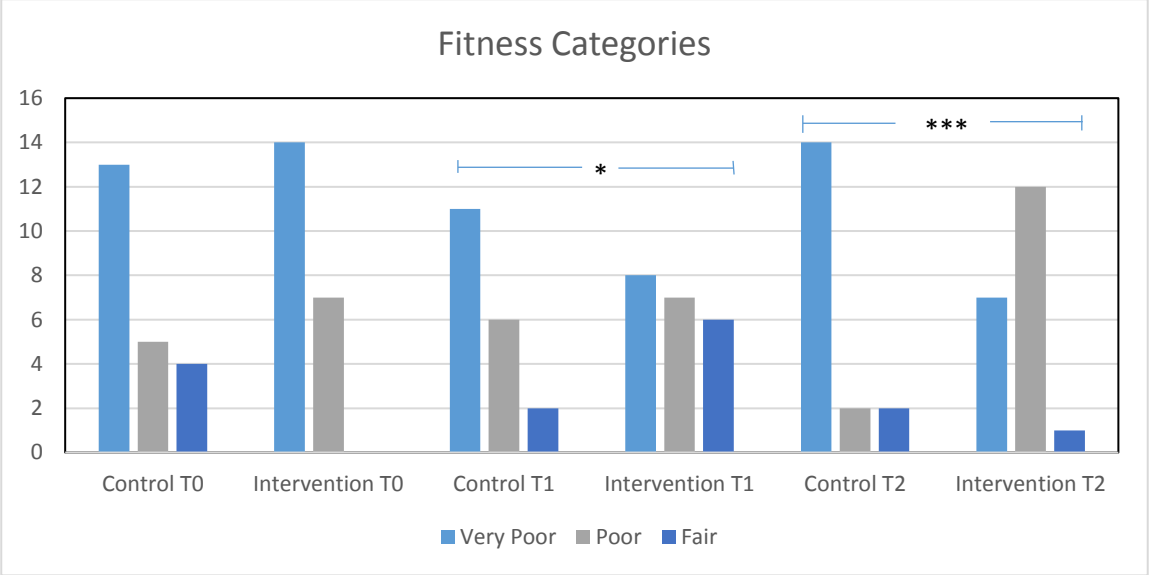

Figure 4-6 Fitness categories

The between group difference in fitness categories was not significant at baseline. However, Quade's test corrected for baseline values found significant differences between the control and intervention group in fitness categories at both T1, F (1,38)=6.793, p=0.013 , η^2 =0.15, and T2, F(1,36)=13.659, p=0.001***, η^2= 0.27.*

4.4.5.2 Changes in functional capacity

Functional capacity was assessed in Study II using the 6MWT and results at each time-point are detailed in Table 4.4**.** Baseline (T0) 6MWTs were completed on 43 participants. At T1 40 6MWTs were performed (1 drop-out and 2 withdrawals due to disease recurrence), and at T2 39 6MWTS were performed (1 withdrawal due to disease recurrence). An ANCOVA was conducted to compare the effect of the two study groups (control vs intervention) on 6MWT distance (metres) at T1 and T2 using baseline (T0) 6MWT distance (metres) as the covariate. After adjusting for T0 6MWT distance (metres) there was no significant difference between the two groups on 6MWT distance (metres) at T1, $F(1,37)=1.76$, $p=0.198$, $\eta_p^2=0.04$, and at T2, $F(1,36)=.597$, $p=0.445$, $\eta_p^2=0.02$. Changes in 6MWT distance (metres) across the three time-points are presented in Figure 4.7.

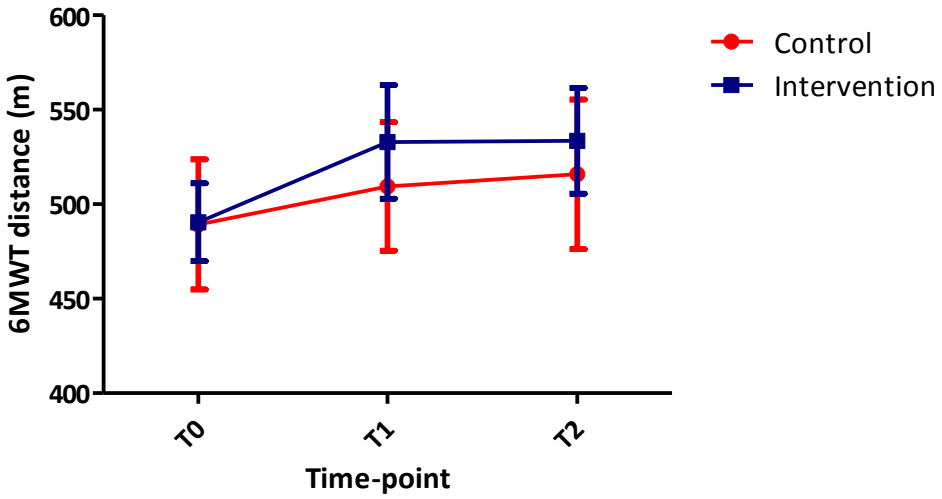

Figure 4-7 Changes in Six Minute Walk Test distance (metres) from T0 to T2

An ANCOVA analysis using baseline values as the covariate was no significant difference between the two groups on 6MWT distance (metres) at T1, $F(1,37)=1.76$, $p=0.198$, $\eta_p^2=0.04$, and at T2, $F(1,36)=.597$, $p=0.445$, $\eta_p^2=0.02$.

4.4.5.3 Changes in muscle strength

Hand grip strength and 1RM results are detailed in Table 4.4. Baseline (T0) HGS testing was completed on 43 participants. At T1 40 assessments of HGS were performed (1 drop-out and 2 withdrawals due to disease recurrence), and at T2 39 tests of HGS were performed (1 withdrawal due to disease recurrence). An ANCOVA was conducted to compare the effect of the two study groups (control vs intervention) on HGS (kg) at T1 and T2, using baseline (T0) HGS (kg) as the covariate. After adjusting for T0 HGS there no significant difference between the two groups in HGS (kg) at T1, $F(1,37)=1.43$, $p=0.240$, $\eta_p^2=0.04$, or at T2, $F(1,36)=3.58$, $p=0.066$, $\eta_p^2=0.09$.

Baseline (T0) 1RM were completed on 40/43 participants. Baseline 1RM testing was not performed on 3 participants due to existing musculoskeletal conditions. At T1 1RM tests were performed on 37/40 (3 due to existing musculoskeletal conditions), and at T2 1RM tests were performed on 34/39 (further 2 participants declined due to musculoskeletal issues). An ANCOVA was conducted to compare the effect of the two study groups (control vs intervention) on 1RM strength (lbs) at T1 and T2, with baseline (T0) 1RM strength as the covariate. After adjusting for T0 1RM strength (lbs) there was no significant difference between the two groups in 1RM strength (lbs) at T1, $F(1,34)=.198$, $p=0.659$, $\eta_p^2=0.01$, or at T2, $F(1,30)=.571$, $p=0.456$, $\eta_p^2=0.02$.

4.4.6 Physical activity level results

Physical activity level results are presented in Table 4.5. Baseline (T0) physical activity was analysed in 43 participants, at T1 40 participants and (1 drop-out and 2 withdrawals due to disease recurrence), and at T2 39 assessments of physical activity were performed (1 withdrawal due to disease recurrence). When baseline activity levels were considered, no statistically significant changes in physical activity levels between the groups were observed at either T1 or T2.

Table 4.4 Effects of the 12 week multidisciplinary programme on physical fitness, physical function, and muscle strength at post-intervention (T1) and at three month follow-up (T2)

Measure	Group	n	T0 Mean (SD)	n	T1 Mean (SD)	P-value	Effect Size η_p^2	n	T2 Mean (SD)	P-value	Effect Size η_p^2
Physical Fitness											
VO_2max (ml/min/kg)	Control	22	21.75 (4.48)	19	21.41(4.49)	0.000*	0.35	18	20.74(4.65)	0.001*	0.28
	Intervention	21	18.72(4.07)	21	22.20(4.35)			20	21.75 (4.27)		
VO_2 at AT (ml/min/kg)	Control	22	12.96 (2.68)	19	13.63 (2.69)	0.110	0.07	18	12.75(3.23)	0.030*	0.13
	Intervention	21	11.94 (2.19)	21	13.34 (2.38)			20	13.44(2.28)		
Physical Function											
6MWT distance (metres)	Control	22	489.32 (77.72)	19	509.37 (70.59)	0.198	0.04	19	515.84(82.04)	0.445	0.02
	Intervention	21	490.47 (45.32)	21	538.95 (63.38)			20	533.60(70.59)		
Muscle Strength											
HGS (kg)	Control	22	37.22(8.98)	19	37.78 (9.82)	0.240	0.04	19	37.01 (7.94)	0.066	0.09
	Intervention	21	35.53 (9.13)	21	36.25(8.50)			20	37.12 (8.05)		
1RM (lbs)	Control	20	166.30 (60.01)	18	180.00(64.72)	0.659	0.01	16	186.25(72.56)	0.456	0.02
	Intervention	20	153.00 (51.20)	19	166.32(48.55)			18	171.30(58.00)		

Results of ANCOVA analysis. The ANCOVA model uses the baseline (T0) value for each measure as a covariate.

Data are presented as mean (standard deviation).

**Statistically significant result.*

Abb: η_p^2 = partial eta squared (effect size); VO_2max = maximal oxygen consumption; VO_2 at AT = oxygen consumption at anaerobic threshold; 6MWT= six minute walk test; HGS= hand grip strength; 1RM = one repetition maximum.

Table 4.5 Effects of the 12 week multidisciplinary programme on physical activity levels at post-intervention (T1), and at three month follow-up (T2)

Measure	Group	n	T0 Mean (SD)/ Median (IQR)	n	T1 Mean (SD)/ Median (IQR)	P-value	Effect Size η^2/η_p^2	n	T2 Mean (SD)/ Median (IQR)	P-value	Effect Size η^2/η_p^2
Freedson (1998) Bouts	Control	22	2.00 (4.5)	19	2.00 (8.00)	0.882	0.00	19	2.00 (7.00)	0.485	0.01
	Intervention	21	4.00 (7.5)	21	3.00 (4.00)			20	4.50 (5.50)		
Total Time in Freedson (1998) Bouts (minutes)	Control	22	30.50 (65.75)	19	33.00 (107.00)	0.919	0.00	19	33.00 (124.00)	0.293	0.03
	Intervention	21	56.00 (151.00)	21	55.00 (122.00)			20	67.50 (140.75)		
Sedentary (minutes)	Control	22	3773.50 (975.25)	19	2904.00 (1605.00)	0.161	0.05	19	3674.00 (1704.00)	0.669	0.01
	Intervention	21	3449.00 (1511.00)	21	3641.00 (1334.00)			20	3671.00 (1471,25)		
Light (minutes) ┼	Control	22	1655.73 (648.32)	19	1794.89 (777.81)	0.978	0.00	19	1649.37 (620.44)	0.724	0.00
	Intervention	21	1491.57 (473.16)	21	1488.00 (580)			20	1484.50 (654.00)		
Moderate (minutes)	Control	22	136.00 (125.50)	19	146.00 (153.00)	0.967	0.00	19	148.00 (197.00)	0.486	0.01
	Intervention	21	132.00 (278.50)	21	125.00 (230.00)			20	163.50 (148.50)		
Vigorous (minutes)	Control	22	0.00 (0.50)	19	0.00 (0.00)	0.651	0.01	19	0.00 (1.00)	0.349	0.02
	Intervention	21	0.00 (2.50)	21	0.00 (1.25)			20	0.00 (2.00)		
Very Vigorous (minutes)	Control	22	0.00 (0.00)	19	0.00 (0.00)	N/A		19	0.00 (0.00)	N/A	
	Intervention	21	0.00 (0.00)	21	0.00 (0.00)			20	0.00 (0.00)		
Total MVPA (minutes)	Control	22	136.00 (136.75)	19	146.00 (153.00)	0.998	0.00	19	148.00 (198.00)	0.472	0.01
	Intervention	21	132.00 (280.50)	21	125.00 (234.50)			20	165.00 (145.00)		

Results are presented as mean (standard deviation) for normally distributed variables, and median (inter quartile range) for non-normally distributed variables.

┼ *Light activity was the only normally distributed physical activity level variable. ANCOVA using baseline light activity as the covariate was used to analyse between group changes in light activity at T1 and T2. All other physical activity variables were analysed with the non-parametric Quade's test using baseline values for each variable as the covariate for each test.*

N/A – unable to run analysis on very vigorous activity as median (IQR)=0.

Abb: η^2 = eta squared (effect size for Quade's test results); η_p^2= partial eta squared (effect size for ANCOVA results); MVPA = Moderate and vigorous physical activity.

4.4.7 Analysis of body composition

Results for the analysis of body composition are presented in Table 4.6. Anthropometric measurements were taken on 43 participants at T0, 40 participants at T1 (1 drop-out, and 2 withdrawals due to disease recurrence), and 39 participants at T2 (1 withdrawal due to disease recurrence). BIA was performed on 30/44 participants at T0, 31/40 participants at T1, and 30/39 participants at T2. Nine participants were unable to complete BIA due to contraindications including: metal joint replacements, or internal cardiac devices. Baseline BIA data was missing on a further five participants as the SECA machine was out of order at that time period.

A one-way between-groups ANCOVA was conducted to compare the effect of the two study groups (control vs intervention) on body composition variables at T1 and T2 using baseline values as the covariate. Non-normally distributed body composition variables were transformed using $\log_{10}$. With the exception of $\log_{10}$mid-arm circumference which was higher in the intervention group at T1($F(1,37)=6.024$, $p=0.019$*, $\eta_p^2=0.14$), no other significant differences in body composition variables between the control and intervention group were observed at either T1, or T2. BMI was used to categorise body composition (Figure 4.8). Quade's test was used to analyse changes between the groups in BMI categories at T1 and T2 using baseline BMI category as the covariate. After adjusting for baseline BMI category no significant between group changes in body composition category were observed at either T1 ($F(1,38)=3.919$, $p=0.06$, $\eta^2=0.09$), or T2 ($F(1,37)=1.800$, $p=0.188$, $\eta^2=0.05$).

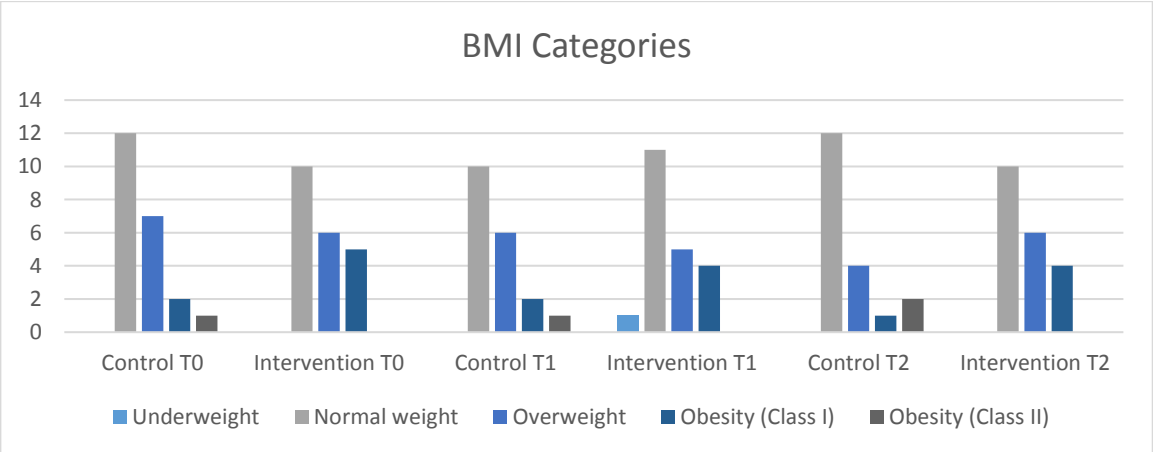

Figure 4-8 BMI Categories

No significant differences in BMI categories were observed between groups at T1 or T2.

Table 4.6 Effects of the 12 week multidisciplinary programme on body composition at post-intervention (T1) and three month follow-up (T2)

Measure	Group	n	T0 Mean (SD)/Median (IQR)	n	T1 Mean (SD)/Median (IQR)	P-value	Effect Size η_p^2	n	T2 Mean (SD)/ Median (IQR)	P-value	Effect Size η_p^2
Weight (kg)	Control	22	70.40 (22.60)	19	71.20 (29.05)	0.596 [a]	0.01	19	70.55 (23.95)	0.284[a]	0.03
	Intervention	21	73.35 (21.77)	21	73.18 (21.15)			20	73.12 (23.32)		
BMI (kg/m^2)	Control	22	24.30 (5.40)	19	24.90 (5.90)	0.670[a]	0.01	19	24.50 (5.30)	0.427[a]	0.02
	Intervention	21	25.00 (6.79)	21	24.90 (5.25)			20	24.80 (5.80)		
Waist Circumference(cm)	Control	22	91.55 (13.39)	19	91.92 (12.95)	0.659	0.01	19	91.72 (12.85)	0.356	0.02
	Intervention	21	92.33 (13.37)	21	92.53 (12.42)			20	92.80 (13.27)		
Mid-Arm Circumference(cm)	Control	22	28.90 (4.90)	19	28.35 (4.70)	0.019*[a]	0.14	19	28.75 (5.55)	.688[a]	0.01
	Intervention	21	28.50 (5.60)	21	28.55 (5.57)			20	28.20 (4.50)		
Bioimpedance Analysis											
Fat Mass (kg)	Control	14	21.81 (12.19)	15	20.66 (11.59)	0.609[a]	0.01	15	20.87 (11.68)	0.905[a]	0.00
	Intervention	16	22.77 (11.04)	16	21.47 (13.13)			15	21.54 (11.42)		
Fat Mass Percentage (%)	Control	14	31.00(13.08)	15	29.00 (13.00)	0.920[a]	0.00	15	30.00 (11.00)	0.738[a]	0.01
	Intervention	16	30.00 (9.93)	16	30.60 (9.55)			15	30.00 (9.00)		
Fat Free Mass (kg)	Control	14	53.01 (15.91)	15	54.13 (18.36)	0.555[a]	0.01	15	51.91 (18.22)	0.237[a]	0.06
	Intervention	16	50.11(18.22)	16	50.55 (16.16)			15	50.84(15.28)		
Fat Mass Index (kg/m^2)	Control	14	8.10 (3.88)	15	7.40 (4.70)	0.383[a]	0.03	15	7.50 (4.30)	0.972[a]	0.00
	Intervention	16	7.25 (3.62)	16	7.20 (4.02)			15	7.10 (4.10)		
Fat Free Mass Index (kg/m^2)	Control	14	17.54 (2.84)	15	18.34 (2.61)	0.379	0.03	15	18.24 (2.62)	0.886	0.00
	Intervention	16	17.28 (3.16)	16	17.39 (2.81)			15	17.86 (2.73)		
Skeletal Muscle Mass (kg)	Control	14	25.85 (9.34)	15	25.60 (11.68)	0.761[a]	0.00	15	26.38 (11.02)	0.158[a]	0.08
	Intervention	16	23.89 (10.50)	16	23.24 (9.74)			15	24.48 (8.15)		
LST Left arm(kg)	Control	14	2.87 (1.29)	15	2.77 (1.62)	0.427[a]	0.02	15	2.96 (0.97)	0.708[a]	0.01
	Intervention	16	2.59 (1.65)	16	1.82 (1.88)			15	2.61 (1.25)		
LST Right arm (kg)	Control	14	2.91 (1.38)	15	2.92 (1.86)	0.426[a]	0.03	15	3.18 (1.20)	0.784[a]	0.00

	Intervention	16	2.70 (1.63)	16	2.00 (1.95)			15	2.87 (1.18)		
LST Left leg (kg)	Control	14	7.70 (1.53)	15	7.48 (2.15)	0.536	0.02	15	8.04 (1.95)	0.771	0.00
	Intervention	16	7.57 (1.89)	16	6.64 (2.28)			15	7.90 (1.75)		
LST Right leg (kg)	Control	14	7.93 (2.74)	15	7.86 (4.18)	0.508[a]	0.02	15	8.59 (3.47)	0.705[a]	0.01
	Intervention	16	8.19 (3.19)	16	6.73 (4.03)			15	8.35 (2.66)		
Total body water (L)	Control	14	38.55 (12.00)	15	38.90 (14.50)	0.853[a]	0.00	15	40.10 (14.00)	0.247[a]	0.05
	Intervention	16	36.65 (13.05)	16	37.10 (11.72)			15	37.20 (10.40)		
Extra cellular water (L)	Control	14	16.94 (2.92)	15	17.23 (2.98)	0.982	0.00	15	17.07 (2.95)	0.356	0.03
	Intervention	16	16.96 (2.79)	16	17.05 (2.88)			15	17.18 (2.97)		
Hydration (%)	Control	14	80.00 (17.75)	15	81.00 (7.60)	0.657[a]	0.01	15	81.00 (9.00)	0.539[a]	0.02
	Intervention	16	84.35 (10.00)	16	85.70 (12.00)			15	84.00 (7.00)		
Xc (Ω)	Control	14	44.60 (11.73)	15	46.60 (4.80)	0.476[a]	0.02	15	47.80 (11.00)	0.074[a]	0.12
	Intervention	16	47.05 (8.20)	16	45.85 (7.45)			15	44.70 (8.60)		
R (Ω)	Control	14	579.15 (119.67)	15	556.30 (135.30)	0.920[a]	0.00	15	560.60 (120.70)	0.317[a]	0.04
	Intervention	16	566.20 (103.60)	16	577.15 (78.92)			15	567.20 (70.90)		
Phase Angle (Ψ)	Control	14	4.90 (1.28)	15	4.92 (0.51)	0.302[a]	0.04	15	4.80 (1.00)	0.161[a]	0.08
	Intervention	16	4.80 (0.60)	16	4.75 (0.72)			15	4.70 (0.60)		

Results of ANCOVA analysis. The ANCOVA model uses the baseline (T0) value for each measure as a covariate.

Data are presented as mean (standard deviation) for normally distributed values and median (interquartile range for non-normally distributed variables).

**Statistically significant result.*

[a] *Data that was not normally distributed was transformed using a log10 transformation to achieve the assumption of normality for ANCOVA.*

Abb: η_p^2 *= partial eta squared (effect size); LST = lean soft tissue, Xc =reactance; R =resistance; L =litres; kg =kilograms; m =metres*

4.4.8 Changes in quality of life and well-being

4.4.8.1 EORTC-QLQ-C30 and EORTC-QLQ-OES18

HRQOL of life data as measured by the EORTC-QLQ-C30 and EORTC-QLQ-OES18 are presented in Table 4.7 and 4.8 respectively. The EORTC questionnaires were completed by 43/43 participants at T0, 40/40 at T1 and 39/39 at T2. The results of the oesophageal cancer specific EORTC-QLQ-OES18 of 8 of the participants who had gastric cancer were excluded from the analysis as the EORTC-QLQ-OES18 is validated for oesophageal cancer only. Results of both the EORTC-QLQ-C30 and EORTC-QLQ-OES18 were not normally distributed, and normality could not be achieved through transformations. Quade's test was conducted to compare the effect of the two study groups (control vs intervention) on quality of life at T1 and T2. Baseline values were used as the covariate in each test. With the exception of cognitive function (higher in control group) at T1 ($F(1, 38) = 4.992$, $p = 0.031^*$, $\eta^2 = 0.12$), and trouble swallowing saliva at T2 (worse in control group) ($F(1, 29) = 5.419$, $p = 0.027^*$), no other statistically significant differences between the groups were observed at either time-point.

4.4.8.2 Perceived well-being questionnaire

Results of the perceived well-being questionnaire are presented in Table 4.9. The perceived well-being questionnaire were completed by 41/43 participants at T0 (2 questionnaires missing due to an error when printing questionnaire pack), 39/40 completed it at T1 (again due to printing error) and 39/39 completed the questionnaire at T2. The perceived well-being questionnaire uses an ordinal likert scale, therefore a non-parametric test (Quade's test) was used for analysis. When baseline well-being scores were considered, no significant differences in overall well-being or any of the well-being subscales were observed between the control and intervention group at T1 or T2.

Table 4.7 Effect of the 12 week multidisciplinary programme on EORTC-QLQ-C30 at post-intervention (T1) and three month follow-up (T2)

EORTC-QLQ-C30 subscale	Group	n	T0 Median (IQR)	n	T1 Median (IQR)	P-value	Effect Size η^2	n	T2 Median (IQR)	P-value	Effect Size η^2
Global health status	Control	21	66.67 (33.33)	19	66.67 (25.00)	0.433	0.02	19	75.00 (16.66)	0.887	0.00
	Intervention	21	75.00 (20.83)	21	83.33 (20.83)			20	79.17 (29.16)		
Function Scales											
Physical function	Control	22	83.33 (20.00)	19	86.67 (20.00)	0.448	0.02	19	83.33 (26.67)	0.866	0.00
	Intervention	21	93.33 (20.00)	21	86.67 (9.99)			20	93.33 (20.00)		
Role function	Control	22	100.00 (33.33)	19	100.00 (33.33)	0.865	0.00	19	100.00 (33.33)	0.349	0.02
	Intervention	21	83.33 (33.33)	21	83.33 (33.33)			19	100.00 (33.33)		
Emotional function	Control	22	91.67 (33.33)	18	87.50 (31.25)	0.570	0.01	19	91.67 (33.33)	0.109	0.07
	Intervention	20	70.84 (16.67)	21	75.00 (25.00)			20	83.33 (31.25)		
Cognitive function	Control	22	91.67 (16.67)	19	100.00 (16.67)	0.031*	0.12	19	100.00 (16.67)	0.125	0.06
	Intervention	21	83.33 (33.33)	21	83.33 (16.67)			19	83.33 (33.33)		
Social function	Control	22	91.67 (37.50)	19	100.00 (16.67)	0.065	0.09	19	100 (33.33)	0.575	0.01
	Intervention	21	66.67 (41.67)	21	83.33 (33.33)			20	66.67 (45.83)		
Symptom Scales											
Fatigue	Control	22	22.33 (25.08)	19	22.33 (22.33)	1.000	0.00	19	22.33 (44.67)	0.201	0.04
	Intervention	21	33.33 (27.67)	21	33.33 (11.00)			20	22.33 (11.00)		
Nausea/vomiting	Control	22	0.00(4.17)	19	0.00 (0.00)	0.790	0.00	19	0.00 (16.67)	0.421	0.02
	Intervention	20	0.00 (29.17)	21	0.00 (16.67)			20	0.00 (16.67)		
Pain	Control	20	0.00 (29.17)	19	0.00 (33.33)	0.541	0.01	19	0.00 (33.33)	0.448	0.02
	Intervention	20	0.00 (29.17)	21	0.00 (16.67)			20	0.00 (29.17)		
Dyspnoea	Control	22	0.00 (33.33)	19	0.00 (33.33)	0.116	0.06	19	0.00 (33.33)	0.305	0.03
	Intervention	21	0.00 (33.33)	21	0.00 (33.33)			20	0.00 (33.33)		
Insomnia	Control	22	0.00 (33.33)	19	33.33 (33.33)	0.374	0.02	19	0.00 (33.33)	0.079	0.08
	Intervention	21	0.00 (33.33)	21	0.00 (33.33)			19	0.00 (33.33)		
Appetite Loss	Control	22	0.00 (41.67)	18	0.00 (0.00)	0.268	0.09	19	0.00 (33.33)	0.899	0.00
	Intervention	21	0.00 (33.33)	21	0.00 (33.33)			20	0.00 (33.33)		
Constipation	Control	22	0.00 (33.33)	19	0.00 (0.00)	0.062	0.03	19	0.00 (33.33)	0.691	0.00

	Intervention	21	0.00 (0.00)	21	0.00 (33.33)			20	0.00 (25.00)		
Diarrhoea	Control	22	0.00 (33.33)	19	0.00 (33.33)	0.426	0.02	19	0.00 (0.00)	0.667	0.01
	Intervention	21	33.33 (33.33)	21	33.33 (33.33)			20	0.00 (33.33)		
Financial difficulties	Control	22	0.00 (16.67)	19	0.00 (0.00)	0.269	0.03	19	0.00 (33.33)	0.809	0.01
	Intervention	21	0.00 (33.33)	21	0.00 (33.33)			20	0.00 (33.33)		

Results of Quade's test. Quade's test uses the baseline (T0) value for each measure as a covariate.

Data was not normally distributed and therefore results are presented as median (interquartile range (IQR))

**Statistically significant result.*

Abb: η^2 *= eta squared (effect size)*

Table 4.8 Effects of the 12 week multidisciplinary programme on EORTC-QLQ-OES18 at post-intervention (T0) and three month follow-up (T2)

OES18 Symptom Subscales	Group	n	T0 Median (IQR)	n	T1 Median (IQR)	P-value	Effect Size η_p^2	n	T2 Median (IQR)	P-value	Effect Size η_p^2
Dysphagia	Control	16	22.16 (33.33)	14	5.50 (25.08)	0.689	0.00	14	5.50 (22.31)	0.061	0.11
	Intervention	20	5.50 (30.83)	20	5.50 (30.58)			19	22.33 (33.33)		
Eating Problems	Control	16	12.50 (47.92)	14	8.33 (20.84)	0.289	0.03	14	12.50 (26.39)	0.677	0.01
	Intervention	20	16.67 (27.09)	20	16.67 (16.67)			19	16.67 (16.67)		
Reflux	Control	16	0.00 (16.67)	14	0.00 (33.33)	0.783	0.00	14	0.00 (33.33)	0.675	0.01
	Intervention	20	25.00 (33.33)	19	16.67 (33.33)			19	16.67 (16.67)		
Pain	Control	16	11.00 (11.00)	14	0.00 (13.83)	0.641	0.01	14	5.50 (13.83)	0.642	0.01
	Intervention	20	11.00 (30.58)	20	0.00 (11.00)			19	11.00 (22.33)		
Trouble swallowing saliva	Control	15	0.00 (0.00)	13	0.00 (0.00)	0.720	0.00	14	0.00 (66.67)	0.027*	0.16
	Intervention	19	0.00 (0.00)	20	0.00 (0.00)			19	0.00 (0.00)		
Choked when swallowing	Control	15	0.00 (0.00)	14	0.00 (8.33)	0.551	0.01	14	0.00 (0.00)	0.803	0.00
	Intervention	20	0.00 (25.00)	20	0.00 (25.00)			19	0.00 (33.33)		
Dry mouth	Control	16	0.00 (33.33)	14	0.00 (41.67)	0.677	0.01	14	33.33 (66.67)	0.212	0.05
	Intervention	20	33.33 (66.67)	20	0.00 (66.67)			19	33.33 (33.33)		
Trouble with taste	Control	16	0.00 (33.33)	12	0.00 (33.33)	0.951	0.00	14	0.00 (41.67)	0.365	0.02
	Intervention	20	0.00 (25.00)	20	0.00 (33.33)			19	0.00 (33.33)		
Trouble with coughing	Control	16	0.00 (0.00)	14	0.00 (0.00)	0.690	0.00	14	0.00 (0.00)	0.950	0.00
	Intervention	20	16.67 (33.33)	20	11.11 (25.00)			19	0.00 (33.33)		
Trouble talking	Control	16	0.00 (0.00)	14	0.00 (0.00)	0.638	0.01	14	0.00 (8.33)	0.363	0.03
	Intervention	20	0.00 (0.00)	20	0.00 (0.00)			19	0.00 (0.00)		

Results of Quade's test. Quade's test uses the baseline (T0) value for each measure as a covariate.

