Determining the feasibility and effectiveness of high intensity interval training in preoperative colorectal cancer patients

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6MWT	6 minute walk test
ASA	American Society of Anaesthesia
AT	Anaerobic threshold
ATP	Adenosine triphosphate
Bp	Blood pressure
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CRCa	Colorectal cancer
DASI	Duke activity status index
DBp	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DEXA	Dual xray absorptiometry scan
ECG	Electrocardiogram
EET	Endurance exercise training
EFS	Edmonton frail scale
EORTC QLQ-C30	European organisation for research and treatment of cancer quality of life questionnaire
EQ-5D	EuroQol 5 dimension
ERAS	Enhanced recovery after surgery
FMD	Flow mediated dilation

GCP	Good clinical practice
HADS	Hospital anxiety and depression scale
HIT	High intensity interval training
HITCa Study	HIT study in colorectal cancer patients
HIT Study	HIT study in healthy, older volunteers
HbA1c	Glycated haemoglobin
IL1	Interleukin 1
IL6	Interleukin 6
IPAQ	International physical activity questionnaire
MAP	Mean arterial blood pressure
MET	Metabolic equivalent of task
MI	Myocardial infarction
NACRT	Neoadjuvant chemoradiotherapy
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
p53	p53 tumour suppressor gene
PFK	Phosphofructokinase
PGC1 α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PHF20	PHF20 gene
PIS	Participant information sheet

POSSUM	Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity
QoL	Quality of Life
REC	Research ethics committee
RET	Resistance exercise training
RPE	Rating of perceived exertion
R&D	Research and development department
SBp	Systolic blood pressure
SF-36	Short form health survey
SPPBT	Short physical performance battery tests
TNFα	Tumour necrosis factor **α**
USS	Ultrasound scan
VO_2 max	Maximal oxygen consumption
VO_2 peak	Peak oxygen consumption
WEMWBS	Warwick-Edinburgh mental well-being scale

V. Publications and presentations from this work

- Forming a consensus opinion on exercise prehabilitation in elderly colorectal cancer patients: a Delphi study, C.L.Boereboom, J. P. Williams, P. Leighton, J. N. Lund, Exercise Prehabilitation in Colorectal Cancer Delphi Study Group, Tech Coloproctol (2015), Volume 19, Issue 6, p347-354. DOI 10.1007/s10151-015-1317-2

- Systematic review of preoperative exercise in colorectal cancer patients. C Boereboom, B Doleman, J N Lund, J P Williams, Tech Coloproctol (2016), Volume 20, Issue 2, p81-9. DOI 10.1007/s10151-015-1407-1

- A 31 day time to surgery compliant exercise training programme improves aerobic health in the elderly, CL.Boereboom, BE Phillips, JP Williams, JN Lund, Tech Coloproctol (2016), Volume 25. DOI 10.1007/s10151-016-1455-1

- High Intensity Interval Training Improves Fitness Within Recommended 31 day, Decision to Treat, Cancer Targets, C. Boereboom, B. Phillips, J. Lund, J. Williams

  (Poster presentation at American College of Sports Medicine, Integrative Physiology of Exercise Meeting, Miami, USA, September 2014)

- High intensity interval training (HIT) significantly improves fitness within 31 days in the elderly, C.Boereboom, B. Phillips, J. Lund, J. Williams, BJS 2015; 102 (S5): 3–52 *(Oral presentation at SARS, Durham, UK, January 2015, abstracts published in BJS, abstract number O152)*

- Forming a consensus opinion on exercise prehabilitation in elderly colorectal cancer patients: A Delphi study, C.L.Boereboom, J. P. Williams , P. Leighton, J. N. Lund, Exercise Prehabilitation in Colorectal Cancer Delphi Study Group *(Poster presentation at Digestive Disease Federation, London, UK, June 2015)*

1 Introduction

1.1 Colorectal cancer

Colorectal cancer (CRCa) is the 4th most common cancer in the United Kingdom with 41,265 new cases diagnosed in 2014 (Cancer Research UK, 2017). Advancing age is an established risk factor for the development of CRCa (Figure 1.1); between 2012 and 2014 44% of new cancers were diagnosed in patients aged 75 years and over (Cancer Research UK, 2017).