Data was not normally distributed and therefore results are presented as median (interquartile range (IQR))

**Statistically significant result.*

Abb: η^2 *= eta squared (effect size)*

Table 4.9 Effects of the 12 week multidisciplinary programme on well-being scores at post-intervention (T1) and three month follow-up (T2)

Measure	Group	n	T0 Median (IQR)	n	T1 Median (IQR)	P-value	Effect Size η^2	n	T2 Median (IQR)	P-value	Effect Size η^2
Overall well-being score	Control	20	15.00 (3.75)	19	16 (5.00)	0.490	0.01	19	17.00 (6.00)	0.870	0.00
	Intervention	21	16.00 (3.50)	20	16.50 (4.50)			20	16.00 (3.75)		
Subscales											
Fatigue	Control	20	3.00 (1.00)	19	3.00 (0.00)	0.659	0.00	19	3.00 (1.00)	0.691	0.00
	Intervention	21	3.00 (1.00)	20	3.00 (1.00)			20	2.00 (1.00)		
Sleep quality	Control	20	3.00 (2.00)	19	3.00 (2.00)	0.704	0.00	19	4.00 (2.00)	0.383	0.02
	Intervention	21	4.00 (1.00)	20	4.00 (1.00)			20	4.00 (1.00)		
General muscle soreness	Control	20	3.00 (0.75)	19	3.00 (1.00)	0.827	0.00	19	3.00 (1.00)	0.694	0.00
	Intervention	21	3.00 (2.00)	20	3.00 (2.00)			20	3.00 (0.75)		
Stress levels	Control	20	3.00 (1.00)	19	3.00 (0.00)	0.484	0.01	19	3.00 (1.00)	0.369	0.02
	Intervention	21	3.00 (0.00)	20	3.00 (1.00)			20	3.00 (1.00)		
Mood	Control	20	4.00 (0.75)	19	4.00 (1.00)	0.905	0.00	19	4.00 (1.00)	0.691	0.01
	Intervention	20	4.00 (0.75)	20	4.00 (0.75)			20	4.00 (1.00)		

Results of Quade's test. Quade's test uses the baseline (T0) value for each measure as a covariate.

Likert scale data is presented median (interquartile range (IQR))

Abb: η^2 *= eta squared (effect size)*

4.5 Discussion

Study II demonstrated that participation in a 12 week multidisciplinary rehabilitation programme resulted in statistically significant improvements in cardiorespiratory fitness (VO_2max) in a nutritionally vulnerable cohort of oesophago-gastric cancer survivors without compromise to body composition. However, no improvements in secondary measures including physical performance (6MWT), physical activity levels, muscle strength (HGS and 1RM), HRQOL and well-being were observed as a result of participation in the intervention.

This is the first study to examine the effect of a structured exercise intervention on cardiorespiratory fitness in oesophago-gastric cancer survivors, and results of Study II compare well to previous exercise intervention studies in cancer survivorship. A meta-analysis by Jones et al. (2011) reviewed the effects of exercise interventions on cardiorespiratory fitness of 571 (exercise n=344, control (usual care) n=227) cancer survivors and reported that participation in exercise interventions was associated with significant improvements in VO_2peak (WMD=2.90ml/min/kg, 95% CI, 1.16-4.64). The results presented by Jones et al. (2011) are also similar to an earlier meta-analysis by McNeely et al. (2006) which reported statistically significant gains following participation in an exercise intervention in 95 breast cancer survivors (WMD=3.39, 95% CI 1.67 to 5.10). Akin to these results, in Study II participants randomised to the intervention group experienced a 3.47(2.59)ml/min/kg improvement in VO_2max following completion of the 12 week multidisciplinary rehabilitation programme. In comparison, control participants experienced a decline of 0.86 (2.50)ml/min/kg during the same time period. The review by Jones et al. (2011), reported similar levels of decline in VO_2peak (WMD=-1.02ml/min/kg, 95% CI, -1.46 to -0.58) in control participants randomised to usual care. As the improvement in VO_2max achieved by the intervention group is close to 1 MET (1 MET =3.5ml/min/kg) similar to Study I the result can be considered clinically important. Although the impact of this improvement in oesophago-gastric cancer survivorship is unknown, as previously discussed in Chapter 3, a 1 MET improvement in physical fitness is associated with significant reduction in all-cause mortality risk (Gulati et al., 2003, Myers et al., 2002).

Despite significant improvements in cardiorespiratory fitness, Study II did not detect any statistically significant improvements in other measures of physical function including the 6MWT, and accelerometer measured physical activity levels. Although greater improvements in 6MWT were observed at T1 in the intervention group compared to the control group

(+42.48(47.87)m vs +24.42(45.66)m) when baseline values were considered the between group difference was not statistically significant (p=0.198). As highlighted in Chapter 1, the 6MWT may lack the specificity to detect small improvements in physical performance in oesophago-gastric cancer patients. Despite the increase observed in cardiorespiratory fitness, physical activity did not change as a result of the 12 week intervention. Participants in both Study II groups failed to achieve the recommended guidelines of 150 minutes of moderate intensity physical activity per week at baseline, or at T1. However, at T2 the intervention group did achieve a median (i.q.r) 165(145) minutes engaged in MVPA. While this is clinically important, this improvement was not statistically significant. As with Study I these results highlight the inherent difficulty in attempting to modify the exercise behaviour of cancer survivors. As discussed in Chapter 3, a systematic review by Bourke et al. (2013) reported it is extremely difficult to get sedentary cancer survivors to engage in the recommended levels of physical activity. To tackle this problem there has been a growing research focus on interventions which combine exercise with behaviour change programmes to improve engagement in physical activity. Rogers et al. (2015) recently reported on the BEAT programme for breast cancer survivors, which compared a 3 month intervention of exercise and a behavioural change programme, to usual care in 222 breast cancer survivors. Rogers et al. (2015) found that those who participated in the 3 month BEAT programme experienced significant improvements in accelerometer measured physical activity levels, physical fitness, and HRQOL, and that these improvements were maintained at three months post-intervention. Accordingly, the addition of a behavioural change programme to an exercise intervention may have considerable potential to improve physical activity levels in oesophago-gastric cancer survivors and is a worthy area for future study.

Study II participants demonstrated excellent adherence to supervised exercise sessions (93.88 (11.58)%), however, adherence to unsupervised sessions was poorer (77.99 (27.31)%) exercise diaries and 65.95(32.60)% polar monitors). This result is comparable to other exercise studies in cancer survivors .A systematic review by Kampshoff et al. (2014) reported adherence in included studies ranged from 62-78%. Reported determinants of exercise adherence include self-efficacy, socioeconomic status, education, attitude, fatigue, and previous exercise history (Kampshoff et al., 2016, Kampshoff et al., 2014). In recent times there has been a growing research emphasis on strategies to improve adherence to exercise interventions. In particular the use of mobile health technology to improve adherence to exercise adherence is a promising area of research. Study II piloted the use of a mobile application (app), Salaso to prescribe home exercise sessions and monitor adherence. Mobile apps offer many advantages over traditional information

materials. Interventions can be personalised, and the content of the intervention can be delivered anytime to a device anywhere in the world. They also allow participants to record exercise adherence, and record subjective information in real time allowing for a much more cost-effective interactions between patients and health care professionals. Patients can be sent reminders regarding their exercise schedule using notifications and, accordingly, mobile apps have the potential to improve adherence rates to home based exercise sessions (Voth et al., 2016, Direito et al., 2015). However, the uptake of the Salaso app in Study II was very poor. Only two participants used it for the duration of the study. In 2016 the Irish Central Statistics Office (CSO) reported that 41% of older adults aged 60-74 in Ireland have never used the internet (CSO, 2016). Moreover, risk factors for oesophago-gastric cancer; older age, lower socioeconomic status, and male gender, are associated with reduced ability to engage in mobile health activity (Kontos et al., 2014). Therefore, until greater attempts are made to improve the internet usage of older adults, particularly those from lower socioeconomic backgrounds, the perusal of mobile health technology to monitor and improve exercise adherence in oesophago-gastric cancer patients may be of limited value.

An important outcome of Study II is that body composition remained stable throughout the intervention, and at three months follow-up. As previously discussed in section 1.1.6 and 1.2.6 unintentional weight loss is a significant issue for survivors of oesophago-gastric cancer. Therefore it is a very positive finding of Study II that engagement in a structured exercise programme combined with dietary counselling resulted in no significant weight loss. As described in Chapter 1, weight loss in oesophago-gastric cancer consists of both loss of fat mass and muscle mass, and sarcopenia (loss of muscle mass and strength) is prevalent among oesophago-gastric cancer survivors. Although muscle mass and strength (HGS and 1RM) stayed stable throughout Study II, it is disappointing that the addition of the resistance training component to the exercise intervention failed to result in any statistically significant improvements in muscle mass or strength, particularly given the positive results achieved by previous studies implementing resistance training in cancer survivorship. A meta-analysis by Strasser et al. (2013) found that resistance training in cancer survivorship is associated with significant improvements in both muscle strength and body composition. Strasser et al. (2013) reported cancer survivors experienced improvements in upper limb (WMD =+6.90kg, $p<0.001$) and lower limb strength (WMD=+14.57kg, $p=0.0005$), and an increase in lean mass (WMD=+11.07kg, $p<0.001$) and a reduction in fat mass (WMD=-2.08kg, $p=0.003$) following participation in resistance training. Furthermore, Hardee et al. (2014) reported that participating

in resistance training in cancer survivorship was associated with a 33% lower risk of all-cause mortality (95% CI, 0.45-0.99).

A limitation of the resistance training programme in Study II was that it was not possible to provide the participants with the same weights equipment to use for their home resistance training sessions as they used in the supervised environment. Accordingly, the home resistance training programme may not have been completely comparable to the supervised resistance training intervention. Therabands, which are elastic resistance bands, were provided to participants to use at home as they are easy to use and much more convenient to carry than free weights (Yeun, 2017), have been shown to improve muscle cross sectional area and maximal muscle strength in older adults (Yasuda et al., 2015), and also have been found to have a similar effect on muscle activity as free weights (Saeterbakken et al., 2014). An additional limitation of the Study II resistance training component was the poor compliance rate of the Study II participants to the home resistance training sessions, with patients reporting an adherence rate of 60.48(34.42)% (range 0-10). This potentially would have negatively impacted on outcomes. Furthermore, to the author's knowledge, there is no previous published literature regarding resistance training specifically in oesophago-gastric cancer survivorship. Therefore, the resistance training intervention in Study II was based on previous research in predominantly breast and prostate cancer survivors. There are two trials ongoing at present, the PERFECT trial (van Vulpen et al., 2017), and the PRESET trial (Christensen, 2016), which are both investigating resistance training in combination with aerobic training in oesophageal/ oesophago-gastric cancer survivors. These studies will provide much needed evidence regarding the efficacy of resistance training in oesophago-gastric cancer survivorship.

Disappointingly, results of Study II did not show any statistically significant improvements in any domain of HRQOL or well-being as a result of participation in a 12 week multidisciplinary rehabilitation programme. This is in contrast to the findings of Study I, where statistically and clinically meaningful improvements in HRQOL were observed. This may have been due to a number of factors. Firstly, Study II was powered to detect a change in cardiorespiratory fitness and as such may not have been adequately powered to detect a change in HRQOL or wellbeing. Secondly the measures of HRQOL and wellbeing used in Study II may have lacked the specificity to capture meaningful changes in HRQOL and well-being experienced in survivorship. To overcome this difficulty a mixed method study approach may be used to address this deficit in

quantitative research. Mixed methods studies integrate quantitative with qualitative research, and aim to offset the weakness of either approach alone (Green et al., 2015). In cancer rehabilitation trials, qualitative methods have been used in conjunction with quantitative research to explore further patient's experiences of rehabilitative interventions. For example, recently Martin et al. (2015a) explored the experiences of breast and prostate cancer survivors who underwent a 8 week group exercise and psychotherapy intervention and reported that the intervention aided participants' return to normality and emphasised the importance of peer support. Separately to the work contributing to this thesis, our research group carried out focus groups with 19/21 participants randomised to the intervention group upon completion of the 12 week rehabilitation programme. Interestingly in contrast to the results of the quantitative questionnaires, the focus group findings indicated that participation in the Study II programme resulted in improved confidence and well-being, improved role and social functioning, and also highlighted the importance of peer support in survivorship (Bennett et al, 2017(manuscript under review)).

4.6 Study Limitations

Study II has a number of limitations which warrant discussion. Firstly, the supervised rehabilitative intervention took place in one research centre, therefore it was not feasible for patients that lived outside a commutable parameter of SJH to commit to taking part in the study. Accordingly the generalisability of the results to the general oesophago-gastric cancer population is restricted. However, SJH is the national centre for oesophago-gastric cancer, and as such has a nationally representative patient cohort. Participants travelled up to 150km to participate. Secondly, the follow-up time from surgery varied from 6 months to 5 years post-op further limiting the homogeneity of the sample, and restricting generalisability of results. It is also impossible to conclude from the results of this study what the ideal timing for the introduction of such an intervention is. Furthermore, Study II excludes those who were less than six months post-surgery, those with significant comorbidities, and those with recurring diseases. Accordingly the rehabilitative needs of these cohorts require exploration in future studies.

Study II failed to detect significant improvements in secondary measures including 6MWT, muscle strength, HRQOL and well-being. This may have been due to lack of power. Study II was powered to detect a 1 MET change in physical fitness, and this accrual target was feasible and affordable within the timeframe for study completion. A further limitation of the secondary

measures included in Study II is that it was not feasible to blind the assessor. Budgetary constraints meant that it was only possible to blind the assessor to the primary outcome (CPET). Finally, the use of a pure control group (usual care), may have induced a risk of contamination between the groups. Participants that agree to take part in exercise trials are typically highly motivated to exercise, and subsequently the control group may also have increased their participation in exercise, which may have reduced the effect size of some results (Steins Bisschop et al., 2015).

4.7 Conclusion

The 12 week multidisciplinary rehabilitation programme, consisting of supervised and unsupervised aerobic and resistance exercise, dietary counselling, and education sessions resulted in significant improvements in cardiorespiratory fitness without compromise to body composition in survivors of oesophago-gastric cancer. The efficacy of resistance training in oesophago-gastric cancer requires further exploration, as do strategies to improve adherence to exercise prescription and recommended physical activity levels.

Chapter 5 Qualitative Methods

5.1 Introduction

This chapter will describe the study designs, sampling methods, procedures and data analysis for the qualitative part of this thesis, Study III (Chapter 6).

5.2 Qualitative research

Qualitative research has been defined by Creswell (2013) as 'an inquiry process of understanding based on distinct methodological traditions of inquiry that explore a social or human problem. The researcher builds a complex holistic picture, analyses words, reports detailed views of informants, and conducts the study in the natural setting'. Qualitative research helps answer the questions that quantitative research cannot (Huston and Rowan, 1998). In healthcare, qualitative research provides insight into patients attitudes, beliefs, and experiences which can help guide evidence based practice, ensure care is patient centred, give an evaluation of quality of life, and help generate hypotheses for future research (Carpenter and Suto, 2008, Huston and Rowan, 1998). In oesophago-gastric cancer, qualitative research has been utilised to examine patient's experiences of both curative and palliative treatments, and also their attitudes to recovery and experiences of survivorship (Malmstrom et al., 2013a, Henselmans et al., 2012, Andreassen et al., 2006).

Qualitative research originated in the social sciences, particularly in the study of sociology and anthropology (Huston and Rowan, 1998). Many different methodological approaches to qualitative research have been described in the literature, including narrative research, phenomenology, grounded theory, ethnography, and qualitative description (Creswell, 2013). Narrative research involves the exploration of the life of an individual, such as biographical or autobiographical writings. Phenomenology involves an in-depth analysis of a persons lived experience of a concept or a phenomenon. Grounded theory involves the development of a theory grounded in the views of the participants. Ethnography involves the describing and interpreting the culture within a group (Creswell, 2013, Carpenter and Suto, 2008). In many cases researchers report their work as narrative, phenomenology, grounded theory or ethnography, when in fact it does not truly reflect that methodological approach (Neergaard et

al., 2009, Sandelowski, 2000). Qualitative description is an alternative methodological approach which is less theoretical, but is simple and easy to implement in health research (Neergaard et al., 2009).

Qualitative description involves a comprehensive, plain language description of an event or experience (Carr and Weir, 2016, Neergaard et al., 2009). Qualitative description embraces the principle of naturalistic inquiry. This implies there is a commitment to studying something in its natural state (Carr and Weir, 2016, Sandelowski, 2000). During qualitative description analysis the researchers stay very close to the data (Neergaard et al., 2009), and there is minimal theoretical interpretation (Sandelowski, 2010). As the goal of the qualitative research in this thesis was to identify and describe the experience and opinions of patients with oesophago-gastric cancer in their early recovery period from surgery, qualitative description was deemed the most appropriate methodological approach for Study III.

5.3 Study designs

Several different design strategies may be implemented in qualitative research. These include observation, interviewing, and examination of documents (Carter and Lubinsky, 2016).

The main strength of observation as a study design is that it identifies exactly *what people do* rather than *what they report they do* (Huston and Rowan, 1998). However, observation is a challenging method of qualitative research. It is very time consuming, as it requires researchers to enter a setting and to carry out fieldwork over a prolonged period of time (Carpenter and Suto, 2008). The role of the observer has been described as a continuum between complete observation and participation. Four points have been identified over this continuum: complete participant, participant as observer, observer as participant, and complete observer (Creswell, 2013). Whatever role participants take, it is their main task is to turn observations into data. Observations may be recorded using field notes, video recordings, audio recordings, and photographs (Carter and Lubinsky, 2016, Carpenter and Suto, 2008).

Interviews are the most commonly used method of data collection in qualitative studies. Interviews can be classified by structure, number of interviewees, and the proximity of the interviewer to the interviewee. In terms of structure, interviews may be structured (e.g. oral administration of a questionnaire), unstructured where interviews are free flowing, or semi structured where the interview is based on previously developed questions but there is flexibility to clarify or explore further the experiences of the interviewee. Interviews may be individual or group based. Individual interviews have the advantage that the interviewee may feel more comfortable discussing personal issues. Group interviews are termed focus groups and may provide a more relaxed atmosphere for sharing information. Interviews may be carried out face to face or via telephone, or through modern communication methods such as Skype (Carter and Lubinsky, 2016).

The other main method of qualitative data acquisition is through the analysis of documents. Documents that are typically analysed include; public records such as census data, and the register of births, marriages, and deaths, personal documents such as diaries, letters, photo albums etc., and popular media documents such as newspapers, television programmes, films, and magazines. Physical artefacts including common tools and utensils of everyday living may also be analysed (Merriam, 2009).

Semi-structured interviews were chosen as the method of qualitative data collection for this thesis, as they are a recommended method of data collection for qualitative descriptive studies (Neergaard et al., 2009, Sandelowski, 2000). Semi structured interviews are organised around an interview guide (Carter and Lubinsky, 2016), and are a useful tools in health research as the interview guide can be based on expert knowledge to focus on an area of health that needs further exploration (Neergaard et al., 2009). The questions in the interview guide should be open-ended and directed towards discovering the who, what, where and how of events and experiences (Sandelowski, 2000).

The purpose of the semi-structured interviews in Study III was to examine patient's perspectives of their physical recovery in the first six months following oesophago-gastric cancer surgery. The semi-structured interviews in this thesis were held face to face, individually with participants. Individual interviews were favoured over focus groups for this thesis as participants were in their

first few months of recovery following oesophago-gastric cancer surgery. The first few months of recovery can be a difficult time for patients as they try to adjust to a 'new normal' following their treatment. The early recovery period may involve many hospital visits, continuing treatments, and patients are heavily burdened by issues such as dietary symptoms and fatigue. The recovery process can also vary significantly from person to person. In this regard, focus groups were deemed inappropriate as the research team feared bringing a group of people together so early in the recovery process that some patients might be upset if they saw other people recovering at a faster rate. Individual interviews were also more feasible, as they could easily be scheduled to a time of preference for each patient.

5.4 Sampling

As discussed in Chapter 2, Section 2.2 there are two types of sampling, random (probability) sampling and non-probability sampling. Random sampling is not necessary or justified in qualitative research, as the research question tends to be specific to the individuals being studied and not on the generalisability of results to a wider population (Merriam, 2009). In broad terms, sampling in qualitative studies is by convenience. Convenience sampling involves recruiting participants that are readily available for study (Carter and Lubinsky, 2016, Merriam, 2009). More distinct methods of sampling used in qualitative research are purposive and snowball sampling. Purposive sampling involves the selection of individuals that are deemed to be information-rich cases, i.e., individuals that can provide important information about the topic under study (Carpenter and Suto, 2008). Purposive sampling may also be termed criterion sampling as participants must have certain attributes to meet the criteria for the study (Merriam, 2009). Snowballing may be referred to as chain or network sampling. It involves identifying a few key participants who easily meet the study criteria, interviewing them, and then asking them to refer you on to another suitable participant (Merriam, 2009).

In this thesis criterion or purposive sampling was used to select participants. Details of the sampling criteria for Study III are detailed in Chapter 6.

5.5 Sample size

In qualitative research sample size is normally determined by data saturation. Data saturation is difficult to define, but is based more so on the depth of the data rather than the number of participants. Data saturation occurs when little or no new information is being acquired, further coding is not feasible, and enough information has been collected that the study could be replicated (Fusch and Ness, 2015, Carpenter and Suto, 2008). When data saturation is reached there is no benefit from continuing with data collection. Recruitment for Study III of this thesis ceased when data saturation occurred.

5.6 Procedural aspects of interviews

All interviews for this thesis took place in a private room in either the Trinity Centre for Health Sciences or the Clinical Research Facility at St James's Hospital, Dublin. Participants were required to attend for interview on one occasion. Interviews were scheduled at a time of convenience for participants and were frequently arranged to coincide with other planned hospital appointments to avoid any additional travel burden on participants. All interviews were carried out by the lead investigator (LON).

Although interviews were focused on the perspectives of patients with oesophago-gastric cancer of their early physical recovery, participants sometimes requested that a close family member or friend accompany them for their interview. As family members and close friends can give invaluable insight into the experiences of patients, any contributions by them during study interviews were recorded also and included in the analysis of results. A flexible interview guide was used during all interviews. LON, a physiotherapist, generated the interview guide, and a focus was placed on issues pertaining to physical recovery following oesophagectomy or gastrectomy. A copy of the interview guide is enclosed in Appendix XVII. Respondent validation was used if necessary during the interview to clarify any points that needed clarification. Field notes were used to record any relevant non-verbal communication that occurred during the interview, and to report the interviewers overall impressions of the interview. All interviews were recorded using a Philips Voice Tracer Digital Recorder DVT2000 (China).

5.7 Data analysis

5.7.1 Data preparation

Interviews were listened to once and then transcribed verbatim by the main investigator (LON). Transcription is a key phase of the data analysis process as it allows the researcher to familiarise themselves with the data (Braun and Clarke, 2006). During Study III the main investigator (LON) transcribed each interview as the study was progressing. By listening to the interviews LON was able to reflect on her interviewing style, which helped her to improve her interviewing skills, and reduced the risk of interviewer bias in subsequent interviews.

Every nuance of the participants' narrative was recorded by transcribing pauses, and silences. Any field notes were read as the recording was replayed to ensure all non-verbal information was captured in the transcription. To ensure accuracy, the transcripts were checked back to the original recording for omissions. All participants were assigned a study code to ensure confidentiality. For Study III, the first participant received the code QS1, the second QS2, and so on and so forth. Transcripts were stored in password protected files and printed for the purposes of data analysis. Printed transcripts were stored in a locked filing cabinet. Any identifiable data such as names were removed from transcripts.

5.7.2 Qualitative data analysis

Qualitative data analysis was performed in this thesis using thematic content analysis as described by Braun and Clarke (2006). In thematic analysis, data is analysed for the purpose of identifying, analysing, and reporting patterns or themes in the data. Thematic analysis was chosen for this thesis as it is a simple approach, free from theoretical framework, which instead involves an inductive approach, meaning the themes are strongly linked to the data (Braun and Clarke, 2006). It is therefore an ideal approach to analysis for a qualitative descriptive study. The thematic analysis approach is detailed in Table 5.1.

Table 5.1 Phases of thematic analysis (Braun and Clark, 2006)

Phases of thematic analysis		
Phase		**Description of the process**
1	Familiarisation with the data:	Transcribing the data, reading and re-reading the data, noting down initial ideas.
2	Generating initial codes:	Coding interesting features of the data in a systematic fashion across the data set collating data relevant to each code.
3	Searching for themes:	Collating codes into potential themes, gathering all information relevant to each potential theme.
4	Reviewing themes:	Checking if themes work in relation to the coded extracts (Level 1) and the entire data set (Level 2), generating a thematic map of analysis.
5	Defining and naming themes:	Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.
6	Producing the report:	The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and the literature, producing a scholarly report of the analysis

The thematic analysis for this thesis was carried out using qualitative data analysis software (CAQDAS) with the programme NVivo 11 for Windows (QSR International Pty Ltd, Victoria, Australia). Phase 1 of the data analysis was performed manually using printed versions of the transcriptions. As per Table 5.1 the data analysis began with familiarisation with the data during the transcription process by LON. Two researchers, the lead investigator (LON) and Dr Annemarie Bennett (AB), a research dietitian then read, and re-read each interview transcript several times independently. This allowed both researchers to get a good grasp on the content of the interviews. During this phase, the two researchers analysed the text line by line, highlighted ideas for coding, and made notes about the content along the page margins. When the researchers were happy they had familiarised themselves with the data they proceeded onto phase 2.

Phase 2 involves the generation of initial codes from the data. Researchers used the NVivo software from phase 2 onwards. Codes are labels assigned to data fragments considered to share a common meaning (Carpenter and Suto, 2008). Both researchers coded the transcripts independently, and worked systematically through the data set, giving full and equal attention to each data item (Braun and Clarke, 2006). Coding involves developing a catalogue of codes (codebook) and screening each aspect of the data for the presence of codes. In Study III the initial codes were developed based on the study objectives and familiarisation with the data. Transcripts were then re-read, and scanned closely line by line to identify additional codes, missed codes, and sub-categories within codes. The inter-rater reliability of the coding system was then checked by the two reviewers (Section 5.7.3).

Phase 3 involves sorting the codes into potential themes. Themes consist of several codes which are aggregated together to form a common idea (Creswell, 2013). In phase 3 the list of codes generated in phase 2 was sorted into potential themes. Within themes, codes were sub categorised into subthemes. Subthemes are essentially themes within a theme that give structure to large themes (Braun and Clarke, 2006). In phase 4, both researchers worked together to further refine the identified themes, before committing to the final themes in phase 5. The final version of the codebook is included in Chapter 6, Table 6.4. Table 5.2 provides examples of how the coding system worked in Study III. Phase 6 then involved the production of results and the discussion of findings (Chapter 6).

Table 5.2 Examples of the coding system

Raw data	Coded text unit	Code	Sub-theme	Theme
No no worries, when I did go out walking there was always a member of my family out with me, because I was a bit slow in the beginning. And then we began to go further and further.	When I did go out walking there was always a member of my family out with me, because I was a bit slow in the beginning	Supervisory support from family	Facilitator of physical activity	Barriers to, and facilitators of, returning to physical activity post-operatively
Yeah I certainly feel physio would have been good and would have maybe, had me more advanced than I am. But I've done exercises and tried to stretch my arm up and that sort of thing but I feel if I had have had professional help yeah maybe it would have advanced me a little more. And I can understand being in and out of hospital so often the services can't always fall back on the hospital but there are enough physios out there to do something.	Yeah I certainly feel physio would have been good and would have maybe, had me more advanced than I am. But I've done exercises and tried to stretch my arm up and that sort of thing but I feel if I had have had professional help yeah maybe it would have advanced me a little more.	Management of musculoskeletal issues post-operatively	Physiotherapy input	Recommendations for health services on measures which may enhance the return to physical activity following oesophago-gastric cancer surgery
Oh I'm really happy now. I have my energy almost back and you know I can play with my grandkids and I can carry them because I wasn't able to carry them or anything because you know when I went home I wasn't able to carry anything.	I can play with my grandkids and I can carry them because I wasn't able to carry them or anything because you know when I went home I wasn't able to carry anything.	Return to familial roles and responsibilities	Personal roles	Challenges of returning to pre-operative societal roles

5.7.3 Reliability and validity

Both inter-rater and intra-rater reliability was assessed in this thesis. Inter-rater reliability refers to the level of coding agreement between different researchers. The two researchers (LON and AMB) coded all 20 transcripts independently and then a sample of 5 (25%) were checked for level of agreement (inter-rater reliability). Intra-rater reliability was assessed by the lead investigator (LON) on the same subset of transcripts by reviewing the initial codes after a period of one month had passed. All agreements and disagreements were counted to quantify the level of reliability. Table 5.3 displays the formula used to calculate both inter-rater and intra-rater reliability and is expressed as percentage agreement (Miles and Huberman, 1994). Validity of qualitative work is often carried out by participant or member checking (Creswell and Miller, 2000, Sandelowski, 1993). This involves sending participants a copy of their transcript and asking them is the transcript a true reflection of how they felt that day. In Study III of this thesis member checking did not occur as the time-course of oesophago-gastric cancer is such that post -operative morbidity, and high risk of reoccurrence, in the first six postoperative months, mean the patient condition may change or deteriorate rapidly. It was therefore deemed insensitive to return transcripts to participants and request feedback.

Table 5.3 Formula used to calculate the reliability of the coding system (Miles and Huberman, 1994)

$$\frac{\text{Number of agreements} \times 100}{\text{Total number of agreement + disagreements}}$$

Chapter 6 Study III: Patient's perspectives of returning to physical activity and their rehabilitative needs in the first six months following oesophagogastric cancer surgery

Abstract

Aims

Whilst Study I and II addressed the rehabilitative needs of those greater than six months post curative surgery for oesophago-gastric cancer, the rehabilitative needs of those earlier in recovery require exploration. Accordingly, Study IIII aimed to investigate patients' perspectives of their physical recovery in the first six months post oesophago-gastric cancer surgery to aid design of rehabilitative strategies at this timepoint.

Methods

Semi-structured interviews were held at St James's Hospital, Dublin with participants who were 4 weeks to 6 months post-oesophagectomy/gastrectomy. Interviews were an average of 14 minutes and included questions pertaining to physical recovery post-oesophagectomy/gastrectomy. Interviews were audio-taped, transcribed verbatim, and analysed by thematic analysis.

Results

Twenty participants (mean age 63.35(7.50) years) were recruited. Five themes were identified: i) challenges of recovery and impact on physical activity, ii) facilitators of, and barriers to, returning to physical activity, iii) physical challenges of returning to pre-operative societal roles, iv)importance of personal and professional support during recovery, v) recommendations for health services on measures which may enhance the return to physical activity. Post-operative barriers to physical activity included dietary issues, continuing treatments, pain, breathlessness, muscle weakness, fatigue, and anxiety. Participants identified that strategies such as a gradual return to activities, rest, and family support facilitated return to physical activity. Participants recommended that i) greater physiotherapy input, ii) psycho-social support, and iii) fatigue management may aid physical recovery:

Conclusions

Following oesophago-gastric cancer surgery, patients experience difficulties which can hamper physical recovery, many of which are amenable to rehabilitative intervention. Accordingly rehabilitative measures at this time-point require investigation.

6.1 Introduction

Study I and Study II of this thesis established the initial feasibility and efficacy of a multidisciplinary rehabilitation programme for patients with oesophago-gastric cancer who were a minimum of 6 months post-surgery. However, a limitation of this work is that it does not address the rehabilitative needs of those earlier in their recovery following oesophago-gastric cancer surgery. As previously described in Chapter 1, the first few months following oesophago-gastric cancer surgery can be an extremely challenging time for patients, with reports of significant deficits in nutritional status, physical function, and HRQOL (Scarpa et al., 2011, Tatematsu et al., 2013b, Fagevik Olsen et al., 2005). However, little research has been carried out regarding the rehabilitative needs of this complex cohort during the early recovery period following oesophago-gastric cancer surgery. Therefore, the efficacy of rehabilitation strategies in the first six month post oesophago-gastric surgery to combat physical decline and manage the side effects of treatment is unknown. In Chapter 1 (section 1.5), the systematic review identified only one study which examined a rehabilitation programme in the first six months following oesophago-gastric cancer surgery. Lococo et al. (2012) examined the feasibility of a multidisciplinary rehabilitation programme during the inpatient post-operative period following oesophagectomy. The results of this study demonstrated the potential of such programmes, but the study had a high risk of bias, and thus its results should be interpreted with caution. Furthermore, no research was identified which addressed the rehabilitative needs of patients with oesophago-gastric cancer in the first six months post-discharge following oesophago-gastric cancer surgery.

Clearly given the known difficulties experienced by patients at this early time of their recovery, the potential of rehabilitative interventions to expedite recovery warrant investigation. Particularly, as given the uncertain prognosis, and high risk of recurrence in oesophago-gastric cancer, there is a need to optimise the quality of life throughout survivorship. Indeed the initial six months following oesophagogastric cancer surgery may indeed provide the ideal teachable moment for oesophago-gastric cancer survivors to adapt rehabilitative strategies to enhance the quality of survivorship. In order to successfully develop rehabilitative strategies for patients at this time point, exploration of their perceived rehabilitative needs and perceived physical deficits is required. Study III utilised qualitative methods to explore patient's perspectives of physical recovery. This approach will lead to the development of a patient centred programme.

6.2 Study aims and objectives

The overall aim of this study was to describe patient's perspectives of their physical recovery in the early stages post-oesophagectomy/gastrectomy. The specific objectives of the study were:

- To describe the perspectives of patients of their ability to return to physical activity in the first six months post-oesophagectomy/gastrectomy.
- To identify barriers patients may face in returning to their activities of daily living and to physical activity in the first six months of recovery post-oesophagectomy/gastrectomy.
- To explore the rehabilitative needs of patients in first six months of recovery post-oesophagectomy/gastrectomy.

6.3 Methods and measures

6.3.1 Study design

As discussed in Chapter 5 (section 5.2), the methodological approach to this study was qualitative description using semi-structured interviews.

6.3.2 Sampling and recruitment

The method of sampling was purposive/criterion (section 5.4). The criterion for inclusion was that participants were between 4 weeks and 6 months post curative surgery for cancer of the oesophagus or stomach. The presence of any of the following deemed participants ineligible for study recruitment; i) unsuccessful treatment outcome ii) evidence of metastatic disease, iii) communication difficulties which would impair ability to take part in semi-structured interview.

Recruitment was completed by the lead investigator (LON). Participants were recruited from the Upper Gastrointestinal Cancer Registry at St James's Hospital (SJH) and via the upper Gastrointestinal Cancer Surgery Clinic at SJH. LON screened the database for eligible participants. Participants deemed suitable for participation from the registry were mailed patient information leaflets (PIL) (Appendix XVIII) and expression of interest forms inviting them to contact the study investigators if interested in participating, or were invited to participate directly from the Upper Gastrointestinal Surgery clinic at SJH.

6.3.3 Ethical Approval

Ethical approval was obtained from the SJH/AMNCH REC (REC Reference: 2016-11 Chairman's Action (9)). Confirmation of ethical approval is included in Appendix XIX. All participants were required to provide written informed consent.

6.3.4 Interview guide

The interview guide was developed by the lead researcher, LON, and contained questions pertaining to patient's experiences of their physical recovery following oesophageal/ gastric cancer surgery. Developing the interview schedule involved i) reviewing the literature regarding physical function in the early recovery period following oesophago-gastric surgery (Chapter 1, section 1.5), ii) examining the literature on qualitative descriptive research, iii) reviewing qualitative research in cancer populations, and iv) referring back to study objectives listed in section 6.2. A copy of the interview guide is contained in Appendix XVII.

6.3.5 Data collection and analysis

Demographic data was collected from the Upper Gastrointestinal Cancer Registry database at SJH. Demographic data was collated in a table using Microsoft Excel. The procedural aspects of the qualitative data collection are described in section 5.6. Transcripts were analysed by thematic analysis as described by Braun and Clarke (2006) (section 5.7).

6.4 Results

6.4.1 Participant selection and identification of saturation

Screening of the Upper Gastrointestinal Cancer Registry at SJH database during the study period, identified fifty-six potentially suitable participants who were 4 weeks to six months post oesophago-gastric cancer surgery, of which 19/56 were deemed unsuitable for recruitment due to death, recurrence, continuing ill health, and hospitalisation. Thirty-seven patients were deemed eligible for participation. Between January and June 2017, three patients received the study PIL at the Upper Gastrointestinal Surgery clinic visit at SJH, and thirty-four patients received an invitation via mail to participate in this study. Three recipients invited by mail-drop declined participation, and no response was received from 12. Another two recipients from the mail-drop expressed an interest in participation but as they had no other scheduled appointments at SJH during the study

period and travel was quite arduous for them, they declined participation. A total of 20 participants were recruited for this study. Seventeen of the participants were recruited via the mail-drop and the other 3 participants were recruited in-person from clinic. The flow diagram for study recruitment is presented below (Figure 6.1). As described in section 5.5, recruitment was ongoing until data saturation was reached. It was apparent from the analysis of interviews 17 to 20 that no new information or codes were emerging, and consequently recruitment was stopped at 20 participants.

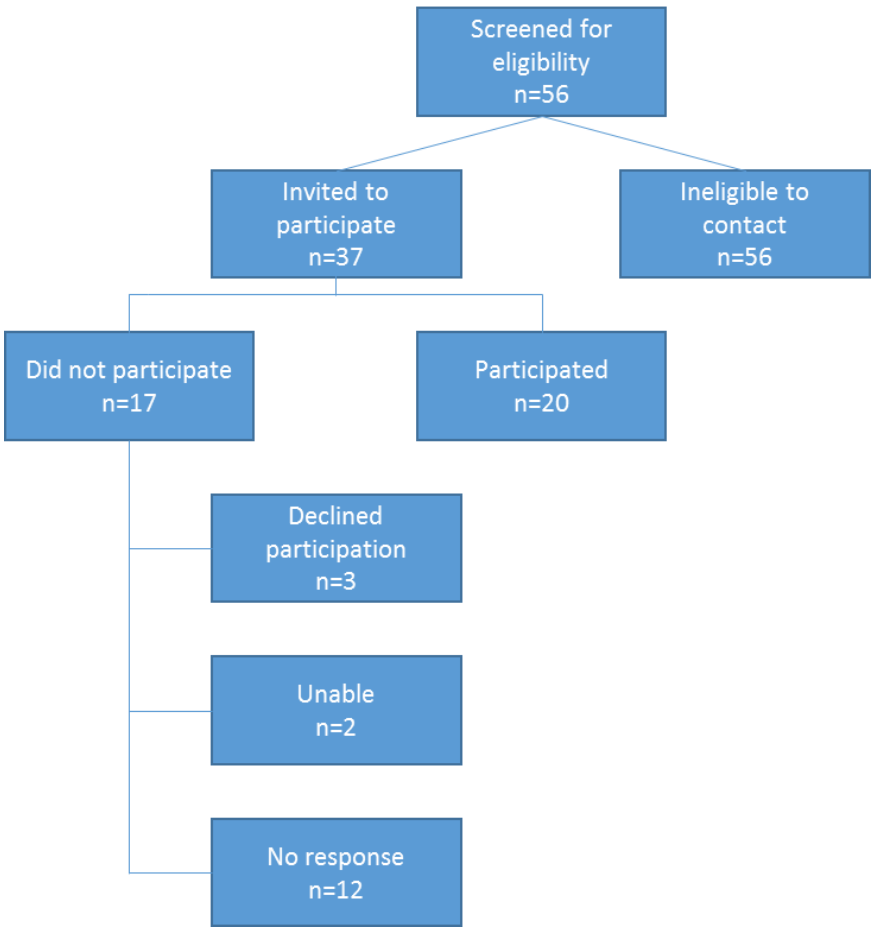

Figure 6-1 Recruitment of study participants

6.4.2 Participant characteristics

Demographic characteristics of participants are presented in Table 6.1. Age was the only normally distributed characteristic and is presented as mean (SD). Non-normally distributed continuous variables are presented as median (IQR) and categorical variables are presented as frequency (%). Time post-surgery is presented as range. The average interview length was 14 minutes with a range from 6 to 39 minutes. A total of 47,785 words of original content was transcribed.

Table 6.1 Demographic characteristics of participants

		Mean (SD) /Median (IQR)/ Frequency (%)
Gender		
	Male	17 (85%)
	Female	3 (15%)
Age at study enrolment (years)		63.35 (7.50)†
BMI at diagnosis (kg/m^2)		25.04 (6.48)
Time since initial diagnosis (months)		10.00 (3.50)
Time post-surgery (months)		Range (2.5 – 6)
Type of surgery		
	Transthoracic Oesophagectomy	9 (45%)
	Transhiatal Oesophagectomy	8 (40%)
	Oesophago-gastrectomy	1 (5%)
	Gastrectomy	2 (10%)
Cancer Type		
	Oesophageal	15 (75%)
	Oesophago-gastric Junction	4 (20%)
	Gastric	1 (5%)
Tumour Type		
	Adenocarcinoma	13 (65%)
	Squamous Cell Carcinoma	6 (30%)
	Associated Barrett's	1 (5%)
Neoadjuvant Rx		
	Yes	16 (80%)
	No	4 (20%)
Adjuvant Rx		
	Yes	4 (20%)
	No	16 (80%)
Barrett's Oesophagus		
	Yes	11 (55%)
	No	9 (45%)
Length of Hospital Stay (Days)		14.5 (5.75)
No. ICU/HDU Days		3.00 (2.75)

Post-operative complications		
	Yes	12 (60%)
	No	8 (40%)
Discharge destination		
	Home	16 (80%)
	Convalescence	3 (15%)
	Local Hospital	1 (5%)
Employment Status		
	Retired	9 (45%)
	Working	9 (45%)
	Unknown	2 (10%)

†*Age was normally distributed, therefore results presented as mean (SD). SD= Standard deviation, IQR = inter-quartile range, BMI = body mass index, Rx = Treatment, ICU = Intensive Care Unit, HDU = High Dependency Unit.*

6.4.3 Inter-rater and intra-rater reliability

The inter-rater and intra-rater reliability of the coding system in Study III was determined as outlined in section 5.7.3. Most discrepancies that occurred were errors of omission. Any coding disagreements between raters were resolved through discussion. Reliability results are presented in Table 6.2 and 6.3.

Table 6.2 Inter-rater reliability of the coding system (Miles and Huberman, 1994)

$$\frac{\text{Number of agreements x100}}{\text{Total number of agreement + disagreements}}$$

$$= \frac{139 \times 100}{139 + 10}$$

$$= 93.28\%$$

Table 6.3 Intra-rater reliability of the coding system (Miles and Huberman, 1994)

$$\frac{\text{Number of agreements x100}}{\text{Total number of agreement + disagreements}}$$
$$= \frac{137 \times 100}{137 + 12}$$
$$= 91.94\%$$

Acceptable levels for inter-rater reliability and intra-rater reliability are ≥70% and ≥80% respectively (Miles and Huberman, 1994). Accordingly, the coding system in Study III demonstrated inter and intra rater reliability.

6.4.4 Results of Thematic Analysis

The results of this study were classified into five major themes, and a number of subthemes (Table 6.4). Results are presented in more detail in the following sections with examples of quotations which reflected participant's experience of their physical recovery following oesophago-gastric cancer surgery.

Table 6.4 Themes and sub-themes generated through interview analysis

Themes	Subthemes	Codes
Impact of the recovery process on return to physical activity	Progress and expectations of recovery	• Return to physical activity • Recovery progressing positively • Recovery progressing slower than anticipated • Unsure of expectations of recovery
	Issues affecting general recovery	• Difficult journey and finding a 'new normal' • Dietary issues • Fatigue • Pain • Neuro-musculoskeletal issues • Respiratory problems • Mental health and concentration • Speech problems
	Symptom management	• Management of dietary issues • Fatigue management • Pain management • Management of breathlessness
	Other issues affecting recovery	• Post-operative complications • Continuing treatments • Other medical issues
Barriers to, and facilitators of, returning to physical activity post-operatively	Facilitators of post-operative physical activity	• Graded return to activities • Pre-operative education • Pre-operative fitness aided physical recovery • Motivation • Home modification • Supervision
	Barriers to post-operative physical activity	• Environmental barriers • PEG feeding • Concerns regarding body image • Unsure of safe limitations of exercise post-operatively • Family members anxious about return to activity • Age

Challenges of returning to pre-operative societal roles	Personal roles	• Return to familial roles and responsibilities • Return to leisure pursuits • Impact of recovery on social life
	Professional responsibilities	• Experience of returning to work • Importance of a facilitated return to the workplace • Social benefits of returning to work
Importance of personal and professional support during recovery	Support of friends and family	• Provision of convalescence • Assistance with ADLS • Assistance with management of condition • Maintaining family business • Providing important mental support
	Professional Support	• Support from St James's Hospital • Support from community health services
Recommendations for health services which may enhance the return to physical activity following oesophago-gastric cancer surgery	Physiotherapy input	• Management of musculoskeletal issues post-operatively • Maintenance/prevention of muscle loss • Guidance/ goal setting regarding return to physical activity
	Fatigue management	• Advice regarding fatigue • Provision of fatigue management classes
	Psychological support	• Provision of mental health support pre-operatively to prepare patients for recovery • Provision of post-op mental health support and support groups

6.4.4.1 Theme 1: Impact of the recovery process on return to physical activity

This theme will be discussed under the following sub-themes; i) progress and expectations of recovery, ii) difficulties affecting general recovery, iii) symptom management, and iv) other issues affecting recovery.

Progress and expectations of physical recovery

All participants reported they had returned to a level of physical activity since their operation *'I'm able to do now basically anything I want to do, I can do work, I can do a little bit on the farm as well, and plenty of gardening – pulling weeds and digging and everything, no problem'* (QS14), '*I was able to get out and do a bit of walking and do a bit of swimming within a period of time'* (QS2), and '*I'm pretty good, pretty good at the moment I can go for a walk, I can easily walk three mile now not a problem like'* (QS5). However many reported difficulties in returning to physical activity '*if I walk a couple of miles I can feel it, a bit of a pain in my back*' (QS18), '*when I want to try and take exercise I find myself relapsing into a worse state of fatigue'* (QS19), and *'I felt like an old man (laugh) going out for a walk. If I could walk as far as the gate and back that was an achievement some days*' (QS3).

Participants reflected on the general progress of their recovery. Many participants reported they were largely satisfied with how they had progressed '*I feel I've come out the other end at this stage'* (QS1), and that their recovery was better than anticipated '*I'd say it's much better than I expected it to be. I thought I'd be knocked out a lot longer, like wouldn't be as good as I am now*' (QS14), *'better than I expected it to be really. I think so, there was nothing too difficult about it really* '(QS18). Others reported a longer recovery period '*it's quite slow but that's to be expected*' (QS20), *'you know the recovery took a long time*' (QS8), and felt they were not near their baseline yet '*I still haven't got myself up to the full level I was'* (QS2), '*I'm clearly a kilometre down on my 40 minute walk. So if you think a kilometre in 40 minutes I'm down that so that gives you a very precise indication of how much less I can do now'* (QS15). A few participants also stated that their recovery was more challenging than they had anticipated '*my recovery was worse than I expected*' (QS3), and '*but it was bad, I wouldn't like to go through it again, that's one thing definitely not'* (QS8).

Several participants were uncertain about how their recovery was progressing and reported that it had been turbulent or variable '*no it's just very hard to predict. Like even now today (…) I was so*

well coming in here and prepared for today and looking forward to seeing people again, and then I had a pastry and a coffee and all of a sudden I just felt awful, I feel ok now, so you just, it's just the way it is you know and I mean I can't control that, there is no warning' (QS16). Furthermore, several participants reported that they were unsure of what their expectations of recovery should be after their operation '*I didn't really have any sensible expectations. I didn't really know what the hell was going to happen*' (QS15) and '*I suppose if I had have known like if it was going to take so long I wouldn't have being expected to get better so quickly'* (QS5).

Issues affecting general recovery

Participants reflected on the difficult treatment journey they had undertaken '*the cancer never worried me. It never worried me for some reason it was the chemo I was more worried about'* (QS6), '*I had gone through multiple EMRs [endoscopic mucosal resection], RFAs [radiofrequency ablation] and I had 4 dilations the year before I went to the surgery. So although I didn't have chemo I had so, my diet was very bad, I've lost about 3 stone in the last two years'* (QS2), and their struggle to discover a new-normal for themselves particularly with regards to management of dietary issues *'I've struggled to find what my new normal is'* (QS2).

Participants particularly reported struggling to adapt to the impact of their altered physiology on food intake '*mmmm I think the eating really. You know making myself gradually to be able to eat a bit more and to go on to solid food. That's a huge adjustment because I like the food. You know I used to eat out a lot. So that was the main thing'* (QS7) and '*but say with my diet I'd eat things and if it doesn't agree with me I don't eat it again and that's it you know what I mean'* (QS6). Participants expressed concerns about weight loss *'I've lost about 3 stone in the last two years. So there were (…) side effects, like I can't sit for long periods, and that was frustrating me in my recovery'* (QS2), swallowing difficulties '*I had a little problem swallowing for the first two or three weeks'* (QS11), '*Yeah everything got stuck now everything even the tablets'* (QS10), nausea '*well for me the nausea, was the worst. I couldn't look at food, I couldn't the smell of food, and you know I just needed plenty of fresh air'* (QS1), and dumping syndrome '*I get flashing in the eyes sometimes after eating. It's not bad now at the moment. It's not bad but I get weak and I start to sweat like anything'* (QS5), '*I went out on the bike I started getting the dumping syndrome after about 15 minutes so I had to come back'* (QS20).

Participants discussed other difficulties that they faced in their recovery that had affected physical activity either directly or indirectly. These included fatigue, pain, neuro-musculoskeletal issues, respiratory problems, mental health issues, and impaired concentration, and speech problems. Many participants reported that fatigue was a huge issue affecting their return to post-operative activity '*I suppose at first I was tired all the time'* (QS12), *'there is days I do stuff and I do get tired quickly like*' (QS13), '*Just tiredness, tiredness and I would reach a point I would just hit a fatigue bump and I would just have to accept that'* (QS17), '*the one big problem I had was fatigue. Which was permanent up to about ten days ago until I began to be aware of increased level of horse power as it were. But that's… I'm still well below what my usual energy levels but that's the way it has been*.' (QS19). Pain was also reported as a barrier to physical activity. Participants reported pain affected different areas of their bodies post-operatively '*the soreness under my ribs'* (QS9), '*my stomach was so sore, and my whole body was so sore*' (QS8) and '*my whole right hand side even six months after the operation is very tender and sore, front and back*' (QS3).

Aside from pain, participants also reported a number of other neuro-musculoskeletal difficulties that had affected their physical recovery to date. Participants reported difficulties with muscle atrophy '*I mean I'm conscious of the fact that I've lost a lot of muscle*' (QS19), weakness '*you know I was quite weak for a while*' (QS7), muscle tightness '*my right hand side could work surely you know I wouldn't have pain or anything but to lift anything, you could feel the stretch, like a tightness and it came all around here*' (QS8), sensation disturbances '*pins and needles, the feet and me hands numb*' (QS6) and impaired coordination '*the right side of my body and hand coordination and all that seemed to be affected. That I wasn't able to get it up to wash my face or wash my teeth really and that was it*' (QS3).

Respiratory issues also inhibited participant's physical recovery. Participants reported difficulty with coughing '*I found I would start coughing and spluttering'* (QS2), and shortness of *breath 'my land is a bit hilly like and I felt a bit out of breath at times that I use not to that kind of thing*' (QS12), '*I walk straight but when I go up a hill I'm puffed, you know when I'm at the top I'm puffed and I feel I never used to be like that*' (QS8).

Participants also reported their mental health had been affected during their recovery. Several reported anxiety in particular with regard to fears of not being fully recovered '*I still felt I was not*

fully healed' (QS2), fear of relapsing '*you weigh yourself and you're down it makes you worse like you know so I don't*' (QS6), and the fear of recurrence '*you can't have a magic wand and say it's not going to come back'* (QS8). Others reported a general low mood and lack of interest in activity *'you lose a certain amount of interest in what is going on around you'* (QS19) and '*no interest in anything at all. The Olympics were on at the time, I didn't even want to get out of bed and look at television*' (QS3). Concentration was also reported to be affected during recovery '*the real down side is intellectual activities which have been impinged, very much slowed down by my lack of concentration and ability to plunge into things you know hold things, hold an idea'* (QS15).

Speech difficulties were also reported by several participants, which may have impeded participation in social activities '*like it is hard sometimes to speak the way the voice is sometime*s' (QS10), '*I had the voice lost and I had to get that back again'* (QS11).

Symptom management

Participants identified strategies they had adapted to help aid their recovery and counteract the difficulties described in the previous section. With regards to diet management, most participants reported adapting the little and often approach '*just smaller portions and more regular meals that's the secret to it*' (QS18), several reported it was a learning experience to establish what foods they could tolerate post-operatively '*then I learned I was able to eat you know a tin of spaghetti and it would just go down nice and slowly'* (QS8). Others reported they had to time their meals with regards activity and some even reported that they avoided eating before going out to prevent unwanted side effects of eating particularly dumping syndrome '*people talk about dumping symptom so I sometimes do get that (…). It would mean sometimes if you were going somewhere you'd be more careful like you won't eat before you go out sometimes, it usually occurs within 15 minutes so you can work around it*' (QS20).

With regards to fatigue management many participants reported that having a rest or sleep in the middle of the day was their main coping strategy '*yeah from maybe four o'clock I might go have a lie down listen to the radio, and by 6 I'm able to get back up again and I'm feeling ok*' (QS16), '*I mean I can't do awful long days like I used to but if I take a rest in the middle of the day, I can go at it again in the evening'* (QS18), '*after coming up here now I'd be alright but when I get home that'll be.. I'll be out for the count for about an hour and a half to two hours you know*' (QS4). One

participant had turned to alternative therapies to manage their fatigue '*I was on quite an extensive course of acupuncture and who knows but I think that helped'* (QS17).

Participants reported managing pain by rest and adopting particular positions '*what I do is I just lie down and have the pillows propped up and once I lie down for an hour, maybe an hour and a half I can get back up and continue on'* (QS1) and '*I find it more comfortable to lie, than to sit for long periods*' (QS2). Rest was also a coping strategy reported to manage breathlessness '*So I'd relax, sit down for a few minutes and then carry on*' (QS1).

Other issues affecting recovery

Participants addressed issues they had experienced in the recovery process which had impacted on their return to physical activity. Several reported post-operative complications had impeded their recovery '*after 2 or 3 weeks for some reason I ended up back in here, it seemed to have been something to do with the medication, but the body just crashed and after that I spent a month, the month of August in St James's'* (QS3), '*em that's then when I got the bug and they had to take the feeding tube off me so they tried to feed me more and I got a very bad bug of diarrhoea so then I moved on from there to eh it was very sore I could hardly walk eh I wasn't used to that either I was never hardly sick in my life'* (QS8). Continuing treatments post-operatively particularly chemotherapy was reported as being difficult for several participants '*because after the operation I got more chemo. But I only got one dose because they couldn't give it to me because my body wouldn't take it. That took an awful lot out of me*.' (QS8), *'most difficult part after were the chemo after the operation. Oh sickness sure, diarrhoea, I just wasn't able for it, it wasn't on!*' (QS9). Other medical issues also impacted on some participant's recovery, for example one participant had to undergo cardiac surgery shortly following his oesophagectomy '*only 3 weeks after having that I had open heart surgery, a quadruple bypass!'* (QS4) and another was awaiting surgery for a hernia repair '*and I've also had problems obviously with the hernia and now I'm going for surgery on that. So it's hard to know sometimes whether my recovery was interfered a bit'* (QS2).

6.4.4.2 Theme 2: Barriers to, and facilitators of, returning to physical activity post-operatively

This theme will be discussed under the sub-themes of; i) facilitators of, and ii) barriers to post-operative physical activity.

Facilitators of post-operative physical activity

Participants identified the following as facilitators of physical activity in the first few months following oesophagectomy/gastrectomy; i) a graded return to physical activity, ii) pre-operative education, iii) motivation, iv) home modification, and v) supervision during physical activity.

Most participants reported that a graded return to physical activity had worked well for them *'I went nearly every day for a walk and then I began to walk further and further'* (QS1), '*I just tried to walk down the road a bit I'd walk a bit farther every day'* (QS12), '*I've actually just gone this week from walking 30 minutes to 40 minutes'* (QS15). Participants also reported that advice given pre-operatively and in the early post-operative period from the hospital physiotherapy team was helpful '*you know the physiotherapists they all come in and tell you exactly this is going to happen and it does happen'* (QS6). Participants also reported that they felt their pre-operative fitness had aided them in their recovery '*well I think it really stood me like I don't smoke or that and I think the fact that I had been so physically active and felt so strong that really helped me with the surgery'* (QS16). Motivation and goal setting was also an important facilitator of physical recovery for several participants '*I really had to push myself to go 100 metres'* (QS3) '*It was a goal that I had to get back to it. No matter what!'* (QS6).

Modifications to the home environments were required by some participants to help with activities of daily living '*what I was afraid of was falling in the bathroom. Because I had a step about that height, up into the shower so I just decided I was going to get a new bathroom. So I went ahead and I done that*' (QS10). Family members also helped facilitate the return to physical activity for several participants through supervision '*when I did go out walking there was always a member of my family out with me, because I was a bit slow in the beginning'* (QS1) and '*you know my daughters used to go with me for the walk' (QS2).* Indirect supervision during physical activity was also reported as reassuring *'it's an army camp where (…) if anything did happen I was going to be found,*

because if I went on the plains you would be found at some stage but that was basically one of the reasons walking in area where there would be, there is always someone around yeah' (QS6).

Barriers to post-operative physical activity

The following barriers to physical activity following oesophago-gastric cancer surgery were identified by participants; i) environmental barriers, ii) JEG feeding iii) concerns regarding body image, iv) unsure of safe limitations of exercise post-operatively, v) family members anxious regarding return to activity, and vi) age.

Environmental barriers to physical activity reported by participants included the weather '*no as I said the weather has been so bad I can't get outside the door*' (QS11), '*ah well just now and again the weather wouldn't be fit kind of for it now, but yeah I'd go up and hit a few golf balls, a few balls you know yeah*' (QS6), and the darkness of the winter months '*just the long nights at the moment. The darkness that I can't really go on my own and you know'* (QS1).

JEG feeding was also reported as a significant barrier to physical activity by several participants. Participants reported the JEG made some ADLs difficult '*washing is tiresome because of the JEG'* (QS15), '*em I used to have problems even tying my shoe laces, because it was sore, bending was quite sore and eh walking*' (QS2), and impaired sleep quality '*it was probably annoying more than anything else. It was only half a litre a night anyway so but it took four hours, (…) I was one of these people that couldn't sleep through it, so you were four hours stuck to the machine so it was great (…) when I came off that so am yeah it means 4 hours extra sleep at night as well*' (QS20).

Concerns regarding body image were identified as a barrier to physical activity by a few participants, particularly to swimming '*and it's not for the fact that I can't do it. I just don't want to get into the pool this way. And I'm not getting in with a jumper or a yoke on me'* (QS10), '*Swimming I didn't go because there was a little bit of an embarrassment side for the fact with the scars and with the stitching and I was a bit, very much thinking about appearance that everyone would be gawking and seeing*' (QS2).

Several participants also identified fear and uncertainty regarding safe exercise limitations as a barrier to physical activity '*eh I was a bit worried yeah at the start because as I say I didn't know if I'd make it back home again. I used to go for a walk and feel weak. And I didn't know if I could make it back so I didn't go too far'* (QS5), and '*I didn't know how far to go'* (QS2). Participants also reported that some family members had anxieties regarding their return to physical activity and sometimes discouraged activity '*ah they were when I went home first, don't do this and don't do that*' (QS14), '*I think my family were concerned that I was doing too much too early. But that's family*' (QS17). Age was another barrier to physical activity reported by participants '*well no I've gone too old for kicking soccer*' (QS11).

6.4.4.3 Theme 3: Challenges of returning to pre-operative societal roles

This theme will be discussed under the sub-themes of; i) personal roles, and ii) professional responsibilities.

Personal roles

Participants discussed their return to familial roles and responsibilities, leisure pursuits and the impact of their recovery on social life. Most participants reported they had been able to return to most of their familial roles and responsibilities in the home '*I can do a little bit on the farm as well, and plenty of gardening – pulling weeds and digging and everything, no problem*' (QS14), '*but like now I'm doing things like cutting grass, cutting hedges, I help with the housework things like that*' (QS20). However some participants reported fatigue affected engagement in family activities '*if the family come I'm cooking the dinner like you know, by the time I have dessert and everything served I'm exhausted. I'd have to go and lie down again at that stage just after getting the dinner you know*' (QS1), '*last night our granddaughter was in a school play but I didn't go, I just didn't feel up to sitting there for two hours, whereas normally I would have gone you know?*' (QS16).

Participants reported returning to some leisure activities such as hunting '*yeah, yeah, start of the year now I wouldn't be as fast as the other lads now but I don't know now whether they wait for me or not but I seem to have caught up with them*' (QS11), gardening '*absolutely fantastic! I was able to get out in the garden and work!*' (QS4), and reading '*I got stronger then and I've a conservatory and I'd just sit there reading'* (QS8). However others reported they had been unable to return fully

to some activities '*there are certain tasks, I sail during the summer, and there are certain tasks in sailing that I haven't taken on yet'* (QS17), and unable to return at all to others like golf *'well I suppose its early days still, I haven't attempted to get back to golf yet'* (QS3) and travelling '*I go to Sri Lanka like and all these places but I just can't, I won't go now because I'm not able to eat put it that way. I mean you're not going to get liquidised food everywhere sure you won't?*' (QS10).

Participants reported they had returned to some social activities '*I say I'll be out just doing a bit of walking and meeting the boys again you know and I go up to the field and especially at night now when the boys be out training for the hurling and that you could go up at night and stay there maybe until about 9 o'clock'* (QS11). Difficulties with social activities were reported by some participants *'I went to the pub at Christmas and it was crowded and I left. I just felt uncomfortable, I felt weak, weaker there that I wouldn't be able to stay'* (QS2), particularly social activities that involved eating or drinking '*going out for a few pints I can't manage that at all now. If I went out now I'd have a drink once a week but even sometimes I won't bother*' (QS16).

Professional responsibilities

Several participants that were not retired, reported they had returned to work or were planning to return to work '*I've been back at work , working mornings from early October to Christmas time with no, no real problems really*' (QS3), '*I went back to work about 3 weeks after, I went back to work after and that was it'*(QS6). However some participants had been unable to return to their job '*the fishing end of it (…) I'm sure if I could get out I'd be able for the work it's just I have to be more careful now and you know I need to be near home and that kind of thing you know*' (QS12), and '*yeah, yeah, so when your job involves a lot of sitting talking, I've struggled at that. Also the job was going anyway at the end of the year, which it is gone now, so I didn't go back into the workplace, you know em I don't know if I would have'* (QS2).

For those who had returned to work, employer flexibility and a reduction in working hours was reported to have facilitated the return to work '*I'm not working to the level I used to work to. I'm working part-time you could nearly call it now*' (QS16), '*if I didn't want to come in to work I didn't have to come in. You know I'd come in and I'd do a little bit and they'd be thankful and they'd let me home*' (QS6). Participants also reported that getting back to work was important for their sense of feeling involved and the social interaction *'I enjoy it. I was missing work both in terms of just eh*

the activity of it and eh just being involved' (QS16), '*oh it did it certainly did yeah. Like when I was in chemo you'd be talking to people and I was talking to one person and he couldn't get to see his friends. I said what do ya mean and he said he was on a building site and health and safety you know they can't go in in case something happens to ya and there wasn't a bother on him you know. Whereas I could go in every morning if I wanted to or you know and see them. I think yeah the job was a big part of it'* (QS6).

6.4.4.4 Theme 4: Importance of personal and professional support during recovery

This theme will be discussed under the sub-themes of support of; i) support of friends and family, and ii) professional support.

Support of family and friends

The support of family and friends was reported as an important part of recovery following oesophago-gastric cancer surgery. Participants reported family and friends played a vital role in providing convalescence care, assisting with ADLs, assisting with the medical management, maintenance of family businesses, and social support.

Participants reported depending on family members and friends to provide convalescence care following their discharge from hospital. Several reported going to stay with family or friends *'I stayed with a friend of mine for another couple of weeks out in Malahide'* (QS7), '*when I went home I went and stayed with my sister*' (QS11), whereas others reported family members had come and stayed with them in their own home to care for them '*I didn't want to go home on my own because I lived on me own and I knew I couldn't cope on me own'* (QS8)), '*I've been looked after. I have to say now big time. And only for the young one. She looks after me 24/7 like'* (QS10). A few participants reported they were dependent on family members to assist them with ADLs when they first returned home from hospital '*well my daughters did it for me in the beginning when I went home because I was so nauseated.. I em just couldn't do anything as such'* (QS1), '*my wife helped me a good lot you know?*' (QS18). Participants also reported they relied on family members to help them with their medical management post-discharge particularly assisting with the implementation of their diet plan '*sister of mine eh did all the grub'* (QS11), '*the biggest worry was just to make sure the Jevity feed, managing that every night you know! That was a full feed every night and Ann was*

great with that she was able to do all that' (QS16). Family members were also reported to assist with maintaining family businesses such as farms during the recovery period '*well I'm doing bits but I need help, like lucky enough I have my two sons there, who are good help there (family farm)*' (QS13). Participants also reported the importance of the social support of friends and family in the recovery process '*cos I get around the boys would be up I could go for a spin with them I could go anywhere with them you know to pass the day if they had an auld day off they'd come up and collect me and go anywhere you know just to pass the day really*' (QS11).

Professional support

Participants reported how they were unanimously satisfied with the follow-up care they had received from SJH, the importance of convalescence care for those without family support, and disappointment with the follow-up provided by the local health authorities.

Participants reported they were very grateful for the support they had received from the team at SJH and felt their advice had helped them through their recovery '*I got such great help from the hospital. And.. eh.. the information I was given really helped me as I knew I was going to come out the other end*' (QS1), '*overall anytime we've rung up the dietitian or anybody there's no problem straight away, things like that no problem*' (QS10), '*certainly the back-up services here have been phenomenal. I've been in to Prof's team I dunno how often and everything else and into the dietitian, and that so I had numerous feeding problems so I was back to the dietitian a number of times and I had a feeding tube in for a long time, so and I wasn't putting on weight*' (QS3). In particular the provision of an educational DVD was reported to be beneficial for participants regarding what to expect from their recovery '*the DVD was a great help, it was it was. I was half afraid to watch it at first. And then I watched it, and I kind of went through the whole lot and how your man came out you know, I have a bit to go to be as good as he is, but I can see myself getting closer to it every day, he told the story and he was 7 years down the road and he could just about remember his surgery, and I could see that happening to me in even a shorter length of time you know*' (QS12).

Participants particularly those without family support identified the importance of local convalescence providers in facilitating recovery '*well I was very glad to go into Our Ladies Manor and that… you definitely need support, because I live on my own. So you need support, you know if I could manage that between Our Lady's Manor and friends I could stay with but I don't know about*

everybody. Certainly you would need some follow-on support, you know not go two weeks after your operation to your house. I think that, that would be difficult' (QS7). Participants also reported perceived inadequacies in the follow-up they had received from local community health care providers '*and I got a visit from the health nurse and all she wanted to do was interested in was that she was going to get paid and I've never seen her since'* (QS10), '*there was a social worker that was supposed to call but that was minimum. But it wasn't important. We were able to manage without it. Other people might not be able to be we were able*' (QS9).

6.4.4.5 Theme 5: Recommendations for health services which may enhance the return to physical activity following oesophago-gastric cancer surgery

This theme will be discussed under the sub-headings of; i) physiotherapy input, ii) fatigue management, and iii) psychological support.

Physiotherapy Input

Several participants reported they would have liked further input from physiotherapy both during their inpatient stay and post-discharge '*After the operation I had quite limited contact with your colleagues the physio. I think that's probably I didn't need them. When they said you need to walk I would walk. So I didn't need them to help me out of bed to go and start walking. The only one I felt I didn't like doing and probably if your colleague had been available more was the coughing in the early days'* (QS17), '*I felt I was let down on the physio side of things'* (QS3), '*I mean the physio came, but she clearly lost interest in me because I was clearly quite fit*' (QS15). Participants felt further physiotherapy could have helped them in their physical recovery with regard to management of musculoskeletal issues post-operatively *'maybe a bit of physical exercise, a bit of physiotherapy particularly on my shoulder. Yeah I think a little bit of physiotherapy on that would have helped. But that's about all. There must be some kind of exercises that would help the shoulder'* (QS18), '*Yeah I certainly feel physio would have been good and would have maybe, had me more advanced than I am. But I've done exercises and tried to stretch my arm up and that sort of thing but I feel if I had have had professional help yeah maybe it would have advanced me a little more.*' (QS3), and muscle atrophy *'On the physio side. I don't think through all the stages and processes there was ever the impact of weight loss, (…), I went myself to a physio as I couldn't sit at all. I couldn't sit in the car... I had to get cushions. Because the weight when it comes off you makes it quite uncomfortable. So I'm not too sure whether that should be something to think about weight loss and whether there is*

exercising to help it. I would have liked to have a programme of how to handle that side of things' (QS2). Participants also reported help with goal setting would have been helpful '*and maybe I was setting goals which were too aggressive but that does come from the physical side'* (QS2).

Fatigue management

Participants also reported that a greater emphasis on fatigue management would have been helpful for their physical recovery. Patients suggested that a number of potentially helpful strategies such as Advice '*I'd love to talk to someone about how you might deal with tiredness or how do you make that go away'* (QS16) and fatigue management classes '*yeah, well unless I don't know if there are programmes or things that would help people manage fatigue. My daughter tells me there is a local organisation that offers fatigue management classes but I never, that's the first I've heard of it. I don't know whether there are such things or whether they are effective*.' (QS19).

Psychological support

Participants also highlighted the need for psychological support in recovery. In particular they suggested the provision of more supports pre-operatively to mentally 'prepare' patients for their recovery *'no the only thing that really shocked me was the, and as I said it was fully explained to me before the surgery what it was about and what it involved but it was overwhelming. Yeah and I don't know whether you could do more to prepare somebody for that. How you would prepare somebody for the extent of that kind of surgery I just don't know how you could do that*!' (QS16), post-operative mental health support and the establishment of support groups as ideas to enhance psychological support in recovery '*I never found I could ring anyone, I didn't see any support groups or anything like that, that maybe I could have gone to, except for maybe going on the internet and googling it. And maybe that's something you know. I know where you say be cautious when you read what other people have been through but it's nice to have support and back up.*' (QS2).

6.5 Discussion

Study III provides an in depth exploration of patients perspectives of their physical recovery in the first 6 months following oesophago-gastric cancer surgery. Although some participants reported a return to some level of physical activity, most reported that their physical activity levels were suboptimal, and experienced difficulties returning to personal and professional roles. Participants identified a number of barriers to, and facilitators of, physical activity following oesophagectomy/gastrectomy. Participants highlighted the need for more supportive care interventions to facilitate return to normal activities following oesophago-gastric cancer surgery, and suggested several potential rehabilitative strategies that may be beneficial for patients in their early recovery.

In their discussions, Study III participants outlined how there are multiple factors which can make it difficult for patients to engage in physical activity following oesophago-gastric cancer surgery. Identifying barriers to physical activity in oesophago-gastric cancer survivors is important as it highlights issues that may be addressed through rehabilitation. Previous research, particularly in colorectal cancers, has highlighted how side effects of treatment and the presenting disease can negatively impact on physical activity engagement following cancer surgery (Fisher et al., 2016, Lynch et al., 2010). With regards to treatment side effects, participants in Study III reported how post-operative complications, continuing treatments (chemotherapy), and other medical issues had directly impeded on their ability to return to pre-operative physical activity levels. Furthermore, participants described how physical side effects of their treatment including fatigue, pain, neuro-musculoskeletal issues, and dyspnoea had negatively impacted on their physical recovery.

Most profoundly, participants in Study III reported that the disease specific dietary issues had negatively impacted on their physical recovery. Both oesophagectomy and gastrectomy involve a significant altering of the anatomy and physiology of the digestive tract (Waddell et al., 2014, Enzinger and Mayer, 2003), and as such patients must adapt to a new digestive system post-operatively. A qualitative study by Wainwright et al. (2007) described the experiences of patients learning to eat again following oesophagectomy, and outlined a number of patient reported difficulties including appetite loss, changes in taste and smell of food, swallowing difficulties, early satiety, pain, nausea, reflux, diarrhoea, and vomiting. These symptoms were also highly reported by the participants in Study III. Dietary difficulties can have a significant effect on the ability to engage in physical activity, poor nutritional status results in poor energy levels and reduced physical

performance, and symptoms such as diarrhoea and vomiting also prevent engagement in physical activity (Rock et al., 2012). Furthermore, following oesophago-gastric cancer surgery supplemental feeding via jejunostomy tube is often required for a period of time, and although associated with greater maintenance of physical function and body weight (Bowrey et al., 2015, Wu et al., 2011), it poses a significant barrier to physical activity following oesophago-gastric surgery. Study III participants reported how their supplemental feeding had restricted their ability to engage in activities of daily living including, washing and dressing themselves, had impaired their sleep quality and consequently their energy levels, and how prolonged need for supplemental feeding had prevented a return to water based activities such as swimming.

It is clear from the evidence presented in the previous two paragraphs that patients' presenting condition, arising from both the cancer and its' treatments, has a direct impact on their ability to engage in physical activity in the first six post-operative months. Moreover, Study III participants identified a number of other barriers to physical activity following oesophago-gastric cancer surgery that cannot be directly attributed to the disease or its treatments. Generic barriers to post-operative physical activity were reported such as lack of facilities, bad weather, and age. These barriers to activity have been well reported in other populations previously including older adults (Rasinaho et al., 2007), and diabetics (Thomas et al., 2004). Both personal fears, and the fears of family members, regarding the safe return to physical activity were acknowledged by many participants as a significant barrier to physical activity post-oesophago-gastric cancer surgery. Several participants reported that they were personally unsure of the safe limitations of exercise post-operatively, highlighting the need for guidance in this regard. Many participants also reported that their close family members had concerns regarding their return to physical activity. Several reported that family members had a traditional 'need to look after yourself' mentality and that family members favoured rest rather than physical activity. This mind-set stems from the past whereby clinicians advised patients with cancer to rest and avoid activity, however, given the current evidence base regarding the benefits of physical activity across the cancer continuum, it is vital going forward that greater emphasis is placed on the avoidance of physical inactivity (Schmitz et al., 2010).

Study III also identified several facilitators of physical recovery following oesophago-gastric cancer surgery. Firstly, several Study III participants reported that their good level of pre-operative fitness had helped them in their recovery following oesophagectomy/gastrectomy. This subjective

reporting concurs with the findings of quantitative research in this population (Chapter 1, section 1.5). Second, motivation was reported by the Study III cohort as an important facilitator of return to physical activity. Motivation has been reported as a key predictor of physical activity in survivors of other cancers, and strategies to improve motivation for exercise are being investigated in cancer survivor cohorts (Pinto and Ciccolo, 2011). Study III participants reported that not only did family and friends play a key care role in their early recovery, assisting with activities of daily living, they also supported them in their return to physical activity through supervision of activities such as walking. The importance of good social support for cancer survivors has been well documented previously, with those with greater support networks likely to experience better recovery (Adler and Page, 2008). Participants in Study III also reported that the support of the multidisciplinary upper gastrointestinal surgery team at SJH was a key facilitator of their physical recovery, highlighting pre-op education from the physiotherapist, post-operative follow-up from the dietitian, and the ease of accessibility to the surgical team and nursing staff via telephone and through clinics as particularly helpful.

A good physical recovery was considered an important facilitator by Study III's participants with regards to returning to both personal and professional responsibilities, in particular return to work, both inside and outside of the home. Hoving et al. (2009) previously reported that physical functioning was an important predictor of return to work in cancer survivors. Participants in Study III identified that being able to return to work was an important landmark of recovery for them. Previous research in cancer survivors has highlighted that return to work is important following cancer treatment as patients associate it with a return to normality, and benefit from the structure work places on daily living, the financial income, and the sense of identity that comes with being employed (Leensen et al., 2017, Malmstrom et al., 2013b). However, approximately a 1/3 of cancer survivors never return to work (Mehnert, 2011), and this statistic is similar for oesophago-gastric cancer patients. A recent study by Pinto et al. (2016) in a cohort of 50 patients who were working at diagnosis reported that 36% of patients who underwent oesophagectomy had failed to return to work in the first post-operative year. It was not surprising considering their reported side-effects of fatigue, pain, ongoing dietary issues etc. that several participants in Study III reported difficulty returning to work in the first six months following oesophago-gastric cancer surgery, particularly those who had active jobs previously. Furthermore, the extensive nature of oesophago-gastric cancer surgery, and the typically older age of oesophago-cancer patients are considered negative predictors of return to work following cancer surgery (van Muijen et al., 2013).

A number of recommendations were made by Study III participants regarding strategies to enhance physical recovery following oesophago-gastric cancer surgery. Firstly, there was a clear demand for improved physiotherapeutic involvement following oesophago-gastric cancer surgery. A recent review article by Guinan et al. (2017a) described how traditionally the role of physiotherapy following upper gastrointestinal surgery has been to facilitate early post-operative care and the management of PPCs. Accordingly, the goals of physiotherapy following oesophagectomy/ gastrectomy are typically; i) return to independent mobility, and ii) independently able to cough and clear secretions. Clinical services are driven by evidence based practice, and as Chapter 1 described, there is a dearth of literature regarding physiotherapeutic rehabilitation post upper-gastrointestinal surgery. Given this lack of evidence, it is understandable that the role of physiotherapy post-oesophago-gastric cancer surgery has been limited to date. However, as with all physiotherapeutic interventions lack of evidence does not necessarily mean lack of effect. Study III participants identified 3 key issues where they felt physiotherapy input would be helpful; management of musculoskeletal issues such as pain and tightness, prevention of further muscle loss, and guidance regarding the safe return to physical activity. Consequently, there is clear rationale for future research to investigate the efficacy of enhanced physiotherapy involvement post upper-gastrointestinal cancer surgery. This will be discussed further in Chapter 7, section 7.2.3.

Secondly, participants reported that second to ongoing dietary issues, fatigue was their most debilitating symptom in the early post-operative period, and sought additional advice regarding its management, and queried if fatigue management classes would be beneficial. The management of cancer related fatigue has been studied mainly in breast cancer populations to date (Cramp and Byron-Daniel, 2012). A number of non-pharmacological therapies have been reported as beneficial for cancer related fatigue; including aerobic and resistance exercise training, psychosocial support interventions, sleep hygiene, yoga, meditation, and nutritional input (Mustian et al., 2007). However, the non-pharmacological management of fatigue in the first six months post oesophago-gastric surgery has not been discussed in published literature, highlighting the need for research in this regards. Finally participants in Study III advocated the need for improved pyscho-social support in the first few months' post-oesophagogastric cancer surgery. The need for such support is also highlighted in the recently published National Cancer Strategy 2017-2026 (Healthy Ireland et al., 2017). Participants felt mental well-being was important for good physical recovery, and expressed they would have benefited from talking to someone or a group of peers about their mental health following their surgery. This is understandable given the new life situation patients face after oesophago-gastric surgery, and the uncertainty they face with regards prognosis. The importance

of peer support following upper-gastrointestinal cancer surgery has previously been reported by Malmstrom et al. (2013b) who found that following oesophagectomy patients benefited from talking to other patients who had been on a similar journey particularly with regards to understanding symptoms and their management.

6.6 Study Limitations

Study III has several limitations that must be acknowledged. Firstly, as participants were required to volunteer their participation, self-selection bias was unavoidable, and there is a risk that those with a greater interest in strategies to improve physical recovery following oesophago-gastric cancer surgery, such as those with a more difficult recovery, may have been more likely to participate. This, accordingly, restricts the generalisability of the results. A further limitation of Study III was the use of criterion (purposive) sampling. As previously described in section 5.4, criterion sampling involves the selection of a sample considered to be knowledge rich on the phenomenon of interest (Carpenter and Suto, 2008). However, this method can result in the views of other individuals with different experiences not being captured. Another limitation of Study III was the absence of member checking. As aforementioned in section 5.7.3 member checking did not occur as it was deemed insensitive to return transcripts and request feedback from this complex cohort.

6.7 Conclusion

This study indicates that following oesophago-gastric surgery, patients experience many difficulties which can impair their ability to re-engage in physical activity. Many of the physical difficulties described (e.g. fatigue, pain, sensation loss, reduced fitness, and muscle atrophy) are amenable to physiotherapeutic intervention. Since these physical difficulties can profoundly and negatively impact psychosocial wellbeing, the potential positive impact of rehabilitation during this time should not be underestimated. There has been little research to date on rehabilitative interventions in the first six months following oesophago-gastric cancer surgery. This study emphasizes the need for multidisciplinary rehabilitative interventions which aim to improve the physical and mental health and consequently the quality of life of patients recovering from oesophago-gastric cancer surgery.

Chapter 7 Discussion

7.1 Introduction

As survival rates for both oesophageal and gastric cancer slowly improve (Correa, 2013, Holmes and Vaughan, 2007), there has been an emergence of a new group of cancer survivors, who present with multifaceted needs both as a result of the cancer and also its' treatments. At the offset, oesophago-gastric cancer is associated with significant physical and nutritional impairment (ACS, 2014, Maconi et al., 2008), and curative treatment consisting of surgical resection, often in combination with chemotherapy or chemoradiotherapy, may further accelerate these impairments (von Dobeln et al., 2016, Jack et al., 2014). This thesis provided further evidence of the prevalence of physical function deficits in oesophago-gastric cancer survivorship. In addition, Study III of this thesis highlighted the consequences of impaired physical functioning and nutritional compromise, with many participants reporting difficulties engaging in activities of daily living, familial and professional roles, and social activities. Moreover, these documented deficits are considered prognostic of treatment outcomes (Vega et al., 2016), and survival in this cohort (Jack et al., 2014, Adenis et al., 2013), emphasising the importance of developing rehabilitative strategies to help overcome these difficulties in oesophago-gastric cancer survivorship.

In July 2017, Minister for Health, Simon Harris, launched an ambitious new 10 year cancer strategy for Ireland (Healthy Ireland et al., 2017). The National Cancer Strategy 2017-2026 has four main goals; i) reduce the burden of cancer, ii) provide optimal care, iii) maximise patient involvement and quality of life, and iv) enable and assume change. A key focus of the strategy is the development of supports for those living with and beyond cancer, and goal (iii) of the strategy specifically aims to develop and implement survivorship care programmes, which are evidence based, and aim to address the physical, psychological, social, and individual needs of those in cancer survivorship.

In line with this goal of the strategy, this thesis aimed to address the rehabilitative requirements of oesophago-gastric cancer survivors. In designing a rehabilitation programme for this cohort sizable consideration was given to their complex nutritional needs. Accordingly, this thesis aimed to explore firstly the feasibility, and secondly the efficacy of a multidisciplinary rehabilitation programme which combined supervised and home based exercise sessions with 1:1 dietary counselling, and group education sessions in oesophago-gastric cancer survivorship. The following section outlines the key points which emanated from the three studies of this thesis.

7.2 Analysis of key points

7.2.1 Cardiorespiratory fitness in oesophago-gastric cancer

Cardiorespiratory fitness testing evaluates the integrative capacity of the cardiovascular, respiratory, and musculoskeletal systems to effectively transport and utilise oxygen for ATP synthesis under physiological stress (Jones et al., 2012b). As previously described in this thesis, cardiorespiratory fitness is considered an important index of health, and is a strong predictor of both cardiovascular and all-cause mortality, and HRQOL (Myers et al., 2015, Leeper et al., 2013, Jones et al., 2012b, Gulati et al., 2003, Myers et al., 2002). Furthermore, the prognostic relevance of cardiorespiratory fitness in cancer should not be underestimated. There is growing evidence that having a higher level of midlife cardiorespiratory fitness reduces the lifelong risk of cancer development (HR: 0.85, 95%CI 0.68-1.00)(Robsahm et al., 2016), and also risk of death from cancer (HR:0.83, 95%CI 0.77-0.90 (Jensen et al., 2017), and HR:0.68, 95%CI 0.53-0.88 (Robsahm et al., 2016)). Moreover, cardiorespiratory fitness is also considered a strong predictor of cancer treatment outcomes (Moran et al., 2016), and increasingly of cancer survival (Peel et al., 2009a, Peel et al., 2009b). Part of the initial work of this thesis explored the effects of oesophago-gastric cancer and its' treatments on cardiorespiratory fitness, by systematic review. Subsequently, the impact of a structured rehabilitation programme on cardiorespiratory fitness in oesophago-gastric cancer survivorship was explored in Study I and Study II of this thesis. The findings of this body of work with regards to the impact of treatment on cardiorespiratory fitness and the relevance of fitness as a target for rehabilitation is reviewed in the following section.

Chapter 1 of this thesis included a systematic review examining the effects of oesophago-gastric cancer and its' treatments on objectively measured physical functioning, including cardiorespiratory fitness. This systematic review indicated that cardiorespiratory fitness is suboptimal across the oesophago-gastric cancer continuum. Significant reductions in cardiorespiratory fitness were reported following neoadjuvant therapies (NAC/NCRT) (von Dobeln et al., 2016, Lund et al., 2015, Jack et al., 2014), at three months post-operatively (Taguchi et al., 2003), and up to 1-2 years of survivorship (von Dobeln et al., 2016). The review also highlighted the consequences of reduced cardiorespiratory fitness for patients with oesophago-gastric cancer. Firstly with regards to neoadjuvant therapies, Jack et al. (2014) reported that patients with poorer cardiorespiratory fitness are less likely to complete neoadjuvant chemotherapy. Poor cardiorespiratory fitness was also found to be a strong predictor of surgical outcomes, including risk of PPCs (Moyes et al., 2013, Forshaw et al., 2008, Nagamatsu et al., 2001)), and mortality at three months (Liedman et al., 2001, Liedman et al., 1995) and up to one year post-operatively (Jack et al.,

2014). Accordingly, the systematic review highlighted the need for strategies to improve cardiorespiratory fitness in patients with oesophago-gastric cancer.

One of the gaps in the literature highlighted by the systematic review was the dearth of evidence regarding cardiorespiratory fitness in oesophago-gastric cancer survivorship. One report by von Dobeln et al. (2016) showed that fitness is impaired long-term into survival and similar findings were reported prior to the interventions in Study I and Study II of this thesis. In both studies, cardiorespiratory fitness was determined by the gold standard, CPET. Baseline CPET was performed with 12 survivors of oesophageal cancer (mean 22.16(8.54) months post-oesophagectomy) in Study I. Results showed that the majority of participants, when compared to age and gender normal values, had poor (n=5), or very poor (n=6) cardiorespiratory fitness. In Study II, the baseline cardiorespiratory fitness was found to be similarly low. Baseline CPETs were performed with 43 participants (mean 29.38(18.44) months post oesophago-gastric cancer surgery). The cardiorespiratory fitness of participants was categorised as fair (n=4), poor (n=12), and very poor (n=27). Therefore, it is clear from the results of both Study I and Study II that cardiorespiratory fitness is suboptimal in survivors of oesophago-gastric cancer.

The problem of impaired cardiorespiratory fitness in oesophago-gastric cancer survivorship reported in the first two studies of this thesis is not entirely surprising. Previous research has shown that in cancer survivors cardiorespiratory fitness (VO_{2peak}) is consistently 30% below that of age and sex matched sedentary controls (Jones et al., 2011). This is a worrying statistic, as deficits in cardiorespiratory fitness predispose cancer survivors to other comorbidities such as cardiovascular disease (Jones et al., 2012a). While the specific long-term prognostic relevance of impaired cardiorespiratory fitness in oesophago-gastric cancer is unknown, strong associations between cardiorespiratory fitness and all-cause mortality in healthy adults have been identified (Gulati et al., 2003, Myers et al., 2002), and emerging research suggests cardiorespiratory fitness may be associated with survival and risk of recurrence of breast and colorectal cancers (Schmitz et al., 2010, Peel et al., 2009a, Peel et al., 2009b). Consequently there is clear rationale for strategies which aim to improve cardiorespiratory fitness in oesophago-gastric cancer survivorship. In addition, deficits in cardiorespiratory fitness may have a detrimental impact on ability to engage in activities of daily living, and resultantly can negatively impact on HRQOL (Tatematsu et al., 2013b). Accordingly, the findings of this thesis provide justification for strategies which aim to enhance cardiorespiratory fitness in oesophago-gastric cancer survivorship such as the rehabilitation

programme implemented in Study I and Study II. This multidisciplinary programme aimed to improve the cardiorespiratory fitness of oesophago-gastric cancer survivors without any compromise to body composition.

In Study I, significant and clinically meaningful improvements were observed in cardiorespiratory fitness (VO_2max), as a result of the 12 week multidisciplinary rehabilitation programme. Undeterred by improvements in cardiorespiratory fitness, body composition remained stable throughout the 12 week programme. This study provided first evidence of the effect of a structured rehabilitation programme in oesophageal cancer survivorship, and established the safety and feasibility of the multidisciplinary programme. However, as previously described, Study I was a single–arm, pilot study of an intervention, which was designed to determine the feasibility of the programme and therefore was not powered to detect changes in cardiorespiratory fitness. Consequently the efficacy of the intervention required further exploration, and this was completed by RCT in Study II.

Subsequently Study II examined the efficacy of the 12 week multidisciplinary rehabilitation programme to improve the cardiorespiratory fitness of survivors of oesophago-gastric cancer who were >6 months and ≤5years post oesophago-gastric cancer surgery. Study II demonstrated that statistically and clinically significant improvements in cardiorespiratory fitness (VO_2max) could be achieved by participation in the multidisciplinary rehabilitation programme. As previously discussed in Chapter 4, the improvement observed in cardiorespiratory fitness in Study II is on par with fitness gains observed in other cancer exercise trials (Jones et al., 2011, McNeely et al., 2006). Importantly, this improvement in cardiorespiratory fitness was achieved without any compromise to body composition in this nutritionally vulnerable cohort. Although there is limited research regarding exercise and dietary interventions in other complex cancer cohorts with nutritional issues, results of Study I and Study II are akin to findings in advanced lung cancer. A systematic review by Payne et al. (2013) reported that exercise and dietary interventions have beneficial effects on unintentional weight loss and functional performance. The maintenance of body composition is an important finding for survivors of oesophago-gastric cancer, for whom fear of unintentional weight loss is an ongoing concern in survivorship (van Vulpen et al., 2017, Kirby, 1999). This was highlighted in Study III of this thesis, wherein participants reported their concerns, anxieties, and the consequences of unintentional weight loss. Therefore, the evidence presented by this thesis provides a meaningful recommendation for oesophago-gastric cancer survivors, whereby under the

supervision of a physiotherapist and dietitian, clinically important improvements in cardiorespiratory fitness can be achieved whilst maintaining a stable weight.

However, it must be noted that although Study II participants experienced significant improvements in cardiorespiratory fitness over the twelve week intervention period, and maintained significantly higher fitness levels than the control group at the final follow-up assessment, the cardiorespiratory fitness of the intervention group had started to decline in the follow-up period from T1 to T2. The significance of this should not be understated, and accordingly there is considerable need for strategies which help to maintain improvements in cardiorespiratory fitness achieved through exercise rehabilitation. This will be discussed further in relation to oesophago-gastric cancer in section 7.2.3. The evidence from other oncology exercise trials regarding the long term maintenance of fitness improvements achieved through exercise rehabilitation is conflicting, however, strategies such as longer intervention time periods, and the provision of booster sessions are reported to aid long-term adherence to exercise (De Backer et al., 2008, Thorsen et al., 2007). Of further note, in Study II, the cardiorespiratory fitness of the control group consistently declined over the 6 month study period. This finding is similar to other cancer exercise trials where consistent decline in cardiorespiratory fitness has been observed among control group patients assigned to a usual care regime (Jones et al., 2011, Jones et al., 2010). Accordingly, this should be considered when designing future controlled cancer exercise trials.

To conclude this section, this thesis has provided proof of principle for multidisciplinary rehabilitation programmes which aim to improve cardiorespiratory fitness in oesophago-gastric cancer survivorship. Another noteworthy finding, was consistent with the results of the systematic review in Chapter 1, Study I and Study II provided further evidence that cardiorespiratory fitness is suboptimal in oesophago-gastric survivorship.

7.2.2 Patient engagement with rehabilitation following oesophago-gastric cancer surgery

Undoubtedly this thesis has highlighted the significant risks and sequelae associated with oesophago-gastric cancer surgery, and the need for rehabilitative strategies in the aftermath. Incessantly throughout this thesis the physical and nutritional deficits experienced post-oesophago-gastric cancer surgery have been described. As detailed in section 7.2.1, this thesis has provided further evidence that cardiorespiratory fitness is impaired long-term post oesophago-gastric cancer surgery, and furthermore Study III of this thesis emphasised the nutritional and physical challenges that are prevalent immediately following oesophago-gastric cancer surgery. Undisputedly these issues are cumbersome, but yet are amenable to rehabilitation. Consequently, as survival rates for cancer of the oesophagus and stomach slowly improve, it is incumbent upon health researchers to develop strategies to address these issues, and therefore improve the quality of life of survivors. Addressing these rehabilitative needs is not without its challenges. Careful consideration should be taken for the aforementioned cancer specific issues faced by patients following oesophago-gastric cancer surgery, the typical older age profile of patients with the disease, and also the risk of other co-morbid conditions given the known lifestyle risk factors for oesophago-gastric cancer (smoking, obesity etc). The following section will outline the findings of this thesis with regards to patients' perceived needs for rehabilitation following oesophago-gastric cancer surgery. Furthermore, considering the novel design of the Study I and Study II rehabilitation programme, it will also outline patients' ability to engage with rehabilitative services that are offered to them.

As discussed in Chapter 1, both oesophagectomy and gastrectomy are associated with a considerable risk of post-operative morbidity and mortality (Haverkamp et al., 2013, Wolf et al., 2011), and are considered as two of the more difficult cancer surgeries to undergo. Therefore, it is almost impossible to compare the recovery period following oesophago-gastric cancer surgery, to that of any other cancer. A qualitative study by McCorry et al. (2009) involving 12 survivors and 10 carers post-oesophagectomy previously described the patient reported difficulties following oesophagectomy. Survivors reported the struggles of adjusting to an altered self following the permanent changes made to their digestive tract, and also the difficulties in coming to terms with the uncertain prognosis of an oesophageal cancer diagnosis. Similar to the findings reported by McCorry et al. (2009), the results of Study III of this thesis demonstrate that the first 6 months following oesophago-gastric cancer surgery is a challenging time. Ongoing treatments (chemotherapy), other medical conditions, and side effects of the cancer and its' treatment

including pain, dyspnoea, fatigue, and a myriad of dietary problems, were reported as barriers to physical activity following oesophago-gastric cancer surgery.

Unquestionably these difficulties are amenable to multidisciplinary rehabilitation, and Study III participants reported that they felt they would benefit from i) further physiotherapy input, to manage musculoskeletal symptoms such as pain, prevent further muscle loss, and to receive guidance regarding safe return to physical activity, ii) guidance regarding fatigue management, and iii) greater psychosocial support. Furthermore, the anxieties reported by McCorry et al. (2009) highlight that, not only are strategies required to assist with the physical and nutritional issues faced post-oesophago-gastric cancer surgery, but that there is also need for strategies which help the mental health of survivors and their ability to cope with this difficult diagnosis. Given the multifaceted needs of this complex cohort following oesophago-gastric cancer surgery, the development of a unique person centred multidisciplinary approach to rehabilitation is required.

The systematic review in Chapter 1 highlighted the paucity of research investigating the role of multi-disciplinary rehabilitation following oesophago-gastric cancer surgery. The search strategy only identified one study which had implemented a multi-disciplinary intervention following completion of curative treatment for oesophago-gastric cancer in survivorship (Chasen and Bhargava, 2010). However, as described in Table 1.10c the Chasen and Bhargava (2010) study had an overall serious risk of bias in favour of the experimental group, especially with regards to consideration for confounders, selection of participants, and reporting of missing data. So although significant improvements were observed in 6MWT distance as a result of their intervention, severe caution should be taken when considering their results. Clearly Study III identified there is an appetite for rehabilitative strategies following oesophago-gastric cancer surgery. Results of Study I and Study II of this thesis provided further evidence in this regard.

Given the sparsity of previous literature regarding rehabilitative interventions following oesophago-gastric cancer, the first two studies this thesis implemented a unique and novel 12 week multidisciplinary rehabilitative programme. Therefore, the ability of patients to engage with the programme was unknown at study commencement. Participants in Study III of this thesis reported that they would welcome rehabilitative services. Accordingly, it is an important finding of this body of work that when given the opportunity to engage in rehabilitation, patients did so, therefore

emphasising the feasibility of rehabilitation in this cohort. In Study I, the feasibility of the programme was demonstrated by the recruitment rate (55%), study retention (100%), and adherence to the supervised (82(13)%) and unsupervised (78.15(32.36)%) exercise sessions. Furthermore, the feasibility of both the intervention and assessment battery in Study I were vindicated by the lack of adverse events, and the positive impact of the intervention on physical fitness (VO_2max), physical performance (6MWT distance) and quality of life (O'Neill et al., 2017). As described in Chapter 3, these feasibility statistics were comparable with results from other cancer exercise trials. The feasibility of this 12 week multidisciplinary rehabilitation programme was further entrenched in Study II. Good feasibility was demonstrated by the adherence to the supervised (93.88(11.58)%) and unsupervised (77.99(27.31)% (exercise diary)) exercise sessions, and the lack of serious adverse events. In addition, in Study II feasibility of this multidisciplinary programme was further justified by the lack of drop-outs from the intervention group. One drop-out occurred in the control group. This is a positive result considering the findings of a systematic review by Steins Bisschop et al. (2015) which reported higher levels of drop-outs in cancer exercise trials that utilise a pure control group (excess drop-out rate 1.8±6.3% vs -7.1±11.3% for control participants offered any intervention). The other withdrawals that occurred in Study II were due to disease recurrence (n=3), however this was anticipated given the uncertain prognosis of oesophago-gastric cancer survivors.

Undisputedly this thesis highlights the desire among patients following oesophago-gastric cancer surgery for rehabilitative services, and demonstrates the willingness survivors have to engage in rehabilitation when it is offered to them. As a result, this thesis found multidisciplinary rehabilitation to be highly feasible in survivors from 6 months post oesophago-gastric cancer surgery. A proposed framework for a model of rehabilitation following oesophago-gastric cancer surgery will be described in section 7.2.3.

7.2.3 A model of rehabilitation for oesophago-gastric cancer

This thesis established the feasibility of rehabilitation in oesophago-gastric cancer survivorship, however there is more work to be done. It is evident from this thesis that there is a need for rehabilitative interventions not just in survivorship but across the entire oesophago-gastric cancer journey. In line with the PEACE framework (Figure 1.8)(Courneya and Friedenreich, 2007), there are a number of key time points across the oesophago-gastric cancer continuum in which exercise interventions have substantial amenability. The key focus of this thesis has been the period of survivorship following oesophago-gastric cancer surgery. Given the high risk of morbidity following oesophago-gastric cancer surgery, there is sizeable potential for the development of a model of post-operative multidisciplinary rehabilitation for oesophago-gastric cancer. As it is difficult to compare the early recovery period following oesophago-gastric cancer surgery to that of any other cancer, in order to develop rehabilitative measures at this time-point it is essential to review recovery programmes implemented following non-cancer related major surgeries. The best example of multidisciplinary rehabilitation in the early period following major surgery is that of cardiac rehabilitation (Figure 7.1) (IACR, 2013).

Cardiac rehabilitation is a continuous process that commences in hospital following an acute cardiac event, and continues indefinitely post discharge (IACR, 2013). Cardiac rehabilitation consists of four distinct phases, which are presented in Figure 7.1. Phase I cardiac rehabilitation begins during the inpatient stay following a cardiac event. Patients receive advice regarding a return to low level exercise, and both patients and family members are educated regarding the diagnosis, risk factor modifications, and medications. Phase II cardiac rehabilitation occurs in the first 4-6 weeks post-discharge, and involves continued advice regarding return to exercise and lifestyle modifications. Phase III cardiac rehabilitation is a structured exercise and education programme, which is led by allied health professionals. And finally Phase IV cardiac rehabilitation involves the long term maintenance of exercise and lifestyle modifications and this is typically facilitated in a community leisure centre. The benefits of cardiac rehabilitation have been well established, it is vindicated for its' positive effects on both cardiac specific and all-cause mortality, risk of hospital admissions, risk of cardiac events (e.g. myocardial infarction), quality of life, depression, weight management, lipid control, management of comorbidities, and cardiorespiratory fitness (Anderson et al., 2016, Servey and Stephens, 2016).

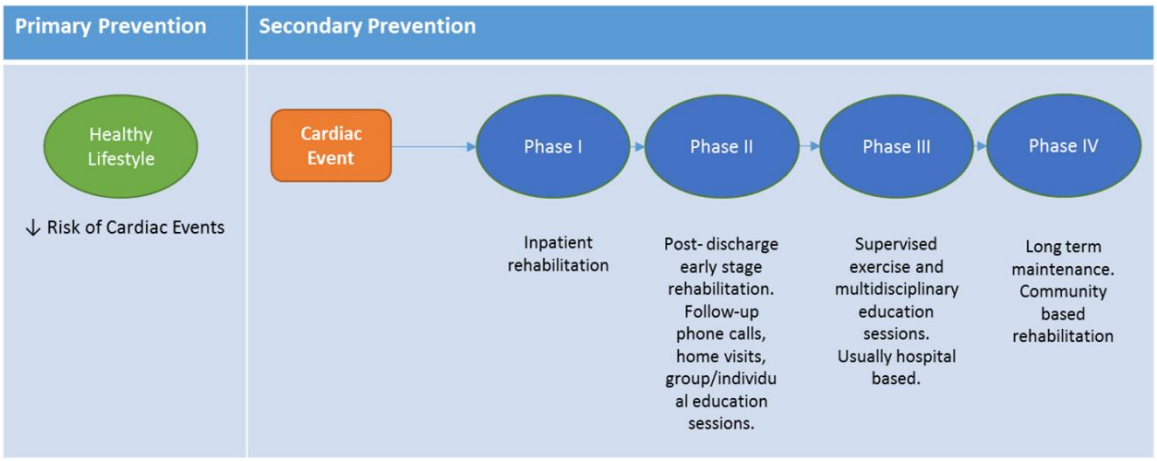

Figure 7-1 Established cardiac rehabilitation model

As highlighted in a recent article by Dittus et al. (2015), the cardiac rehabilitation model provides an ideal framework for developing a model of cancer rehabilitation tailored to specific cancer populations. As aforementioned in this thesis, given the complexity of the oesophago-gastric cancer cohort, a multidisciplinary approach to rehabilitation is favoured, and physiotherapy led exercise rehabilitation should be combined with input from other members of the multidisciplinary team. In particular input is required from the dietitian, to manage dietary issues and monitor body weight. Furthermore, the need for multidisciplinary rehabilitation in oesophago-gastric cancer was highlighted recently by our research group in a letter to the editor piece in the Journal of Thoracic Disease (O'Neill et al., 2017). In line with the National Cancer Strategy 2017-2026 (Healthy Ireland et al., 2017), multidisciplinary rehabilitation should aim to address the physical, psychological, social and individual issues of cancer survivors. A proposed four phase model of oesophago-gastric cancer surgery rehabilitation, is presented in Figure 7.2, and will be discussed now in the forthcoming paragraphs. Further development and validation of such a model was beyond the scope of the work of this thesis, however the work completed in this thesis has informed the principle underpinning this rehabilitation model.

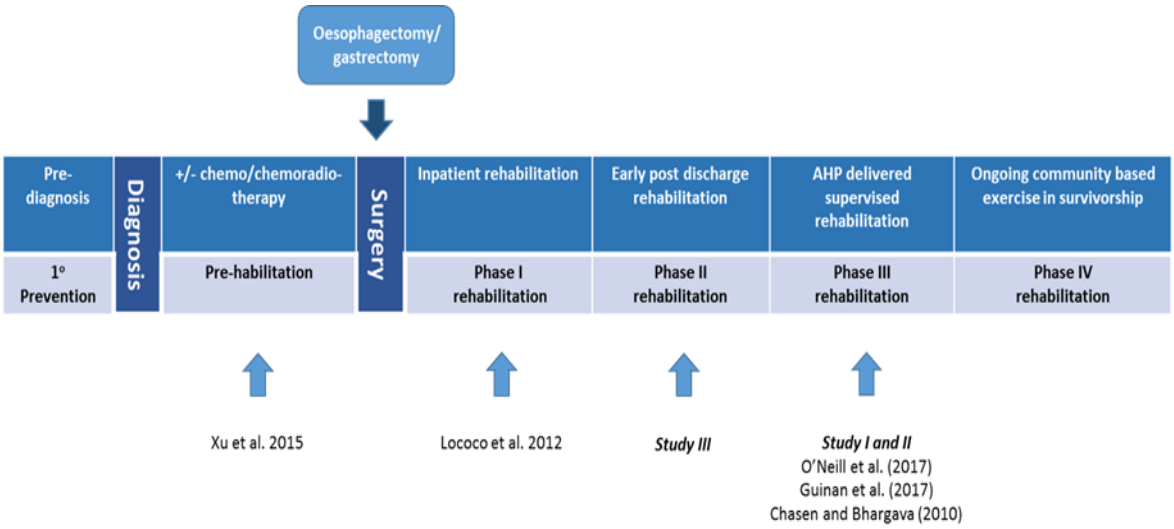

Figure 7-2 Proposed model of oesophago-gastric cancer rehabilitation

Phase I rehabilitation

In this proposed model, as with Phase I cardiac rehabilitation, Phase I oesophago-gastric cancer rehabilitation would involve the development of a standardised care pathway during the inpatient stay following oesophago-gastric cancer resection. Potentially this would involve the dietitian, physiotherapist, and other allied health professionals (AHPs), such as the occupational therapist. The aim of this phase would be to prepare patients for their discharge home. Development of Phase I rehabilitation following oesophago-gastric surgery would aim to further enhance the established ERAS (Enhanced Recovery After Surgery) protocols currently utilised after oesophago-gastric surgery (Pisarska et al., 2017). The current evidence base for rehabilitation at this time-point is limited, the systematic review in Chapter 1, found only one study which examined the effects of such an inpatient rehabilitation programme post-oesophagectomy (Lococo et al., 2012). Moreover, this study had high risk of bias, due to lack of blinding, nil consideration for confounders, and the absence of a control group, and, accordingly, greatly restricts the generalisability of their results. Therefore, there is considerable need for further rehabilitative research at this time-point.

Phase II rehabilitation

Phase II post-oesophagogastric cancer rehabilitation would address the needs of patients in the first six months post hospital discharge following oesophago-gastric cancer surgery. The findings of Study III of this thesis highlight that there is considerable need and demand for the development of a post-discharge programme of rehabilitation following oesophago-gastric cancer surgery. No literature regarding multidisciplinary rehabilitation during this early post-discharge period following oesophago-gastric cancer resection was identified during the work of this thesis, and, accordingly rehabilitative measures at this time-point require investigation.

Probably the best example of an established post-surgical discharge rehabilitation programme is Phase II cardiac rehabilitation. Phase II cardiac rehabilitation involves education regarding risk factor modification and adherence to lifestyle interventions, and also a gradual return to physical activity (Mampuya, 2012). The method of delivery of Phase II cardiac rehabilitation varies across clinical centres, but may involve telephone follow-up, group/individual education sessions, review at outpatient clinics by a member of the cardiac rehabilitation team, or home visits (IACR, 2013). This approach to rehabilitation is well established, and is vindicated for its ability to induce significant improvements in physical capacity, obesity indexes, lipid profiles, and mental health benefits in patients who have recently undergone major cardiac surgery (Araya-Ramirez et al., 2010, Lavie et al., 1993).

Potentially, similar to Phase II cardiac rehabilitation, Phase II oesophago-gastric cancer rehabilitation could be facilitated via outpatient physiotherapy visits, telephone follow-up, or mobile health technology. This programme should be multidisciplinary in nature and would consist of a monitored graded return to exercise combined with an educational component. In contrast to Phase II cardiac rehabilitation, rather than risk factor modification, the educational component of Phase II oesophago-gastric rehabilitation would focus on the development of personalised symptom management strategies for issues such as dietary symptoms, fatigue, and mental health concerns. This programme would address many of the issues highlighted by the participants in Study III, and, potentially could positively impact on physical, nutritional, and mental recovery following oesophago-gastric cancer surgery. Furthermore, and again similar to Phase II cardiac rehabilitation, Phase II oesophago-gastric cancer rehabilitation would help prepare patients for progression to a more intensive structured rehabilitation programme (Phase III).

Phase III rehabilitation

As with Phase III cardiac rehabilitation, Phase III oesophago-gastric cancer rehabilitation would consist of a structured exercise and education programme, which would be led by AHPs. This programme would begin at approximately 6 months post-surgery. Study I and Study II of this thesis, provided evidence in support of a Phase III type, hospital based outpatient multidisciplinary rehabilitation in oesophago-gastric survivorship (O'Neill et al., 2017 , Guinan et al., 2017b). However, despite the positive improvements in cardiorespiratory fitness that were achieved without compromise to body composition there is still considerable need for further research at this time-point. As previously mentioned, disappointingly, no statistically significant improvements with regards to the secondary measures analysed in Study II were achieved. However, it is important to note Study II was only powered to detect a change in the primary outcome, cardiorespiratory fitness. The limitations of the 6MWT, and also of the resistance training component which would have impacted on both HGS and 1RM findings have been discussed in Chapter 4. The lack of statistically significant improvements in physical activity levels in both Study I and Study II is not completely unexpected. This thesis has previously described how it is intrinsically difficult to change the physical activity levels of sedentary cancer survivors (Bourke et al., 2014).

In line with the aims of the National Cancer Strategy 2017-2026 (Healthy Ireland et al., 2017), it is imperative that rehabilitation programmes in survivorship not only address the physical difficulties in survivorship, but also psychological, social and individual needs. Study II examined the impact of the rehabilitation programme on these domains through quantitative assessment of HRQOL and well-being. Disappointingly, no significant changes in HRQOL or wellbeing were observed following participation in the Study II intervention. A previous systematic review by Mishra et al. (2014) reported that vigorous intensity exercise is more effective in inducing improvements in quantitatively measured HRQOL in cancer survivors. Therefore, as Study II implemented a moderate intensity exercise programme, it may have been ineffective at inducing quantitatively measured HRQOL benefits. However, given the low levels of baseline cardiorespiratory fitness in the Study I and Study II cohorts, a moderate intensity exercise regime was more appropriate for the studies' cohorts.

In contrast to the lack of significant change in quantitatively assessed HRQOL in Study II are the results of a qualitative study which was undertaken independently to the work of this thesis

(Bennett et al. (2017) (manuscript under review)). Nineteen of the 21 participants who completed the Study II rehabilitation programme took part in a semi-structured focus group interview. Four audio-taped focus groups were held, ranging in size from two to eight participants, and recordings of the focus groups were transcribed and analysed using a descriptive qualitative approach. Participants reported that meaningful improvements in their quality of life had occurred during the rehabilitation programme. They felt their physical capacity was enhanced and also their ability to carry out activities of daily living. Participants associated these improvements with increased confidence and social connectivity. Analysis of the focus groups indicated that the consensus among participants was that the rehabilitation programme was an indisputably positive experience. One of the greatest benefits they reported attaining from participation was peer support from the other participants, with whom they could share openly their thoughts on the challenges of survivorship, and their experience of the rehabilitation programme. Results of this study highlight the potential rehabilitative programmes have to positively and meaningfully impact on well-being in survivorship.

Phase IV rehabilitation

Given the positive results achieved in Study I and Study II of this thesis regarding Phase III type oesophago-gastric cancer rehabilitation, it is imperative that strategies are developed to ensure that the completion of the Phase III programme does not result in termination of exercise engagement for participants. In the established cardiac rehabilitation model, this is achieved through Phase IV cardiac rehabilitation. Phase IV cardiac rehabilitation involves the long term maintenance of lifestyle modifications including participation in physical activity to optimise health outcomes (IACR, 2013), and is typically based in a community leisure centre. With improving survival statistics, cancer is increasingly considered a chronic condition which can be managed long term similar to cardiac and respiratory disease (Phillips and Currow, 2010). Accordingly, there is a demand for development of strategies to optimise the quality of cancer survivorship, through the long-term management of cancer side-effects and primary prevention of other comorbid conditions. This is emphasised in the new National Cancer Strategy 2017-2026, which places focus on health promotion schemes such as encouragement of physical activity throughout survivorship (Healthy Ireland et al., 2017). Consequently with regards to oesophago-gastric cancer, it is important that strategies are adapted to facilitate a transition from AHP supervised rehabilitation programmes such as the programme implemented in Study I and Study II of this thesis, to community based rehabilitative services to ensure the health benefits achieved from Phase III rehabilitation are maintained.

Therefore, there is considerable rationale for the development of a Phase IV oesophago-gastric rehabilitation programme similar to the rooted Phase IV cardiac rehabilitation model. As per Phase IV cardiac rehabilitation, a key focus of Phase IV oesophago-gastric cancer rehabilitation would be the maintenance of gains achieved in cardiorespiratory fitness through engagement in the recommended levels of physical activity. As discussed in section 7.2.1, it was evident that the cardiorespiratory fitness of the intervention group in Study II of this thesis had started to decline at three month follow-up, therefore highlighting the importance of strategies to maintain or even further improve cardiorespiratory fitness. Similar to Phase IV cardiac rehabilitation, health promotion would also be an important aspect of Phase IV oesophago-gastric cancer rehabilitation. Like those with cardiac conditions, it is important that cancer survivors are educated on healthy lifestyle choices to help minimise the risk of development of other co-morbid conditions. The final component of Phase IV oesophago-gastric cancer rehabilitation would involve the monitoring and management of the lasting side-effects of oesophago-gastric cancer and its treatments such as weight loss and ongoing dietary issues through close collaboration with the Phase III AHP team.

Similar to Phase IV cardiac rehabilitation, Phase IV oesophago-gastric cancer rehabilitation would be delivered in a community leisure centre, wherein patients could exercise independently, with regular monitoring by a gym instructor, or under the direct supervision of a gym instructor, depending on patients' needs. However, at present unlike Phase III cardiac rehabilitation, there is no clear pathway for progressing oesophago-gastric cancer patients from supervised outpatient AHP led rehabilitation programmes such as that implemented in Study I and Study II of this thesis to community based exercise services. Moreover, the development of such a programme in oesophago-gastric cancer is not without its challenges, and requires considerable investigation. Phase IV oesophago-gastric rehabilitation would require close collaboration with Phase III services. This would ensure community based gym-instructors are adequately equipped to deliver exercise instruction to oesophago-gastric cancer survivors through education and training regarding the specific exercise pre-cautions and requirements of the oesophago-gastric cancer population e.g. risk of weight loss, exercising fatigued patients etc. Furthermore, there would need to be a clear referral pathway for Phase IV gym instructors to report any concerns regarding participants to the Phase III AHP team.

In order to address this gap in the literature, Health Research Board KEDs funding has been secured to examine how to enable patients with chronic conditions such as those in oesophago-gastric

cancer survivorship participating in exercise trials at the Clinical Research Facility (CRF) at St James's Hospital to progress to community based exercise following completion of their research exercise intervention. This project will examine barriers to community exercise experienced by patients with chronic conditions, and will also explore the concerns of community gym instructors about supervising exercise programmes for patients with chronic conditions. A training programme will be established for community based gym-instructors regarding the exercise needs of patients with chronic conditions. For example, with regards to patients with oesophago-gastric cancer, gym instructors will be advised regarding the importance of monitoring the weight of participants and the use of resistance training to improve muscle mass. Following completion of this training programme, participants who have completed exercise trials at the CRF will be referred to their local participating gym and provided with four months gym membership to facilitate the transition to community based exercise. It is hoped that this project will establish a clear referral pathway for patients with chronic conditions from research exercise trials to community based exercise.

This thesis highlighted the potential of a model of multidisciplinary rehabilitation following oesophago-gastric cancer surgery. However, although this thesis provides significant evidence in support of Phase III type multidisciplinary rehabilitation, considerable research is required to examine both the feasibility and efficacy of such interventions at other time-points, particularly with regards to the early post-surgery period, and the long-term maintenance of exercise behaviours post Phase III rehabilitation.

7.3 Critical Analysis of this work

It is important to acknowledge the limitations of this body of work. Firstly, the population samples used in all three studies were samples of convenience thus restricting the generalisability of the results. This recruitment approach was used mainly due to the limited patient population who undergo curative treatment for oesophago-gastric cancer in Ireland. Although, it is important to note as previously mentioned in Chapter 4, SJH is the national centre for oesophago-gastric cancer, accounting for 65% of surgical resection nationally (SJH, 2013). In Study I and Study II, patients with a greater interest in exercise may have been more likely to volunteer, and in Study III those with a greater need for rehabilitative measures following oesophago-gastric cancer surgery may have been more likely to volunteer to participate. Furthermore, as all three studies were single centred, based at SJH, participation was generally more feasible for those who lived within a commutable distance of the research centre. It should be noted, however that patients from a wide geographic reach did participate.

Secondly, although the quantitative studies of this thesis implemented a comprehensive battery of assessments that are validated in cancer populations, a number of limitations of these outcomes used in this thesis should be noted. Blinding of assessors was not performed in Study I, and due to financial and staffing resources it was only feasible to blind an assessor to the primary outcome (CPET) in Study II. The 6MWT was used to quantify physical performance in both Study I and Study II, however although it is validated and recommended for use in cancer populations (Schmidt et al., 2013), the findings of both the systematic review and Study II indicate that the 6MWT may lack the specificity to detect small changes in physical function, that CPET can quantify. Body composition was determined using BIA, and although it is considered a valid measure of body composition, it lacks the specificity of imagery techniques such as DEXA, CT, and MRI. However, funding resources were not available to use an imagery technique to determine body composition, therefore BIA was chosen as the best alternative as it is low cost, quick to administer, clinically applicable, and gives a good indication of body composition (Raeder et al., 2017). In Study I and Study II, quality of life was determined using the EORTC-QLQ-C30. In Study II, no significant changes in QOL were observed, despite the considerable benefits reported by participants during a separate focus group study (Bennett et al. (2017) (manuscript under review)). This highlights the need for a mixed methods approach to capturing patient reported outcomes in cancer rehabilitation research. Furthermore, oesophago-gastric cancer subscale data is missing for the 8 participants in Study II with a gastric carcinoma. It was an unfortunate oversight by the lead investigator (LON) not to change the EORTC-

QLQ-OES18 to the EORTC-QLQ-OG25 (van der Schaaf et al., 2012) when the inclusion criteria was expanded to include patients with gastric cancer.

Thirdly, a number of weaknesses with respect to the 12 week multidisciplinary rehabilitation should be mentioned. Most notable is the resistance training component in Study II. It was not feasible to provide participants with the same resistance training equipment to use at home as they used during the supervised exercise sessions. Participants were provided with resistance bands (Theraband) as they are lightweight and easily transported. However, the combined supervised and unsupervised resistance training intervention was ineffective. Discrepancies in the methods of monitoring adherence to home based exercise sessions should also be noted. As mentioned in Chapter 4, there was a significant difference between the numbers of home sessions recorded in the exercise diaries (paper or Salaso app) versus those recorded on the polar heart rate monitors. Both methods of monitoring adherence have limitations. The exercise diary/ Salaso app is dependent on accurate self-reporting of exercise, whereas the Polar heart rate monitor requires a level of technological ability to record sessions accurately. However as described in Chapter 4, survivors of oesophago-gastric cancer are typically an older demographic that may have limited technological skills. Accordingly, neither the exercise diary/Salaso app nor Polar heart rate monitor may be considered the optimal method of measuring exercise adherence in this cohort. Future studies might investigate more recent technology such as the Fitbit which can be worn on the wrist and can be used to track adherence to exercise prescription remotely. Furthermore, with the use of a pure control group, there was a risk that control group participants may also have increased their engagement in exercise and therefore that contamination occurred in Study II between the two groups. This may have minimised the effect size of significant results.

Finally, with regards to the qualitative work of Study III, it is important to mention the risk of researcher bias. In qualitative research, the researcher is the research instrument, and as such any preconceived knowledge or opinions on the subject matter could potentially result in bias. Therefore, it is important that researchers reflect on their own biases and makes attempts to ensure they do not influence results. As previously described in Chapter 5 a number of measures were taken to minimise the risk of researcher bias in Study III including; accurate transcription, a systematic approach to coding and theming, all transcripts were coded by two researchers (LON and AMB), and an assessment of inter-rater reliability was performed. A further limitation of the

qualitative work of this thesis was the absence of member checking. As previously stated it was considered insensitive to return transcripts and request feedback from this complex cohort.

7.4 Implications for future research

Given the sparsity of previous literature investigating rehabilitation strategies in oesophago-gastric cancer survivorship, there is considerable scope for further research in this regard in this complex cohort. Although significant improvements in VO_2max were observed in both Study I and Study II as a result of participation in the multidisciplinary rehabilitation programme, additional research is required to identify the optimum frequency, intensity, type, and timing of exercise interventions in this population. In particular results of Study II indicated that there is a need to investigate further both the feasibility and efficacy of resistance training in oesophago-gastric cancer survivorship. Given the well-documented nutritional deficits and high prevalence of sarcopenia in this cohort, resistance training has ample potential to help minimise these issues for oesophago-gastric cancer survivors. As previously mentioned, there is also a need for investigation into i) behavioural change strategies, which aim to improve adherence, and ensure changes in exercise behaviour are maintained long-term, and ii) endeavours to ensure improvements in HRQOL and well-being are achieved. The cost effectiveness of rehabilitative interventions in survivorship also warrants investigation.

Furthermore, there is a growing focus in cancer exercise trials on examining the biological processes underpinning the protective effects of exercise on cancer (Thomas et al., 2017). Separate to the work of this thesis, blood samples of participants in Study I were analysed both pre and post the 12 week multidisciplinary rehabilitation programme. A reduction in inflammatory status and an improvement in lactate metabolism was observed upon completion of the programme (Guinan et al., 2017b). Blood samples were also collected from Study II participants at each time-point, and the analysis of these samples will provide further knowledge regarding the underlying therapeutic effects of exercise in oesophago-gastric cancer survivorship.

It is also important to acknowledge, that oesophago-gastric cancer, is just one example of a complex cancer cohort in which rehabilitative survivorship programmes have been under explored. Little is known regarding the effects of exercise rehabilitation in other complex cohorts including lung (Brocki et al., 2014), head and neck (Capozzi et al., 2015), and pancreatic cancers (Arthur et al.,

2016). Similarly to oesophago-gastric cancer, impaired physical functioning, unintentional weight loss, and sarcopenia are significant issues for these cohorts (Ninomiya et al., 2017, Mazzola et al., 2016, Collins et al., 2014). Consequently, the feasibility and efficacy of multidisciplinary rehabilitation in these cancers also warrants exploration.

7.5 Conclusion

Returning to the aim presented in Chapter 1 of thesis, it is now possible to state that multidisciplinary rehabilitation consisting of supervised and home based exercise, dietary counselling, and group education sessions, results in statistically significant and clinically meaningful improvements in cardiorespiratory fitness (VO_2max) for oesophago-gastric cancer survivors. Importantly, this gain in physical capacity can be achieved without compromise to body composition in this nutritionally vulnerable population. Accordingly, a multidisciplinary approach to rehabilitation should be advocated in this complex cohort.

Moreover, this thesis identified sub-optimal baseline levels of cardiorespiratory fitness (VO_2max) in participants in both Study I and Study II. This renders further evidence that physical function deficits are prevalent in oesophago-gastric cancer survivorship, and provides further rationale for rehabilitative interventions such as the programme examined by this thesis.

Although this thesis was predominately focused on the period of survivorship from six months post-surgery and onwards, results of both Study III and the systematic review in Chapter 1, highlighted the need for rehabilitative intervention across the oesophago-gastric cancer continuum to improve physical function, alleviate dietary issues, and enhance HRQOL. In advance of upper gastrointestinal cancer surgery pre-habilitative multidisciplinary programmes have the potential to minimise the physical and nutritional deficits experienced during neoadjuvant treatment, and to enhance cardiorespiratory fitness in preparation for surgery. Furthermore, following oesophago-gastric cancer surgery, there is considerable rationale for development of a multi-disciplinary model of rehabilitation, akin to the well-established cardiac rehabilitation model, to aid recovery from surgery, facilitate a return to optimal activity levels, and enhance HRQOL. Future research is required to examine the feasibility and efficacy of such programmes.

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Appendices

Appendix I: Search strategy for systematic review

EMBASE

1 'esophagus surgery'/exp

2 (esophag* NEAR/3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*)):ab,ti

3 (oesophag* NEAR/3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*)):ab,ti

4 (Gastric NEAR/3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*)):ab,ti

5 esophagectom*:ab,ti OR esophagogastroplast*:ab,ti OR esophagogastrectom*:ab,ti OR Gastrectom*:ab,ti

6 oesophagectom*:ab,ti OR oesophagogastroplast*:ab,ti OR oesophagogastrectom*:ab,ti

7 (Gastro-oesophageal NEAR/5 (tumor* OR tumour*)):ti,ab

8 (oesophagogastric NEAR/3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*)):ab,ti

9 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8

10 'exercise test'/exp

11 'cardiopulmonary exercise test'/exp

12 ‘experimental locomotor activity test'/exp

13 'muscle strength'/exp

14 'dynamometry'/exp

15 'isometrics'/exp

16 'ergometry'/exp

17 'physical activity, capacity and performance'/exp

18 'kinesiotherapy'/exp

19 ((exercise OR cardiopulmonary OR submaximal OR walking) NEAR/3 test):ti,ab

20 (exercise NEAR/5 (Test OR training OR program* OR intervention OR performance OR therap*)):ti,ab

21 (cpet OR cpx OR vo2 OR exercise OR strength OR treadmill OR ergometry OR bicycle):ti,ab

22 (physical NEAR/2 (activity OR performance OR capacity OR training OR fitness)):ti,ab

23 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22

24 9 AND 23

PubMED

1 esophageal surgery[tiab] OR oesophageal surgery[tiab] OR esophageal cancer[tiab] OR oesophageal cancer[tiab] OR esophageal neoplasm*[tiab] OR o esophageal neoplasm*[tiab] OR esophageal resection[tiab] OR oesophageal resection[tiab] OR esophageal adenocarcinoma*[tiab] OR oesophageal adenocarcinoma*[tiab] OR esophagectom*[tiab] OR oesophagectom*[tiab] OR esophagogastroplast*[tiab] OR oesophagogastroplast*[tiab] OR esophagogastrectom*[tiab] OR oesophagogastrectom*[tiab]

2 "Esophageal Neoplasms"[Mesh] OR "Esophagectomy"[Mesh] OR "Esophagoplasty"[Mesh]

3 1 OR 2

4 "Exercise Test"[Mesh] OR "Muscle Strength"[Mesh] OR "Motor Activity"[Mesh] OR "Muscle Strength Dynamometer"[Mesh] OR "Exercise Therapy"[Mesh] OR "Physical Endurance"[Mesh] OR "Physical Exertion"[Mesh] OR "Oxygen Consumption"[Mesh] OR "Physical Fitness"[Mesh] OR "Ergometry"[Mesh]

5 exercise[tiab] OR cpet[tiab] OR cpex[tiab] OR cpx[tiab] OR muscle strength[tiab] OR cpet[tiab] OR cpx[tiab] OR vo2[tiab] OR walking[tiab] OR physical activit*[tiab] OR physical performance[tiab] OR fitness[tiab] OR physical endurance[tiab] OR physical training[tiab] OR resistance training[tiab] OR treadmill test[tiab] OR ergomet*[tiab] OR bicycle test[tiab]

6 4 OR 5

7 3 AND 6

CINAHL

1	MH "Esophageal Neoplasms/SU"
2	MH “Stomach Neoplasms/SU”
3	TI (esophag* N3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*)) OR AB (esophag* N3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*))
4	TI (oesophag* N3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*)) OR AB (oesophag* N3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*))
5	TI (esophagectom* OR esophagogastroplast* OR esophagogastrectom* OR Gastrectom*) OR AB (esophagectom* OR esophagogastroplast* OR esophagogastrectom* OR Gastrectom*)
6	TI (oesophagectom* OR oesophagogastroplast* OR oesophagogastrectom*) OR AB (oesophagectom* OR oesophagogastroplast* OR oesophagogastrectom*)
7	TI ((Gastro-oesophageal N5 (tumor* OR tumour*))) OR AB ((Gastro-oesophageal N5 (tumor* OR tumour*)))
8	TI ((oesophagogastric N3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*))) OR AB ((oesophagogastric N3 (surgery OR cancer OR neoplasm* OR resection* OR adenocarcinoma*)))
9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
10	TI ((Exercis* N3 (test OR exam OR capacity OR cardiopulmonary OR performance OR ‘pre operative’ OR preoperative OR presurgery OR ‘pre surgery’ OR presurgical OR ‘pre surgical’)) OR AB ((Exercis* N3 (test OR exam OR capacity OR cardiopulmonary OR performance OR ‘pre operative’ OR preoperative OR presurgery OR ‘pre surgery’ OR presurgical OR ‘pre surgical’))
11	TI ('vo2 max' OR 'aerobic capacity' OR 'anaerobic threshold' OR ‘CPET’ OR ‘CPEX’ OR ‘cpx’ OR ‘peak oxygen’) OR AB ('vo2 max' OR 'aerobic capacity' OR 'anaerobic threshold' OR ‘CPET’ OR ‘CPEX’ OR ‘cpx’ OR ‘peak oxygen’)
12	(MH "Exercise Test") OR (MH "Exercise Test, Cardiopulmonary") OR (MH "Aerobic Capacity") OR (MH "Anaerobic Threshold") OR (MH "Therapeutic Exercise") OR (MH "Exercise")
13	S9 OR S10 OR S11
14	S9 AND S13

Cochrane Library

1	[mh " Esophageal Neoplasms "]
2	[mh “Stomach Neoplasms”]
3	[mh " Esophagectomy"]
4	[mh “Gastrectomy”]
5	[mh " Esophagoplasty"]
6	(esophag* N3 (surgery or cancer or neoplasm* or resection* or adenocarcinoma*)):ti,ab,kw
7	(oesophag* N3 (surgery or cancer or neoplasm* or resection* or adenocarcinoma*)):ti,ab,kw
8	(esophagectom* or esophagogastroplast* or esophagogastrectom* or Gastrectom*):ti,ab,kw
9	(oesophagectom* or oesophagogastroplast* or oesophagogastrectom*):ti,ab,kw
10	#1 OR #2 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	[mh " Exercise Test "]
12	[mh " Muscle Strength "]
13	[mh " Motor Activity "]
14	[mh " Muscle Strength Dynamometer "]
15	[mh " Exercise Therapy "]
16	[mh " Physical Endurance "]
17	[mh " Physical Exertion "]
18	[mh " Oxygen Consumption "]
19	[mh " Physical Fitness "]
20	[mh " Ergometry "]
21	(Exercis* N3 (test or exam or capacity or cardiopulmonary or performance or pre operative or preoperative or presurgery or pre surgery or presurgical or pre surgical)):ti,ab,kw
22	('vo2 max' or 'aerobic capacity' or 'anaerobic threshold' or ‘CPET’ or ‘CPEX’ or ‘cpx’ or ‘peak oxygen’):ti,ab,kw
23	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR 22
24	#10 AND #23

SCOPUS

Esophagectomy OR Gastrectomy AND exercis*

Pedro

Esophageal cancer and Exercise

Gastric cancer and Exercise

WHO Trial Registry

http://apps.who.int/trialsearch/

QUIPS Risk of Bias Assessment Instrument for Prognostic Factor Studies

Modified from: Hayden JA, Côté P, Bombardier C. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Annals of Internal Medicine. 2006;144:427-437, with the assistance of the QUIPS-LBP Working Gro

Author and year of publication				
Study identifier				
Reviewer				
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.		Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for key characteristics (LIST).			
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)			
Recruitment period	Period of recruitment is adequately described			
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described			
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).			
Adequate study participation	There is adequate participation in the study by eligible individuals			
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics (LIST).			
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			

2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.			
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.			
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.			
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).			
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.			
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			
3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).			
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).			
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.			
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.			
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.			
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.			
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.			
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).			
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.			
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			

5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.			
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).			
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).			
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.			
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.			
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).			
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).			
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.			
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.			
	The selected statistical model is adequate for the design of the study.			
Reporting of results	There is no selective reporting of results.			
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			
Modified from: Hayden JA, Côté P, Bombardier C. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Annals of Internal Medicine. 2006;144:427-437.				

The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Possible approach for *summary assessments* outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results.

Criteria for judging risk of bias in the 'Risk of bias' assessment tool

SEQUENCE GENERATION **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: ▪ Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: ▪ Sequence generated by odd or even date of birth; ▪ Sequence generated by some rule based on date (or day) of admission; ▪ Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: ▪ Allocation by judgement of the clinician; ▪ Allocation by preference of the participant; ▪ Allocation based on the results of a laboratory test or a series of tests; ▪ Allocation by availability of the intervention.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.
ALLOCATION CONCEALMENT **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: ▪ Central allocation (including telephone, web-based, and pharmacy-controlled, randomization); ▪ Sequentially numbered drug containers of identical appearance; ▪ Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: ▪ Using an open random allocation schedule (e.g. a list of random numbers); ▪ Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); ▪ Alternation or rotation; ▪ Date of birth; ▪ Case record number; ▪ Any other explicitly unconcealed procedure.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; ▪ Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; ▪ Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient information to permit judgement of 'Yes' or 'No'; ▪ The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No missing outcome data; ▪ Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); ▪ Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; ▪ Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; ▪ 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; ▪ Potentially inappropriate application of simple imputation.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); ▪ The study did not address this outcome.
SELECTIVE OUTCOME REPORTING **Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any of the following: ▪ The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; ▪ The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Not all of the study's pre-specified primary outcomes have been reported; ▪ One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; ▪ One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); ▪ One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; ▪ The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	There is at least one important risk of bias. For example, the study: ▪ Had a potential source of bias related to the specific study design used; or ▪ Stopped early due to some data-dependent process (including a formal-stopping rule); or ▪ Had extreme baseline imbalance; or ▪ Has been claimed to have been fraudulent; or ▪ Had some other problem.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	There may be a risk of bias, but there is either: ▪ Insufficient information to assess whether an important risk of bias exists; or ▪ Insufficient rationale or evidence that an identified problem will introduce bias.

Appendix IV: Cochrane Risk of Bias Assessment Tool for Non-Randomised Studies of Interventions (ACROBAT-NRSI)

7.7 Risk of bias assessment (cohort-type studies)

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	Y / PY / PN / N	[Description]
	If N or PN to 1.1:		
	1.2. Were participants analysed according to their initial intervention group throughout follow up? **If Y or PY to 1.2**, answer questions 1.4 to 1.6, which relate to baseline confounding	NA / Y / PY / PN / N / NI	[Description]
	1.3. **If N or PN to 1.2:** Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? **If Y or PY to 1.3**, answer questions 1.4 to 1.6, which relate to baseline confounding **If N or PN to 1.1 and 1.2 and 1.3**, answer questions 1.7 and 1.8, which relate to time-varying confounding	NA / Y / PY / PN / N / NI	[Description]
	If Y or PY to 1.2, or Y or PY to 1.3		
	1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	NA / Y / PY / PN / N / NI	[Description]
	1.5. **If Y or PY to 1.4:** Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	NA / Y / PY / PN / N / NI	[Description]
	1.6. Did the authors avoid adjusting for post-intervention variables?	NA / Y / PY / PN / N / NI	[Description]
	If N or PN to 1.2 and 1.3		

	1.7. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains and for time-varying confounding?	NA / Y / PY / PN / N / NI	[Description]
	1.8. **If Y or PY to 1.7**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to confounding?	Favours experimental / Favours comparator / Unpredictable	[Rationale]
Bias in selection of participants into the study	2.1. Was selection into the study unrelated to intervention or unrelated to outcome?	Y / PY / PN / N / NI	[Description]
	2.2. Do start of follow-up and start of intervention coincide for most subjects?	Y / PY / PN / N / NI	[Description]
	2.3. **If N or PN to 2.1 or 2.2**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Rationale]
Bias in measurement of interventions	3.1 Is intervention status well defined?	Y / PY / PN / N / NI	[Description]
	3.2 Was information on intervention status recorded at the time of intervention?	Y / PY / PN / N / NI	[Description]
	3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Rationale]
Bias due to departures from intended	4.1. Were the critical co-interventions balanced across intervention groups?	Y / PY / PN / N / NI	[Description]
	4.2. Were numbers of switches to other interventions low?	Y / PY / PN / N / NI	[Description]
	4.3. Was implementation failure minor?	Y / PY / PN / N / NI	[Description]

interventions	4.4. **If N or PN to 4,1, 4.2 or 4.3**: Were adjustment techniques used that are likely to correct for these issues?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to departures from the intended interventions?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Rationale]
Bias due to missing data	5.1 Are outcome data reasonably complete?	Y / PY / PN / N / NI	[Description]
	5.2 Was intervention status reasonably complete for those in whom it was sought?	Y / PY / PN / N / NI	[Description]
	5.3 Are data reasonably complete for other variables in the analysis?	Y / PY / PN / N / NI	[Description]
	5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	NA / Y / PY / PN / N / NI	[Description]
	5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to missing data?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Rationale]
Bias in measurement of outcomes	6.1 Was the outcome measure objective?	Y / PY / PN / N / NI	[Description]
	6.2 Were outcome assessors unaware of the intervention received by study participants?	Y / PY / PN / N / NI	[Description]
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Y / PY / PN / N / NI	[Description]
	6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to measurement of outcomes?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Rationale]
Bias in selection of	Is the reported effect estimate unlikely to be selected, on the basis of the results, from...		

the reported result	7.1. ... multiple outcome *measurements* within the outcome domain?	Y / PY / PN / N / NI	[Description]
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Y / PY / PN / N / NI	[Description]
	7.3 ... different *subgroups*?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to selection of the reported result?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Rationale]
Overall bias	**Risk of bias judgement**	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the overall predicted direction of bias for this outcome?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Rationale]

Appendix V: BORG Scale

BORG Rating of Perceived Exertion Scale

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

Appendix VI: Actigraph activity diary and information sheet

Participant Information Leaflet

ActiGraph Activity Monitor

Thank you for agreeing to wear the ActiGraph Activity Monitor. The ActiGraph measures your physical activity levels and provides us with information on the amount of time you spend engaging in different intensities of activity. The following information leaflet addresses some frequently asked questions. Should you have any queries please contact the Physiotherapy Postgraduate and Research Room at the Trinity Centre for Health Sciences, St. James's Hospital on 01-8963613.

1. How many days do I wear the monitor?

You are requested to wear the activity monitor for one week (7 days) during waking hours.

2. Do I wear the monitor to bed?

No. You put the monitor on first thing in the morning and take it off last thing at night. You are requested to record the time you put the monitor on in the morning and the time you take if off at night in the activity diary provided.

3. Do I wear the monitor in the shower?

No. You should remove the monitor during any water-based activity such as showering, bathing or swimming. You are requested to record these activities, including the times your take the monitor on and off in the activity diary provided.

4. Do I need to press any button to start / finish the monitor?

No. The monitor is set-up by the researcher leading your study. You do not have to press any button to activate or stop the monitor.

5. Where on my body is the monitor worn?

The monitor is connected to a flexible strap with a clip. The strap should be worn like a belt around your waist with the monitor sitting at hip level on the right side of your body (see picture). Ensure the black disk on the side of the monitor is pointing towards your head. The strap should not be too tight or too loose. You can adjust the strap size if necessary. You may wear the monitor under or over your clothes.

Ensure this black disk is facing up towards you head.

6. Do I need to charge the monitor during the week?

No. Do not plug the monitor into any power source or connect to any USB cable during the week and this may wipe the data collected.

7. I forgot to wear the monitor – what should I do?

If you forget to wear the activity monitor on a particular day don't worry. Please write down clearly in the activity diary which day you forgot to wear the monitor and just carry on wearing it as normal the following day.

8. What should I do when I finish wearing the activity monitor?

When you finish wearing the monitor please return it to us in the stamped addressed envelope provided. Please return the monitor to us as soon as possible to ensure that the battery does not die before we receive it.

Try not to change your activity levels while wearing the monitor as our aim is to get an idea of <u>normal</u> activity patterns

Thank you very much for recording your physical activity

Physical Activity Diary

You are requested to wear your ActiGraph Activity Monitor during **all waking hours**. You will have to remove the activity monitor when you are going to bed or during water-based activities such as showering or swimming. Please record the time you put the activity monitor and the time you take it off in the following activity diary. If you forget to wear the monitor for a day please record this clearly in the activity diary. This record will help us to analyse your physical activity data as accurately as possible.

Should you have any queries please contact the Physiotherapy Postgraduate and Research Room at the Trinity Centre for Health Sciences, St. James's Hospital on 01-8963613. The following example outlines the details required.

Example:

On Date	On Time	Off Date	Off Time	Activity completed while not wearing the monitor
04.10.2013	8.20am	04.10.2013	7.10pm	Shower
04.10.2013	7.30pm	04.10.2013	10.30pm	Sleeping in bed
05.10.2013	8.10am	05.10.2013	10.50pm	Sleeping in bed

ReStOre Trial
Rehabilitation Strategies following
Oesophago-gastric Cancer

Participants Name/Study ID: _____

On Date	On Time	Off Date	Off Time	Activity completed while not wearing the monitor

Thank you for taking the time to record your physical activity.

Appendix VII: EORTC-QLQ-C30 and EORTC-QLQ-OES18

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

		Not at All	**A Little**	**Quite A Bit**	**Very Much**
1	Do you have trouble doing strenuous activities like carrying a heavy shopping bag or suitcase?	1	2	3	4
2	Do you have trouble taking a long walk?	1	2	3	4
3	Do you have trouble taking a short walk outside of the house?	1	2	3	4
4	Do you need to stay in bed or a chair during the day?	1	2	3	4
5	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
	<u>During the past week:</u>	**Not at All**	**A Little**	**Quite A Bit**	**Very Much**
6	Were you limited in doing your work or other daily activities?	1	2	3	4
7	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8	Were you short of breath?	1	2	3	4
9	Have you had pain?	1	2	3	4
10	Do you need to rest?	1	2	3	4
11	Have you had trouble sleeping?	1	2	3	4
12	Have you felt weak?	1	2	3	4
13	Have you lacked appetite?	1	2	3	4
14	Have you felt nauseated?	1	2	3	4
15	Have you vomited?	1	2	3	4

		Not at All	A Little	Quite A Bit	Very Much
16	Have you been constipated?	1	2	3	4
17	Have you had Diarrhoea?	1	2	3	4
18	Were you tired?	1	2	3	4
19	Did pain interfere with you daily activities?	1	2	3	4
20	Have you had difficulty concentrating on things like reading a newspaper or watching television?	1	2	3	4
21	Did you feel tense?	1	2	3	4
22	Did you worry?	1	2	3	4
23	Did you feel irritable?	1	2	3	4
24	Did you feel Depressed?	1	2	3	4
25	Have you had difficulty remembering things?	1	2	3	4
26	Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27	Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

29	How would you rate your overall <u>health</u> during the past week?								
	1	2	3	4	5	6	7		
	Very Poor						Excellent		
30	How would you rate your overall <u>quality of life</u> during the past week?								
	1	2	3	4	5	6	7		
	Very Poor						Excellent		

	During the past week:	**Not at All**	**A Little**	**Quite A Bit**	**Very Much**
31	Could you eat solid food?	1	2	3	4
32	Could you eat liquidised food or soft foods?	1	2	3	4
33	Could you drink liquids?	1	2	3	4
34	Have you had trouble swallowing your own saliva?	1	2	3	4
35	Have you choked when swallowing?	1	2	3	4
36	Have you had trouble enjoying your meals?	1	2	3	4
37	Have you felt full up too quickly?	1	2	3	4
38	Have you had trouble eating?	1	2	3	4
39	Have you had trouble eating in front of other people?	1	2	3	4
40	Have you had a dry mouth?	1	2	3	4
41	Have you had trouble with your sense of taste?	1	2	3	4
42	Have you had trouble coughing?	1	2	3	4
43	Have you had trouble talking?	1	2	3	4
44	Have you had trouble acid indigestion or heartburn?	1	2	3	4
45	Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
46	Have you had pain when you eat?	1	2	3	4
47	Have you had pain in your chest?	1	2	3	4
48	Have you had pain in your stomach?	1	2	3	4

Appendix VIII: Scoring procedures for the EORTC-QLQ-C30 and EORTC-QLQ-OES18

Scoring the EORTC QLQ-C30 version 3.0

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left[1 - \frac{(RS-1)}{range}\right] \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS-1)/range\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

EORTC
European Organisation for Research and Treatment of Cancer

EORTC Quality of Life

Oesophageal cancer module: QLQ-OES18

Scope

The oesophageal cancer module is meant for use among patients with oesophageal cancer undergoing any single or combination of treatments including: oesophagectomy, chemoradiation, endoscopic palliation or palliative chemotherapy and/or radiotherapy. It should always be complemented by the QLQ-C30.

Scoring

	Scale name	Number of items	Item range	QLQ-OES18 item numbers
Symptom scales				
Eating	OESEAT	4	3	6 – 9
Reflux	OESRFX	2	3	14,15
Pain	OESPA	3	3	16 – 18
Trouble swallowing saliva	OESSV	1	3	4
Choked when swallowing	OESCH	1	3	5
Dry mouth	OESDM	1	3	10
Trouble with taste	OESTA	1	3	11
Trouble with coughing	OESCO	1	3	12
Trouble talking	OESSP	1	3	13
Functional scales				
Dysphagia	OESDYS	3	3	1 – 3

Remarks

Work to merge this module with the gastric module (EORTC QLQ-STO22) has been performed and this is available within the EORTC QLQ-OG25 questionnaire.

References

Blazeby JM, Conroy T, Hammerlid E, et al. Clinical and Psychometric Validation of an EORTC Questionnaire Module, the EORTC QLQ-OES18, to Assess Quality of Life in Patients with Oesophageal Cancer. *Eur J Cancer* 39:1384-1394, 2003.

Blazeby JM, Alderson D, Winstone K, Steyn R, Hammerlid E, Arraras J, Farndon JR. Development of an EORTC questionnaire module to be used in quality of life assessment for patients with oesophageal cancer. The EORTC Quality of Life Study Group. *Eur J Cancer.* 1996 Oct;32A(11):1912-7.

Lagergren P, Fayers P, Conroy T, Stein HJ, Sezer O, Hardwick R, Hammerlid E, Bottomley A, Van Cutsem E, Blazeby JM; European Organisation for Research Treatment of Cancer Gastrointestinal and Quality of Life Groups. Clinical and

Appendix IX: Perceived well-being questionnaire

Perceived Well-being Questionnaire

Please record the score appropriate to your perception of the following symptoms for you at present in the column on the right hand side of the page.

For example if you feel your level of 'FATIGUE' is Normal right now you should put the number 3 in the scoring column.

	5	4	3	2	1	Record Score
FATIGUE	**Very fresh**	**Fresh**	**Normal**	**More tired than normal**	**Always tired**	
SLEEP QUALITY	**Very restful**	**Good**	**Difficulty falling asleep**	**Restless sleep**	**Insomnia**	
GENERAL MUSCLE SORENESS	**Feeling great**	**Feeling good**	**Normal**	**Increase in soreness/tightness**	**Very sore**	
STRESS LEVELS	**Very relaxed**	**Relaxed**	**Normal**	**Feeling stressed**	**Highly stressed**	
MOOD	**Very positive mood**	**A generally good mood**	**Less interested in others and/or activities than usual**	**Snappiness at team-mates, family and co-workers.**	**Highly annoyed / irritable/ down**	

Appendix X: Diseases of the Esophagus Paper (Study I)

Diseases of the Esophagus (2017) 0, 1–8
DOI: 10.1093/dote/dox012

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original Article

Rehabilitation strategies following esophageal cancer (the ReStOre trial): a feasibility study

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SUMMARY. **As survival rates in esophageal cancer improve, the role of rehabilitation programs in this group is emerging as an important issue. This study aims to determine the feasibility of a multidisciplinary rehabilitation program to optimize physical function and quality of life in esophageal cancer survivors. This single-arm feasibility study recruited patients who had completed curative treatment for esophageal cancer, including esophagectomy, with node-negative postsurgical pathology. The multidisciplinary program consisted of 12 weeks of supervised and home-based exercise, dietetic counseling, and education sessions. Feasibility outcomes included recruitment rates, adherence, adverse events, and retention. Other outcomes included cardiopulmonary fitness (maximal cardiopulmonary exercise test and the six minute walking test), quality of life (QOL) (European Organisation for Research and Treatment of Cancer (EORTC) questionnaires) and body composition (bioimpedance analysis). Change in outcomes from baseline to postintervention was measured using the paired sample t-tests. Twelve participants (mean (standard deviation) age 61.4 (7.29) years, eight male) consented to participate, representing a recruitment rate of 55%. Mean class attendance was 82(13)% and mean adherence to the home exercise program was 118(76)%. No adverse events occurred. Retention to the program was 100%. VO_2max improved by 3.99(2.7) mL/kg/min ($p < 0.004$). The six minute walking test distance increased by 56.3(35.3) m ($p < 0.003$). Global, functional, and symptom QOL scores improved. Body composition remained stable. This pilot study demonstrated high feasibility and acceptability in this complex cohort. Clinically significant improvements in functional performance and QOL were evident without compromise to body composition. The results of this study will help guide the design of a forthcoming larger randomized controlled trial.**

KEY WORDS: **diet, esophageal cancer, rehabilitation.**

INTRODUCTION

Esophageal cancer is traditionally associated with poor prognosis; however, survival rates are improving.[1] Globally, 5-year survival for localized tumors has improved to approximately 40%.[2] Curative treatment for esophageal carcinoma involves surgery (esophagectomy), often combined with a

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Specific Author contributions: Ms Linda O'Neill is a PhD candidate and physiotherapist working predominantly with the esophageal cancer clinical trials program at St James's Hospital. She was involved in the design and implementation of the exercise intervention, acquisition of data, and led the drafting of this manuscript. Dr Emer Guinan is an assistant professor in Interprofessional Learning at Trinity College and a physiotherapist specializing in exercise oncology and works predominantly with the esophageal cancer clinical trials program at St James's Hospital. She was also involved in the design of the intervention, data acquisition, and the drafting of the manuscript through all stages. Dr Suzanne Doyle is an assistant professor at the School of Biomedical Sciences at Dublin Institute of Technology and a research dietitian with a special interest in esophageal cancer. She was responsible for designing and implementing the dietary intervention, data acquisition, and contributed to the manuscript. Dr Jessie Elliott is a surgical research fellow working with the upper gastrointestinal surgery team at St James's Hospital. She assisted with data acquisition and review of the manuscript. Dr Jacintha O'Sullivan is an associate professor in the Department of Surgery at Trinity College Dublin. She contributed to the study design and the manuscript. John Reynolds is the professor of Surgery at St James's Hospital and the national lead for the management of esophageal cancer in Ireland. He contributed to the study design and the manuscript development. Juliette Hussey is a professor in physiotherapy at Trinity College Dublin with a special interest in exercise oncology. She is the principal investigator for the ReStOre (Rehabilitation Strategies Following Esophageal Cancer) trial at St James's Hospital. She led the design of the study and contributed to the manuscript development.

multimodality approach consisting of neoadjuvant chemotherapy or chemoradiotherapy.[3,4] Treatment is associated with high morbidity and a mortality rate of up to 5%.[3,5] Esophageal cancer survivors experience long-term complications including fatigue, reflux, dysphagia, pain, and diarrhoea,[6] which may lead to nutritional and functional compromise resulting in impaired quality of life (QOL).[6-8] Limited literature has measured the deficits in physical performance of esophageal cancer survivors; however, subjectively patients report compromised QOL and functional status.[3,6] The rehabilitative strategies in esophageal cancer (ReStOre trial) will develop a multidisciplinary rehabilitation program to help address the specific issues faced by survivors of esophageal cancer.

It is well acknowledged that there is a need for the development of research into rehabilitation programs in lesser studied cancers, such as esophageal cancer, to help address the multifaceted rehabilitative needs survivors may experience.[7] To date, rehabilitative research in esophageal cancer has focused on prehabilitation, during neoadjuvant treatment, and also on early postoperative inpatient rehabilitation.[8-11] A randomized trial of a 4-week dietary and walking intervention versus usual medical care was performed to preserve walking ability and prevent nutritional decline in 29 participants undergoing neoadjuvant chemoradiotherapy for esophageal cancer.[8] In terms of rehabilitation, a pilot study with eight patients who had undergone esophagectomy reported increased walking distance in the six minute walking test (6MWT) from 159.63 to 223.63 m following an in-patient multidisciplinary-led rehabilitation program during the immediate 4 weeks post-surgery.[11]

This study is the first to investigate the feasibility of a 12-week multidisciplinary-led rehabilitation program consisting of supervised exercise sessions, dietary counseling, and education sessions for survivors of esophageal cancer who are greater than 6 months postcompletion of curative treatment. The primary objective was to examine feasibility as determined by recruitment rate, adherence, acceptability, and adverse events. Secondary objectives were to investigate the impact of the intervention on physical function and QOL.

MATERIALS AND METHODS

Study design

This study was a single-arm feasibility study. Ethical approval was obtained from the St James' Hospital/Tallaght Hospital Joint Research Ethics Committee. Participants provided written informed consent. All study appointments were completed in the Wellcome Trust HRB Clinical Research Facility at St James's Hospital, Dublin.

Study participants

Suitable participants were identified from the Upper Gastrointestinal Cancer Registry of St James's Hospital, Dublin. Twenty-two potential participants were contacted via letter and invited to express an interest in participation. Inclusion criteria included >6 months post successful completion of curative treatment for histologically confirmed esophageal cancer that included esophagectomy with/without neoadjuvant/adjuvant chemo/radiotherapy, medical approval to participate, living within one-hour travel radius of the research facility, and willing to attend the scheduled program of appointments. Exclusion criteria included unsuccessful treatment outcome, comorbidities that would preclude safe exercise participation, and evidence of metastatic or recurrent disease.

Measures

Feasibility

Feasibility was determined through analysis of recruitment rates (percentage of eligible study population that consented to participation), program adherence (number of prescribed supervised and unsupervised sessions completed), retention, acceptability of the intervention and assessments, and improvement of outcomes and adverse events.

Secondary outcomes including physical fitness, QOL, and body composition were assessed at two time points: T1 (prerehabilitation) and T2 (postrehabilitation).

Physical fitness

Physical fitness was examined by cardiopulmonary exercise testing (CPET) and the 6MWT. An accelerometer measured physical activity levels.

The CPET was performed on a cycle ergometer. Expired gases were measured via indirect calorimetry using a portable COSMED metabolic cart. An incremental protocol starting at a power of 10 Watts increasing at increments of 10 Watts per minute was implemented. Criteria for test termination included participants reporting feeling unwell or pain unrelated to the test, extreme hypertension (>250 systolic and/or >115 diastolic), abnormal exercise ECG, severe cardiac arrhythmias, or a reduction in pedal frequency below 50 reps per minute. All participants completed the test until a steady state of oxygen consumption was achieved or until symptoms such as leg fatigue prevented continuation.

The 6MWT was completed as per the American Thoracic Society 2002 Guidelines.[12] Participants walked at their fastest pace along a 30-m course with the aim of walking the furthest distance possible in 6 minutes. Standardized instructions and encouragement were provided. The 6MWT has been

(A) Rehabilitation Schedule

	Supervised Exercise	Home Exercise	1:1 Dietetic Counselling	Multidisciplinary Education
Week 1				
Week 2				
Week 3				
Week 4				
Week 5				
Week 6				
Week 7				
Week 8				
Week 9				
Week 10				
Week 11				
Week 12				

(B) Prescribed frequency, intensity and time of exercise programme

	Frequency*		Intensity†	Time
	Supervised Intervention	Home Exercise Programme		
Week 1	2	1	30-45% HRR	20
Week 2	2	1	30-45% HRR	20
Week 3	2	2	35-50% HRR	20
Week 4	2	2	35-50% HRR	25
Week 5	1	2	35-50% HRR	25
Week 6	1	3	40-55% HRR	25
Week 7	1	3	40-55% HRR	30
Week 8	1	4	40-55% HRR	30
Week 9	0	4	45-60% HRR	30
Week 10	1	5	45-60% HRR	35
Week 11	0	5	45-60% HRR	35
Week 12	1	5	45-60% HRR	35

*Indicates frequency of exercise sessions in days per week. †Based on pilot data from our research group it is anticipated that baseline exercise fitness levels will be "very poor" and "poor". Exercise prescription will commence at 30-45% HRR and progress gradually over the course of the intervention to a maximum of 45-60% HRR (moderate intensity activity)

Fig. 1 Rehabilitation schedule and exercise prescription. (A) The prescribed weekly frequency of supervised and home-based exercise sessions, 1:1 dietary counseling, and education sessions. (B) The prescribed weekly progression of the supervised and home-based exercise sessions. HRR, heart rate reserve.

well utilized in both the research and clinical settings.[13] Its use has also been validated in assessing exercise capacity in cancer and has excellent test–retest reliability.[14]

Activity levels were determined through the use of Actigraph GT3X+ (Actigraph, Pensacola, Florida), a triaxial accelerometer. Accelerometers provide accurate, reliable measurements of activity and sedentary behavior.[15,16] Actigraph data were analyzed using the Actilife 6 software. Participants wore the monitor around their waist secured with an elasticated belt during waking hours for one-week prerehabilitation and one-week postrehabilitation. Monitor wear and nonwear time was logged in an activity diary.

Quality of life

QOL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire, the QLQ-C30 (version 3.0), and the esophageal specific subscale, the QLQ-OES18. The QLQ-C30 is a well utilized and validated tool for the assessment of QOL in cancer survivors.[14,17] It captures QOL measured in separate functional, symptom, and global QOL domains. Scores for each question were calculated and linearly transformed into a 0–100 scale as per the EORTC scoring manual.[18] A high functional score indicated high function, whereas a high symptom score indicated high symptom burden.

Body composition

Weight and height were measured, and body mass index was calculated using a SECA digital medical scale and stadiometer. Bioimpedance analysis was performed using a Seca mBCA machine (Seca, Hamburg). Data results for fat mass, fat mass percentage, fat-free mass, fat mass index, fat-free mass index, and skeletal muscle mass were recorded.

Intervention

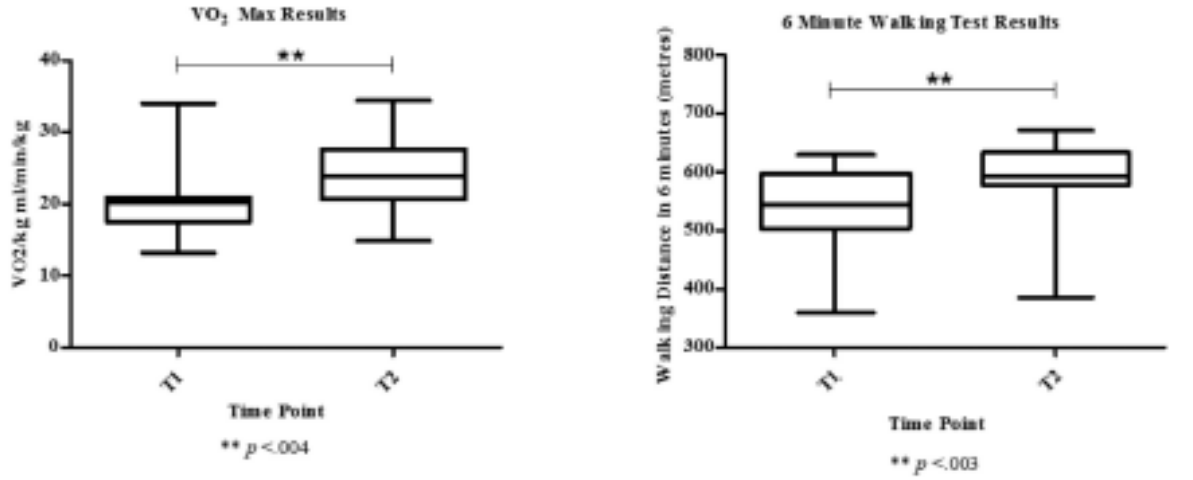
The rehabilitation schedule is illustrated in Figure 1A.

Exercise program

The supervised exercise sessions consisted of a warm-up, a main program of aerobic exercise completed on a treadmill, stationary bike or a cross trainer, followed by a cool down, light resistance work, and stretching exercises. Intensity was prescribed by percentage heart rate reserve (HRR). Subjects commenced exercising at 30–45% HRR. This was based on CPET results of participants, which indicated that participants had mostly either very poor or poor exercise tolerance (Fig. 2). Intensity was monitored during supervised and home sessions using polar heart rate monitors. Home sessions were recorded in an exercise diary. Duration, frequency, and intensity of exercise were increased as the program progressed by the study physiotherapist in line with ACSM guidelines for exercise testing and prescription[19] (Fig. 1B). By the end of the program, participants were prescribed 150 minutes of moderate intensity exercise (60% HRR) per week.

Dietary counseling

Nutritional assessments were carried out in a 1:1 setting by the study dietitian. Dietary intake was assessed using a 24-hour diet recall and semi-structured interview. Gastrointestinal symptoms were assessed using a Gastrointestinal Symptom Rating Score. Participants reported varied dietary issues that included poor appetite, early satiety, weight loss, obesity, dumping syndrome, and malabsorption. Tailored dietary advice



VO_2 max improved from 20.08(5.2) ml/min/kg at T1 to 24.08(4.99) ml/min/kg at T2, which is an increase of 3.99(2.7) ml/min/kg ($p < .004$).

6MWT distance improved from 532.17(78.25)m at T1 to 588.5(73.14) at T2, which is an increase of 56.3(35.33)m ($p < .003$).

Fig. 2 Exercise test results.

Table 1 Demographic characteristics of participants

Characteristic		Mean (standard deviation)/frequency (%)
Sex	Male	8(66.67%)
	Female	4(33.33%)
Age (years)		61.41(7.29)
Height (cm)		171.11(9.37)
Weight (kg)		70.93(19.95)
BMI (kg/m^2)		24.04(8.54)
Time postsurgery at program commencement (months)		22.16(8.54)
Histological type of tumor	Adenocarcinoma	8(66.67%)
	Squamous cell carcinoma	4(33.33%)
Type of surgery	Transhiatal esophagectomy	2(16.67%)
	Two-stage esophagectomy	5(41.67%)
	Three-stage esophagectomy	5(41.67%)
Neoadjuvant treatment (yes/no)	Yes	10(88.33%)
	No	2(16.67%)
Adjuvant treatment (yes/no)	Yes	1(8.33%)
	No	11(91.67%)

and education were delivered to the participants by the dietitian with specific dietary goals set at the end of each session. The number of available dietary reviews within the rehabilitation program is illustrated in Figure 1A; however, the dietitian determined the number of sessions received by each participant based on clinical need.

Education intervention

Group education sessions focused on topics that were of specific relevance to esophageal cancer survivors. Education sessions were delivered by a range of members of the multidisciplinary team and representatives of organizations that support people with esophageal cancer, including a representative of the surgical team, cancer nurse specialist, dietitian, physiotherapist, psycho-oncology, a mindfulness practitioner, and representatives from local cancer charities.

Statistical analysis

Statistical analyses were performed using SPSS 22 (SPSS Inc., Chicago, IL, USA). Data were presented as mean (standard deviation). Prior to analysis, variables were tested for normality of distribution using the Shapiro–Wilk test. Normally distributed data were analyzed using a paired t-test. Nonparametric data were analyzed using the Wilcoxon Signed Rank test. A p value of <0.05 was considered as statistically significant.

RESULTS

Demographic characteristics

Descriptive characteristics for the 12 participants are presented in Table 1.

Table 2 Actigraph activity monitor results

	T1 mean (SD)	T2 mean (SD)	Mean difference (SD)	*p*-value
Total time per activity				
Total sedentary (minutes per week)	3587.00(623.21)	3309.42(582.21)	↓277.58(534.84)	0.100
Total light (minutes per week)	1871.91(542.05)	1690.91(415.88)	↓181.00(339.68)	0.092
Total moderate (minutes per week)	276.50(172.46)	298.92(181.85)	↑22.42(87.84)	0.396
Total vigorous (minutes per week)	16.41(34.11)	17.75(31.79)	↑01.33(14.56)	0.893
Total very vigorous (minutes per week)	00.00(00.00)	01.17(03.73)	↑01.17(03.73)	0.180
Total moderate and vigorous activity (minutes per week)	292.91(192.44)	317.88(187.05)	↑24.92(90.92)	0.363

↑↓ Directions of arrows indicate either increase or decrease in time spent at a particular level of activity. SD, standard deviation.

Table 3 European Organisation for Research and Treatment of Cancer (EORTC), core quality of life questionnaire, the QLQ-C30, and esophageal cancer subscale, the QLQ-OES18 results

	T1 mean(SD)	T2 mean(SD)	Mean difference(SD)	*p*-value
QLQ-C30				
Global health status/ QOL	70.83(20.26)	81.25(11.85)	↑10.42(10.73)†	0.006*
Physical function	81.67(20.52)	87.22(18.74)	↑05.55(10.94)	0.083
Role function	72.22(39.14)	87.50(20.26)	↑15.28(24.06)†	0.160
Emotional function	86.80(13.51)	86.10(13.45)	↓00.70(02.41)	0.317
Cognitive function	77.78(21.71)	80.56(18.58)	↑02.78(18.56)	0.588
Social function	79.17(29.41)	87.50(14.43)	↑08.33(20.72)	0.167
Symptom scales				
Fatigue	28.70(21.95)	28.70(26.15)	↔0.00(14.98)	1.000
Nausea/vomiting	04.17(10.36)	05.55(10.86)	↑01.38(04.81)	0.317
Pain	13.89(18.58)	05.55(12.97)	↓08.34(13.30)	0.063
Dyspnea	25.00(28.87)	22.22(29.59)	↓02.78(09.62)	0.317
Insomnia	36.11(41.34)	22.22(25.95)	↓13.89 (33.21)†	0.102
Appetite loss	22.22(25.95)	22.22(32.82)	↔0.00(24.62)	1.000
Constipation	16.67(30.15)	11.11(16.41)	↓05.56(19.25)	0.317
Diarrhea	25.00(32.18)	11.11(16.41)	↓13.89(30.01)†	0.109
Financial difficulties	25.00(40.51)	11.11(21.71)	↓13.89(33.21)†	0.180
QLQ-OES18				
Dysphagia	11.11(14.98)	09.26(13.26)	↓01.85(15.59)	0.854
Eating problems	14.58(10.73)	11.11(08.21)	↓03.47(06.60)	0.084
Reflux	12.50(20.25)	09.72(19.41)	↓02.78(09.62)	0.492
Pain	09.26(09.28)	06.48(10.00)	↓02.78(08.37)	0.257
Trouble swallowing saliva	05.55(12.97)	02.78(09.62)	↓02.77(09.62)	0.317
Choked when swallowing	05.55(12.97)	11.11(16.41)	↑05.56(12.97)	0.157
Dry mouth	16.67(22.47)	08.33(15.07)	↓08.34(15.07)	0.083
Trouble with taste	08.33(15.07)	08.33(15.07)	↔0.00(0.00)	1.000
Trouble with coughing	16.67(17.41)	05.57(12.97)	↓11.10(25.95)†	0.157
Trouble talking	02.78(09.62)	02.78(09.62)	↔0.00(0.00)	1.000

↓↑↔ Directions of arrows indicate direction of change in each quality of life scale.
†Clinically meaningful improvement. SD, standard deviation.

Feasibility outcomes

Twelve participants out of a potential study population of 22 consented to participate representing a recruitment rate of 55%. The program was well accepted by all participants with 100% completing the program. Adherence to the supervised rehabilitation program was 82(13)%. Adherence to the home exercise program that was assessed using exercise diaries was 118(76)%. No adverse events were recorded during the intervention or assessments.

Physical performance

At T1 participant's average, VO_2max was 20.08(5.2) mL/min/kg. Postintervention this increased by an average of 3.99(2.7) mL/min/kg ($p < .004$) to 24.08(4.99) mL/min/kg at T2 (Fig. 2). Distance walked in the 6MWT also improved from 532.17(78.25) m at T1 to 588.5(73.14) m (mean increase 56.3(35.33) m) at T2 ($p < .003$) (Fig. 2). No significant changes were observed in activity levels as measured by the Actigraph accelerometers (Table 2).

Quality of life

QOL scores from the QLQ-C30 and QLQ-OES18 subscales are detailed in Table 3. The clinically significant difference for the EORTC is defined as an increase of 10% or more in a function scale or a reduction of 10% in a symptom scale.[20] Global QOL showed a statistically and clinically meaningful

Table 4 Anthropometric data

	T1 mean (SD)	T2 mean (SD)	Mean difference (SD)	*p*-value
Weight (kg)	70.93(19.95)	70.29(19.47)	0.65(1.52)	0.169
Height (cm)	171.11(9.36)	171.18(9.26)	0.07(0.35)	0.523
BMI (kg/m^2)	24.04(05.02)	23.79(4.82)	0.25(0.51)	0.121
Bioimpedance analysis ($n = 9$)				
Fat mass (kg)	19.48(08.40)	19.74(8.04)	0.26(1.42)	0.596
Fat mass percentage (%)	27.11(05.86)	28.22(05.38)	1.11(1.61)	0.073
Fat free mass (kg)	50.67(14.99)	49.94(15.02)	0.73(1.10)	0.139
Fat mass index (kg/m^2)	06.47(02.45)	06.62(02.31)	0.16(0.38)	0.252
Fat-free mass index (kg/m^2)	16.78(03.25)	16.53(03.31)	0.23(0.38)	0.093
Skeletal muscle mass (kg) ($n = 8$)	25.44(08.72)	24.86(08.97)	0.58(0.86)	0.093

BMI, body mass index; SD standard deviation.

improvement of 10.42(10.73)% ($p < .006$). The role function scale and symptom scales of sleep, diarrhoea, financial issues, and cough all showed clinically significant improvements (Table 3).

Effects on body composition

Bioimpedance analysis was completed on 9 of the 12 participants. Three participants were unable to be assessed secondary to joint replacements and compression socks. Skeletal muscle mass results are reported for eight of these participants. Muscle mass was too low for the bioimpedance analyzer to detect in one participant. No significant changes occurred in any of the body composition variables (Table 4).

DISCUSSION

This study established that a 12-week multidisciplinary rehabilitation program is safe and feasible for survivors of esophageal cancer. Feasibility was demonstrated through recruitment rates, adherence, acceptability, and lack of adverse events. Participants also showed significant improvements in physical performance measures and QOL following the intervention. This suggests the efficacy of this program warrants further investigation and validation, ideally within a randomized control trial (RCT).

The recruitment rate of 55% was obtained through a maildrop to potential participants. There is limited literature regarding the expected rate of recruitment in cancer survivor exercise trials; however, studies suggest <40% is typical.[21] Good feasibility was also demonstrated by a high adherence rate of 82(13)% to the supervised sessions. A previous review by Kampshoff *et al.* examining exercise adherence in cancer survivors reported that adherence ranged from 62 to 78%,[22] therefore emphasizing the particularly high acceptability of the ReStOre intervention. The majority of participants in the review by Kampshoff *et al.*[22] were breast or colorectal cancer survivors, who typically experience less treatment-related morbidity, and therefore may present fewer barriers to exercise compared to the complex needs of the cohort recruited to ReStOre. Participants in this feasibility study reported that work and family commitments and travel to the research center were barriers to attending supervised sessions. Compliance with the home exercise sessions was monitored using exercise diaries. Participants had a mean compliance of 118(76)%. The large standard deviation perhaps highlights the discrepancies in motivation among participants. The results show that several participants greatly exceeded the prescribed amount of home sessions whereas some participants struggled to comply. Participants reported lack of time, lack of motivation, aversion to instruction, other illness, and work and family commitments as reasons that prevented them from achieving the prescribed number of exercise sessions. The ReStOre trial implemented a number of recommended methods to promote habitual exercise in cancer survivors.[23] These included goal setting, self-monitoring (using polar heart rate monitors), and encouraging participants to repeat the same level of exercise achieved in their rehabilitation class in an unsupervised capacity. The large variance in compliance with the unsupervised sessions in this study concurs with the review findings of Bourke *et al.*[24] that it is difficult to get sedentary cancer survivors to adhere to the recommended 150 minutes of moderate intensity activity per week. All 12 participants completed the intervention signaling high acceptability. In terms of safety, no adverse events occurred during any assessments or treatment sessions.

Clinically meaningful and statistically significant improvements in aerobic fitness were also demonstrated through increases in both VO_2max and 6MWT distance. The use of CPET to measure cardiopulmonary fitness in patients with esophageal cancer has largely been confined to the preoperative setting.[25-27] Little is known about the physical fitness of esophageal cancer survivors as previous work has used subjective measures to determine physical function.[3,6] The results of the T1 assessments demonstrate that survivors of esophageal cancer have very poor or poor levels of aerobic fitness.[28] Postintervention participants demonstrated an improvement in VO_2max

of 3.99(2.7) mL/min/kg, which is an improvement of greater than one metabolic equivalent of oxygen (MET) (1 MET = 3.5 mL/min/kg). In a systematic review and metaanalysis of exercise interventions in breast cancer survivors, Mc Neely *et al.*[29] pooled data from three studies that assessed change in fitness using CPET and deemed an increase in exercise capacity of 3.39 mL/min/kg to be clinically meaningful. An improvement in 1 MET corresponds with a 12% (men) and a 17% (women) reduction in mortality.[29,30] Therefore, the improvement in VO_2max achieved by this feasibility study's participants may be considered a meaningful result. Improvement in physical function was also demonstrated by the 6MWT. In patients with cancer, a change of 54 m is deemed a clinically meaningful difference,[31] and therefore the improvement observed in this study, 56.3(35.3)m, may be considered clinically meaningful for the participants. Large variance was seen in the physical activity scores as measured by the Actigraph activity monitor, and no statistically significant improvements were observed. A small increase of 24.92(90.92) minutes per week in moderate-vigorous physical activity (MVPA) may have contributed to the improvements observed in aerobic fitness. MVPA is an important outcome for cancer survivors as it has been shown to correlate highly with QOL and overall survival in breast and colon cancer survivors.[15,16]

Several domains of QOL improved following the ReStOre intervention. At baseline, participants had global health scores that were slightly lower than normative values (T1 average = 70, normative data = 81).[32] At follow-up, global health scores exceeded the normative data (T2 average = 81). Role function, which, at T1, was below average compared to normative data (T1 = 72, normative data = 85) improved to an average 87.5 at T2 which, although it did not gain statistical significance, is a meaningful clinical change. As survivors of cancer often experience psychosocial issues that may impair their ability to optimally engage in society,[33] it is important to see that participants felt that their role function had improved as a result of the rehabilitation program. None of the symptom scales improved significantly. This may have been due to the small sample size and large variation in the symptoms experienced by participants. The future RCT will aim to detect improvements in symptom scores as previous research has documented the long-term symptom burden survivors of esophageal cancer experience.[6,17]

Body composition did not change with the intervention. Malnutrition is a serious long-term issue for patients postesophagectomy. Other symptoms such as dysphagia and reflux can also impair patient's ability to ingest adequate amounts of food.[34,35] Weight loss post-surgery consists of loss of fat mass and depletion of skeletal muscle mass, termed sarcopenia.[36,37] Postoperative weight loss has been associated with reduced disease-free survival.[34] Therefore, it is an important outcome achieved by this feasibility study that the nutritionally compromised study population, under the guidance of a physiotherapist and dietitian, were able to increase their exercise levels to the internationally recommended amount per week[28] without any compromise to body composition. The severity of the loss of skeletal muscle mass that may occur in esophageal cancer survivors was highlighted by the results of one participant whose skeletal muscle mass was too low to detect by bioimpedance analysis. Sarcopenia has been identified as a potential biomarker for poor prognosis in esophageal carcinoma.[37] The future RCT will incorporate a resistance training component to attempt to counteract the devastating consequences of sarcopenia.

This feasibility study had several limitations. First, as a pilot study, it had a small sample size and a single arm. The primary aim of this study design was to assess feasibility, and a larger adequately powered RCT will be implemented to examine the efficacy of the intervention. Other lessons learned which will inform the RCT program include the need for a resistance training component to combat the loss of muscle mass described in esophageal cancer survivors and also the need for a wellness measure. Postintervention feedback highlighted that there was a great sense of improved confidence and well-being among participants as a result of participation in the multidisciplinary program. In the forthcoming RCT, an outcome that captures the 'wellness' factor will be included. Finally, the cohort of survivors included in this feasibility study were known to have node negative pathology and lived within a manageable commute of the research center. Accordingly, the generalisability of the results to a wider cohort of cancer survivors is unclear.

In conclusion, a 12-week multidisciplinary rehabilitation program consisting of exercise, dietary counseling, and education was found to be feasible for survivors of esophageal cancer who were greater than one year post-treatment completion. Clinically significant improvements in functional performance and QOL were evident without compromise to body composition. While results of this feasibility study are limited, the efficacy of this program will be further investigated in the forthcoming RCT.

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Appendix XI: Study I- Patient Information Leaflet (PIL) and Consent Form

OSPIDÉAL NAOMH SÉAMAS
ST. JAMES'S HOSPITAL

Ospidéal Naomh Séamas, Sráid Shéamais, Baile Átha Cliath 8.
St. James's Hospital, James's Street, Dublin 8.
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ReStOre Trial
Rehabilitation Strategies following
Oesophageal Cancer

Patient Information Leaflet
Feasibility Study

Study Title: Rehabilitation Strategies Following Oesophageal Cancer Feasibility Study
Sponsor: Health Research Board

Principal Investigator	Dr Juliette Hussey
Study Doctor:	Professor John Reynolds
Site Address:	St James's Hospital, Dublin

This is a clinical study, a type of research study. The Research Team will explain the clinical study to you. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

1. Why is this study being done?

The purpose of this study is to investigate the feasibility of a rehabilitation programme on functional performance in people who have completed treatment for oesophageal cancer. Functional performance describes the ability to carry out normal activities such as walking or household tasks. Treatments for cancer of the oesophagus (food-pipe) such as chemotherapy, radiotherapy or surgery may alter normal functional performance. At St. James's Hospital we have been completing research over the past number of years to measure the change that may occur in functional performance during oesophageal cancer treatment. This information has been used to inform the design of a rehabilitation programme to include exercise, diet and education sessions aimed at improving functional performance and well-being for people who have completed treatment for oesophageal cancer.

2. Why am I being asked to take part?

People who have completed treatment for oesophageal cancer are being asked to participate.

3. Do I have to take part?

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

If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

You will still be free to leave the study at any time, with or without giving a reason. If you decide to leave the study, this will not affect your future treatment and care.

4. How many people will take part in the study?

Approximately 10 people will take part in this study, in St James's Hospital, Dublin. The study will last approximately six months and your participation will last three months.

5. What will happen to me if I take part?

The aim of this study is to deliver a rehabilitation programme for patients who are at least six months post completion of all their treatment for oesophageal cancer. You will be invited to participate in this programme when your doctor has indicated to the research team that you are medically well and able for the interventions involved.
If you decide to proceed to the intervention you will be assessed by the research team at two time points: pre-rehabilitation and post-rehabilitation.
Details of the assessments are outlined below.

Functional Performance

1. An exercise test to assess you physical fitness
2. A walking test to assess how far you can walk in six minutes. You will be asked to walk at your own pace during this test.
3. A grip test to measure the strength of your hand grip. This will give a sense of your overall muscle strength.
4. You will be given a physical activity monitor to wear at home for one week to measure the amount of activity you do. You will also wear this monitor while you are in hospital during the first five days following surgery.

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Body Composition

1. We will measures your **height, weight** and **waist circumference**. Waist circumference measures the amount of weight on your stomach using a measuring tape.
2. We will measure our body composition using a SECA bio-impedance machine.

Dietary Intake

1. A **food frequency questionnaire** will capture your normal eating patterns
2. You will **discuss** your diet with your dietician to highlight specific issues

Quality of Life

You will be required to complete two questionnaires pertaining to quality of life.

Blood samples

Blood samples will be taken at both assessments. In total 28mls (approximately 8 teaspoons) of blood will be taken. These samples will be used to measure a range of outcomes including inflammatory markers (e.g. C-reactive protein), gut hormones (e.g. ghrelin) and measures of energy breakdown (e.g. oxidative phosphorylation) in your body. These samples will be used specifically for research purposes. Your GP or hospital doctor will not be directly provided with the results of these blood tests. Other samples will be stored in our blood biobank for use in future research. Blood samples will be stored in the blood biobank for 10 years. These samples may be shared with other researchers for analysis.

Rehabilitation Programme

If you decide to participate the rehabilitation programme will take place for 12 weeks at St James's Hospital. Sessions will last approximately one hour and take place twice per week for the first four weeks, once weekly from week 5-8 and then once per fortnight during the last four weeks. The programme will involve exercise, nutrition advice and education.

This study will be the first of its' kind in people who have completed treatment for oesophageal cancer. Therefore an important aspect of the study will be to evaluate participant satisfaction with the programme. On completion of the programme we will be looking for feedback from you to help guide us in the design of future programmes for people with oesophageal cancer.

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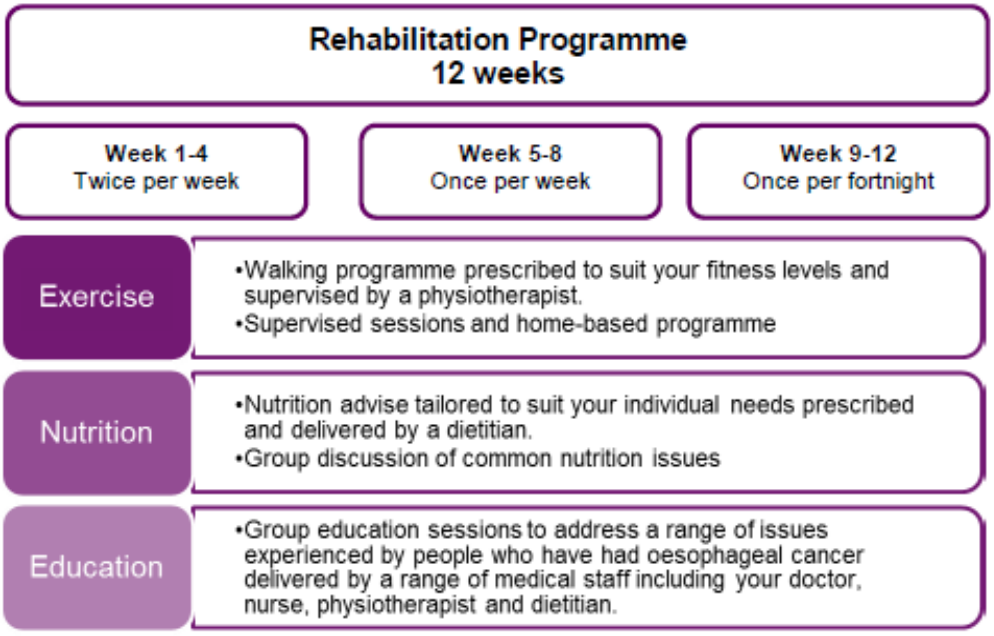

6. What will I have to do?

You will need to attend the Clinical Research Facility at St James's Hospital for the two study assessments which will last approximately 90 minutes. Where possible study appointments will be scheduled on the same day as other appointments you may have at the hospital to see your doctor or to receive treatment. If you are assigned to the rehabilitation group you will be required to attend the rehabilitation programme at the Clinical Research Facility for twelve weeks as detailed above.

7. What are the benefits of taking part?

There are no direct benefits to you for taking part in this study however the results will inform the design of future rehabilitation programmes which may benefit others.

8. What are the risks of taking part?

We do not anticipate adverse effects during the assessments. You may feel a little tired after the walking test however we expect that you will recover quickly. There is a risk of bruising or fainting when taking blood samples. If any results with potentially harmful consequences are discovered your team will be informed immediately. Participation in the rehabilitation intervention and in particular the walking

programme will be with the consent of your doctor and will be supervised closely by your physiotherapist. We do not anticipate that you will be at any risk by participating in the exercise prescribed.

9. Will I receive payment for being part of this study?

You will not be paid for taking part of this study.

10. What happens if I get hurt taking part in this study?

All participants and professional working on the study are covered by clinical indemnity insurance. This insurance covers any damage resulting from the research. For further details please contact the Dr Emer Guinan. Contact details are listed at the end of this document.

11. Will my information be kept private?

If you decide to take part in the study, you give the researchers permission to collect information about you and share it with the Health Research Board. Any information that identifies you (such as your name and address) will not be shared with Health Research Board.

Your study data will be identified with a code number which will not include your name or other information that directly identifies you.

Personal and medical information identifying you will be kept confidential. We will keep it in a secured file. At any time, you may ask to see your personal information.

Your study information will be used to determine the effect of treatment for oesophageal cancer on a functional performance such as physical activity levels and diet. The information gained will help inform the design of rehabilitation programmes to help people recover after treatment has finished.

Your information will be kept on file for up to 15 years and will be destroyed securely after that time.

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.

To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin or the Health Research Board, external auditors or inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

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12. Who should I contact if I have any questions?

For more information or answers to your questions about the study please contact any member of our research team, Monday – Friday from 9.00 am to 5.00pm.

Research Team Contact Details	
Research Team Mobile Number	0876577927
Emer Guinan, Research Physiotherapist	01-8963173
Suzanne Doyle, Research Dietitian	01-8963620
Linda O'Neill, Research Physiotherapist	01-8963613

13. Has this study been approved?

Yes, this study has been reviewed and approved by the AMNCH/SJH Research Ethics Committee (Approval reference number 2014-11 Chairman's Action (2)).

OSPIDÉAL NAOMH SÉAMAS
ST. JAMES'S HOSPITAL

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ReStOre Trial
Rehabilitation Strategies following Oesophageal Cancer

Patient Information Leaflet
Feasibility Study

Study Title: Rehabilitation Strategies Following Oesophageal Cancer Feasibility Study
Sponsor: Health Research Board

Principal Investigator	Dr Juliette Hussey
Study Doctor:	Professor John Reynolds
Site Address:	St James's Hospital, Dublin

Please tick each box to confirm you have read, understood and agreed to each of the points in this form.

1. I have read and understood the Patient Information Leaflet, Version I, dated 17th December 2014. I have had time to consider it and the opportunity to ask questions.	☐
2. I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. If I withdraw, I understand that my data can still be used up to when I withdrew, unless I state otherwise.	☐
3. I understand that my medical records may be looked at by authorised personnel from Health Research Board, the ethics committee, the regulatory authority, where it is relevant to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study.	☐

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4. I understand what will happen to my blood/tissue samples and I consent to the retention of my biological samples for research purposes.	☐
5. I consent to the collection and use of personal and sensitive information about me, including medical information, which will not include my name.	☐
6. I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.	☐
7. I agree to take part in this study	☐

Name of Patient (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*
Name of Person taking Consent (if different to Investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

Appendix XII: Letters of Ethical Approval (Study I and II)

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES
SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Ms. Emer Guinan
Research Fellow
Discipline of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8

26th November 2014

Re: Rehabilitation Strategies Following Oesophageal Cancer

REC Reference : 2014-11 Chairman's Action (2) ***(please quote references and title on all correspondence)***

Dear Ms Guinan,

Thank you for your correspondence in which you requested ethical approval for the above study.

The Chairman, on behalf of the SJH/AMNCH Research Ethics Committee has reviewed your submission and has given ethical approval.

Full ethical approval is now in place for this study.

Yours sincerely

Claire Hartin Secretary,
SJH/AMNCH Research Ethics Committee

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

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Ms. Emer Guinan
Research Fellow
Discipline of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
James's Street
Dublin 8

23rd February 2015

RE: Rehabilitation Strategies Following Oesophageal Cancer

REC Reference: 2014-11 Chairman's Action (2) : 2015-02 List 5 (8) ***Please quote REC reference on all correspondence***

Dear Ms. Guinan,

Thank you for your correspondence dated 20th February to SJH/AMNCH Research Ethics Committee requesting approval for an amendment to the above study.

The Chairman, on behalf of the SJH/AMNCH Research Ethics Committee has given ethical approval to the amendment.

The following documents were reviewed:

- Patient Information Leaflets and
- Patient Consent Forms
- Recruitment letter
- Maximal Exercise Test

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

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Dr. Emer Guinan
Discipline of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8

11th January 2016

RE: Rehabilitation following Oesophageal Cancer: Identifying Rehabilitative Needs and Strategies

REC Reference: 2016 – 01 List 1 (4)
(Please quote reference on all correspondence)

Dear Dr. Guinan,

Thank you for your recent email correspondence and attachments which you sent to the SJH/AMNCH Research Ethics Committee requesting approval of amendments to the above referenced study.

The Chairman, on behalf of the Research Ethics Committee, has reviewed your submission and the documents included and has given ethical approval to this amendment.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

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Dr. Emer Guinan
Research Fellow
Discipline of Physiotherapy
Trinity College Dublin, the University of Dublin
Dublin 2

26th January 2016

RE: Re: Rehabilitation Strategies Following Oesophageal Cancer: ReStOre Trial

REC Reference: 2016 – 01 List 1 (9)
(Please quote reference on all correspondence)

Dear Dr. Guinan,

Thank you for your correspondence to the SJH/AMNCH Research Ethics Committee requesting approval of an amendment, which is concerned with the use of the smartphone app, Salaso to the above referenced study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed your submission and the documents included and has given ethical approval to this amendment.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
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SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

Dr. Emer Guinan
Discipline of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8

23rd February 2016

RE: Rehabilitation following Oesophageal Cancer: Identifying Rehabilitative Needs and Strategies

REC Reference: 2016-02 List 5 (6)
(Please quote reference on all correspondence)

Dear Dr. Guinan,

Thank you for your correspondence to the SJH/AMNCH Research Ethics Committee requesting approval of amendments to the above referenced study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed your submission and has given ethical approval to this amendment.

Yours sincerely

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

Appendix XIII: Instructions for Polar Heart Rate Monitor

Instructions for Polar Heart Rate Monitor

You are required to wear your heart rate monitor while exercising outside of the class. This will help you to monitor the intensity of the exercise that you are performing. We will also provide you with a subjective rating scale to rate your level of exertion.

How to use your polar monitor:

- The heart rate monitor you have is the same as the heart rate monitor used during the class.
- It is made up of three parts; the wrist watch, the connector and the chest strap.

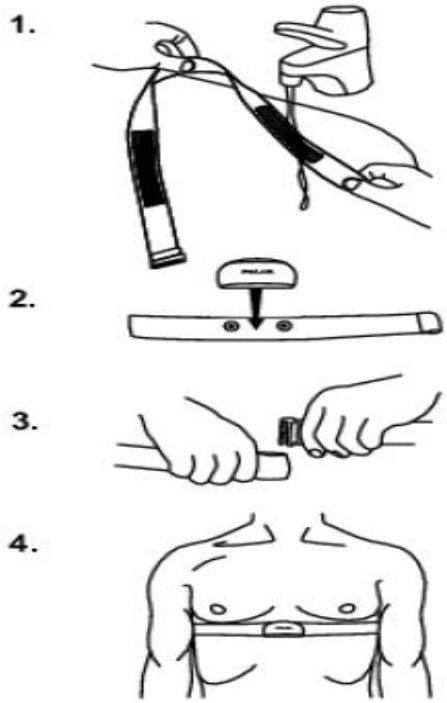
Using your monitor:

1. Wet the electrode areas of the strap well under running water.

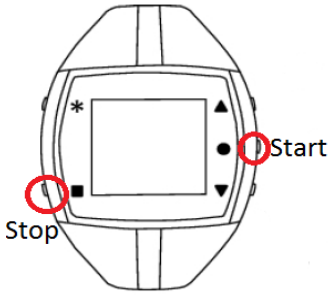
2. Attach the connector to the strap. Adjust the strap length to fit it tightly but comfortably.

3. Tie the strap around your chest, just below the chest muscles, and attach the hook to the other end of the strap.

4. Check that the wet electrode areas are firmly against your skin and that the Polar logo of the connector is in a central and upright position.



Start and Stopping Training:



1. Start recording your training session by pressing the **START** button **twice**.

2. The stopwatch starts running in a few seconds. The outline of the heart symbol flashes until your heart rate is detected (this should not take more than 15 seconds).

Your heart rate is displayed.

HEART RATE
Your current heart rate

3. A flashing heart symbol indicates an ongoing heart rate measurement.

4. To stop training recording, press the **STOP** button **twice** and the stopwatch should return to the Time display.

Cleaning your monitor:

- Clean the chest strap with a mild soap and water solution and dry with a towel after every use.
- Please do not use alcohol or any abrasive material. Do not soak, iron, dry-clean or bleach the strap.
- Do not bend or stretch the transmitter. This may damage the electrodes. Do not press the button of your training computer under running water.
- Keep in a cool and dry place. Do not store in a damp environment, in non-breathable material (a plastic bag or a sports bag) nor with conductive material (a wet towel).
- Do not expose to direct sunlight for extended periods.

Appendix XIV: Study I – Home exercise diary

Exercise Diary

Participant no. : _____ Week: _____

Your target heart rate for the next week is between

_____ and _____ beats per minute.

Date:	Duration:	Type of Exercise:	Max Heart Rate:

Please complete _____ additional sessions(s) this week of _____mins duration, as prescribed in your class

Exercise Information

Warm-up:

Your warm-up should be similar to that preformed in the exercise class. Your warm-up should be ____ mins in duration. You should exercise at < 3 on the RPE scale as explained in class.

Aerobic Component:

The aerobic component of the programme is again set at the same intensity as performed in the exercise class this week. You should exercise for___ mins in duration at a target heart rate of between ___ and _-__beats per minute. You should exercise at 4-6 on the RPE scale.

You do not need to reach the higher heart rate target and you should always exercise at a comfortable level.

Cool-down:

Again your cool-down should be similar to the cool down performed in the exercise class. Your cool-down should last ___ mins in duration. Again your cool down should correspond to <3 on the RPE scale.

Following cool down complete your lower leg stretches as on your exercise handout.

Please be advised to cease any exercise or stretching if pain is produced.

Appendix XV: Study II – PIL and Consent Form

OSPIDÉAL NAOMH SÉAMAS
ST. JAMES'S HOSPITAL

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ReStOre Trial
Rehabilitation Strategies following
Oesophago-gastric Cancer

Patient Information Leaflet
Project II

Study Title: Rehabilitation Strategies Following Oesophago-gastric Cancer Project II
Sponsor: Health Research Board

Principal Investigator	Professor Juliette Hussey
Study Doctor:	Professor John Reynolds
Site Address:	St James's Hospital, Dublin

This is a clinical study, a type of research study. The Research Team will explain the clinical study to you. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

1. Why is this study being done?

The purpose of this study is to investigate the effect of a rehabilitation programme on functional performance in people who have completed treatment for oesophageal cancer. Functional performance describes the ability to carry out normal activities such as walking or household tasks. Treatments for cancer of the oesophagus (food-pipe) such as chemotherapy, radiotherapy or surgery may alter normal functional performance. At St. James's Hospital we have been completing research over the past number of years to measure the change that may occur in functional performance during oesophageal cancer treatment. This information has been used to inform the design of a rehabilitation programme to include exercise, diet and education sessions aimed at improving functional performance and well-being for people who have completed treatment for oesophageal cancer.

2. Why am I being asked to take part?

People who have completed treatment for oesophageal cancer are being asked to participate.

3. Do I have to take part?

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

If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

You will still be free to leave the study at any time, with or without giving a reason. If you decide to leave the study, this will not affect your future treatment and care.

4. How many people will take part in the study?

Approximately 44 people will take part in this study, in St James's Hospital, Dublin.

The study will last approximately two years and your participation will last nine months.

5. What will happen to me if I take part?

The aim of this study is to deliver a rehabilitation programme for patients who are at least six months post completion of all their treatment for oesophageal cancer. You will be invited to participate in this programme when your doctor has indicated to the research team that you are medically well and able for the interventions involved.
If you decide to proceed to the intervention you will be assessed by the research team at three timepoints: pre-intervention, post-intervention and three-months post intervention. Details of the assessments are detailed below.
Functional Performance

1. An exercise test to assess your physical fitness.
2. A walking test to assess how far you can walk in six minutes. You will be asked to walk at your own pace during this test.
3. A grip test to measure the strength of your hand grip. This will give a sense of your overall muscle strength. We will measure the strength in your legs using a leg press machine.
4. You will be given a physical activity monitor to wear at home for one week to measure the amount of activity you do. You will also wear this monitor while you are in hospital during the first five days following surgery.

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Body Composition

1. We will measures your **height, weight and waist circumference**. Waist circumference measures the amount of weight on your stomach using a measuring tape.
2. We will measure our body composition using a Seika bio-impedance machine.

Dietary Intake

1. A **food frequency questionnaire** will capture your normal eating patterns
2. You will **discuss** your diet with your dietitian to highlight specific issues

Quality of Life

You will be required to complete two questionnaires pertaining to quality of life and wellness.

Blood samples

Blood samples will be taken at all assessments. In total 28mls (approximately 8 teaspoons) of blood will be taken. These samples will be used to measure a range of outcomes including inflammatory markers (e.g. C-reactive protein), gut hormones (e.g. ghrelin) and measures of energy breakdown (e.g. oxidative phosphorylation) in your body. These samples will be used specifically for research purposes. Your GP or hospital doctor will not be directly provided with the results of these blood tests. Other samples will be stored in our blood biobank for use in future research. Blood samples will be stored in the blood biobank for 10 years. These samples may be shared with other researchers for analysis.

Rehabilitation Programme

This project will take the form of a **randomised controlled trial**. A randomised controlled trial is a very high quality form of research when participants who share a particular characteristic (i.e. oesophageal cancer treatment) 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 intervention had any effect.

In this project you will be randomly assigned to participate in either the intervention group or to be in the control group. The control group does not attend the rehabilitation programme but does attend the study assessments. If you are randomly assigned to the control group you will not be required to attend the rehabilitation programme. If you are randomly assigned to the intervention group you will attend a **rehabilitation programme** for 12 weeks at St James's Hospital. Sessions will last approximately one hour and will take place twice per week for the first four weeks, once weekly from week 5-8 and then once per fortnight during the last four weeks. The programme will involve exercise, nutrition advice and education.

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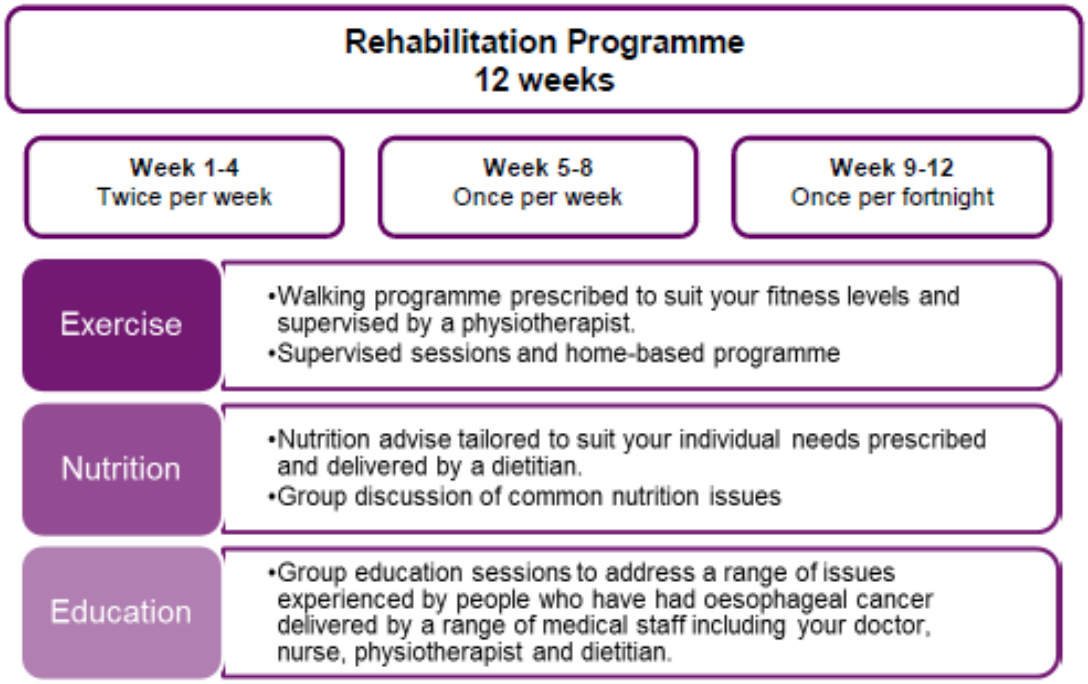

6. What will I have to do?

You will need to attend the Clinical Research Facility at St James's Hospital for the three study assessments which will last approximately 90 minutes. Where possible study appointments will be scheduled on the same day as other appointments you may have at the hospital to see your doctor or to receive treatment. If you are assigned to the rehabilitation group you will be required to attend the rehabilitation programme at the Clinical Research Facility for twelve weeks as detailed above.

7. What are the benefits of taking part?

There are no direct benefits to you for taking part in this study however the results will inform the design of future rehabilitation programmes which may benefit others.

8. What are the risks of taking part?

We do not anticipate adverse effects during the assessments. You may feel a little tired after the exercise test and the walking test however we expect that you will recover quickly. There is a risk of bruising or fainting when taking blood samples. If any results with potentially harmful consequences are discovered your team will be informed immediately. Participation in the rehabilitation intervention and in particular

the walking programme will be with the consent of your doctor and will be supervised closely by your physiotherapist. We do not anticipate that you will be at any risk by participating in the exercise prescribed.

9. Will I receive payment for being part of this study?

You will not be paid for taking part of this study. The cost of your parking at the St James's Hospital car park will be covered by the research team for all assessment and intervention appointments.

10. What happens if I get hurt taking part in this study?

All participants and professional working on the study are covered by clinical indemnity insurance. This insurance covers any damage resulting from the research. For further details please contact the Dr Emer Guinan. Contact details are listed at the end of this document.

11. Will my information be kept private?

If you decide to take part in the study, you give the researchers permission to collect information about you and share it with the Health Research Board. Any information that identifies you (such as your name and address) will not be shared with the Health Research Board.

Your study data will be identified with a code number which will not include your name or other information that directly identifies you.

Personal and medical information identifying you will be kept confidential. We will keep it in a secured file. At any time, you may ask to see your personal information.

Your study information will be used to determine the effect of rehabilitation post treatment for oesophageal cancer on functional performance. The information gained will help inform the design of future rehabilitation programmes to help people recover from treatment for oesophageal cancer.

Your information will be kept on file for up to 15 years and will be destroyed securely after that time.

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.

To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin or the Health Research Board, external auditors or inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

12. Who should I contact if I have any questions?

For more information or answers to your questions about the study please contact any member of our research team, Monday – Friday from 9.00 am to 5.00pm.

Research Team Contact Details	
Research Team Mobile Number	0876577927
Emer Guinan, Research Physiotherapist	01-8964809
Suzanne Doyle, Research Dietitian	01-8963620
Linda O'Neill, Research Physiotherapist	01-8963613

13. Has this study been approved?

Yes, this study has been reviewed and approved by the AMNCH/SJH Research Ethics Committee (Approval reference number 2014-11 Chairman's Action (2)).

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ReStOre Trial
Rehabilitation Strategies following
Oesophago-gastric Cancer

Consent Form
Project II

Study Title: Rehabilitation Strategies Following Oesophago-gastric Cancer Project II
Sponsor: Health Research Board

Principal Investigator	Professor Juliette Hussey
Study Doctor:	Professor John Reynolds
Site Address:	St James's Hospital, Dublin

Please tick each box to confirm you have read, understood and agreed to each of the points in this form.

1. I have read and understood the Patient Information Leaflet, Version IV, dated 1st December 2015. I have had time to consider it and the opportunity to ask questions.	☐
2. I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. If I withdraw, I understand that my data can still be used up to when I withdrew, unless I state otherwise.	☐
3. I understand that my medical records may be looked at by authorised personnel from Health Research Board, the ethics committee, the regulatory authority, where it is relevant to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study.	☐
4. I understand what will happen to my blood/tissue samples and I consent to the retention of my	☐

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biological samples for research purposes.	
5. I consent to the collection and use of personal and sensitive information about me, including medical information, which will not include my name.	☐
6. I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.	☐
7. I agree to take part in this study	☐

Name of Patient (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*
Name of Person taking Consent (if different to Investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

Appendix XVI: Study II- Home exercise diary

Exercise Diary

Participant no. : _____ Week:_

Warm-up:

Your warm-up should be similar to that preformed in the exercise class. Your warm-up should be ____ mins in duration. You should exercise at < 3 on the RPE scale as explained in class.

Aerobic Component:

The aerobic component of the programme is again set at the same intensity as performed in the exercise class this week.

Please complete ____ additional session(s) this week of ___ mins in duration at a target heart rate of between ___ and ___beats per minute.

You should exercise at 4-6 on the RPE scale.

You do not need to reach the higher heart rate target and you should always exercise at a comfortable level.

Date :	Duration:	Type of Exercise:	Max Heart Rate/Intensity Achieved:

Participant no. : _____ **Week:_**

Resistance Component

You should perform ____additional session(s) at home this week of the following resistances exercises.

Please fill in the date(s) you completed the resistance exercise and tick which exercises you completed.

Resistance Component	Exercise and weight	Repetitions	Sets	Session 1 Date completed: _____	Session 2 Date completed: _____

You should always be warmed up before performing your resistance training and you should always exercise at a comfortable level that does not induce any pain.

Cool-down:

Again your cool-down should be similar to the cool down performed in the exercise class. Your cool-down should last ___ mins in duration. Again your cool down should correspond to <3 on the RPE scale.

Following cool down complete your lower leg stretches as on your exercise handout.

Please be advised to cease any exercise or stretching if pain is produced.

Appendix XVII: Study III- Interview guide

Interview Guide

- Hello. My name is Linda O'Neill. This study aims to gain patient's perspectives of their physical recovery in the first few months after oesophagectomy or gastrectomy.
- As part of our work, we are speaking with individuals who have undergone surgery for oesophageal or gastric cancer in the last six months about their recovery. Your input is important to help us understand how we may be best able to help people like you in the future with their early recovery following oesophagectomy/gastrectomy.
- Firstly I would like to thank you for coming in today to talk with us and for fitting this interview into your busy schedule.
- The session is being recorded in audio to make sure we record accurately your response to our questions. You will have access to the transcripts of the interview if you wish and you can request changes to be made to your personal comments if you are unhappy with the content.
- Do you have any questions before we begin?
- What you say in this room stays in this room. As I mentioned, all information discussed today will be held in confidence. So please feel comfortable speaking openly and candidly with me. Please talk in a voice as loud as mine.

Sample questions

- How has your recovery been since your operation?
    - Has it been better/worse than expected?
    - What's been the most difficult thing?
    - How have you been managing with your usual activities of daily living since your operation? – washing/dressing/ cooking/ cleaning/ shopping
    - Is there any activity you have stopped or can't do as a result of your treatment?
    - Do you think you would be able to return to that activity in the near future?

- Since your operation have you engaged in much exercise?
    - Prior to your cancer diagnosis would you have been physically active?
    - Would you have any worries about participation in exercise?
    - Would your family have any concerns about your participation in exercise?
    - Would you like to increase your activity levels in the future?
    - What barriers/ prevents you from exercising

- Would you have liked additional support after your discharge from the multidisciplinary team – dietitian, physiotherapist, nursing team to help guide you during your recovery?
- How best as health care professionals do you think we would be able to help people like you in their recovery following their operation

Appendix XVIII: Study III – PIL and Consent Form

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+353 1 410 3000 www.stjames.ie

Patient Information Leaflet

Study Title: Patient's Perspectives of Physical Recovery in the Early Stages Following Oesophagectomy/Gastrectomy.

Principal Investigator	Professor Juliette Hussey
Study Doctor:	Professor John Reynolds
Site Address:	St James's Hospital, Dublin

1. Why is this study being done?

This study aims to gain patient's perspectives of their physical recovery in the first few months after oesophagectomy or gastrectomy. This information will be used to help us to design future recovery programmes for people in the early stages following oesophageal and gastric cancer surgery. We will gather this information through a one to one semi-structured interview.

2. 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 physical recovery since your operation. The researcher may explore your answers to some questions in more detail and may enquire about your previous physical activity history, the impact of your operation on your physical fitness and your ability to perform daily tasks, and also any barriers you might be experiencing to physical activity since your operation.

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 in a quiet private room at St James's Hospital. If you wish a family member or friend may accompany you for your interview.

3. Do I have to take part?

No, it is up to you to decide whether or not you take part. If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

4. What are the benefits of taking part?

There are no direct benefits to you for taking part in this study however the results will inform the design of future rehabilitation programmes which may benefit others.

5. What are the risks of taking part?

We do not anticipate any harms from taking part in the interview.

6. Will I receive payment for being part of this study?

You will not be paid for taking part of this study. The cost of your parking at the St James's Hospital car park will be covered by the research team for all assessment and intervention appointments.

7. Will my information be kept private?

If you decide to take part in the interview, you give the researchers permission to collect an audio-recording of your discussion. Your data will be identified with a code number which will not include your name or other information that directly identifies you. Personal and medical information identifying you will be kept confidential. All data will be filed and stored securely. At any time, you may ask to see your personal information.

Your information will be kept on file for up to 5 years and will be destroyed securely after that time. 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. To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin, external auditors or inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

8. Who should I contact if I have any questions?

For more information or answers to your questions about the study please contact Linda O'Neill, Research Physiotherapist on the research team mobile number 0876377927 or at 01 8963613, Monday – Friday from 9.00am to 5.00pm

9. Has this study been approved?

Ethical approval has been obtained from the AMNCH/SJH Research Ethics Committee REC Reference: 2016-11 Chairmen's Actions (9).

OSPIDÉAL NAOMH SÉAMAS
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Ospidéal Naomh Séamas, Sráid Shéamais, Baile Átha Cliath 8.
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+ 353 1 410 3000 www.stjames.ie

Consent Form

Study Title: Patient's Perspectives of Physical Recovery in the Early Stages Following Oesophagectomy/Gastrectomy.

Principal Investigator	Professor Juliette Hussey
Study Doctor:	Professor John Reynolds
Site Address:	St James's Hospital, Dublin

Please tick each box to confirm you have read, understood and agreed to each of the points in this form.

1. I have read and understood the Patient Information Leaflet, Version I, dated 19th October 2016. I have had time to consider it and the opportunity to ask questions.	☐
2. I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. If I withdraw, I understand that my data can still be used up to when I withdrew, unless I state otherwise.	☐
3. I understand that my data may be looked at by authorised personnel from the ethics committee, the regulatory authority, where it is relevent to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study.	☐
4. I understand that I will participate in an interview that will discuss my return to physical activity following my surgery. I understand that my interview will be recorded and then transcribed by a member of the research team. I understand that I may request a copy of my audio recording or transcript and that I may request to make an amendment to my interview.	☐
5. I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.	☐

6. I consent to my data being processed.	☐
7. I agree to take part in this study	☐

Name of Patient (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*
Name of Person taking Consent (if different to investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

Appendix XIX: Study III – Letter of Ethical Approval

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
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THE NATIONAL CHILDREN'S HOSPITAL

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TELEPHONE +353 1 4142000

Ms. Linda O'Neill
Discipline of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8

8th November 2016

Re: A qualitative Study of patient's perspectives on physical recovery in the early stages post-oesophagostomy/gastrectomy

REC Reference: 2016-11 Chairman's Action (9)
(Please quote reference on all correspondence)

Dear Ms. O'Neill,

Thank you for your recent application to SJH/AMNCH Research Ethics Committee in which you requested ethical approval for the above named study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed this application and grants ethical approval for it to proceed.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH 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.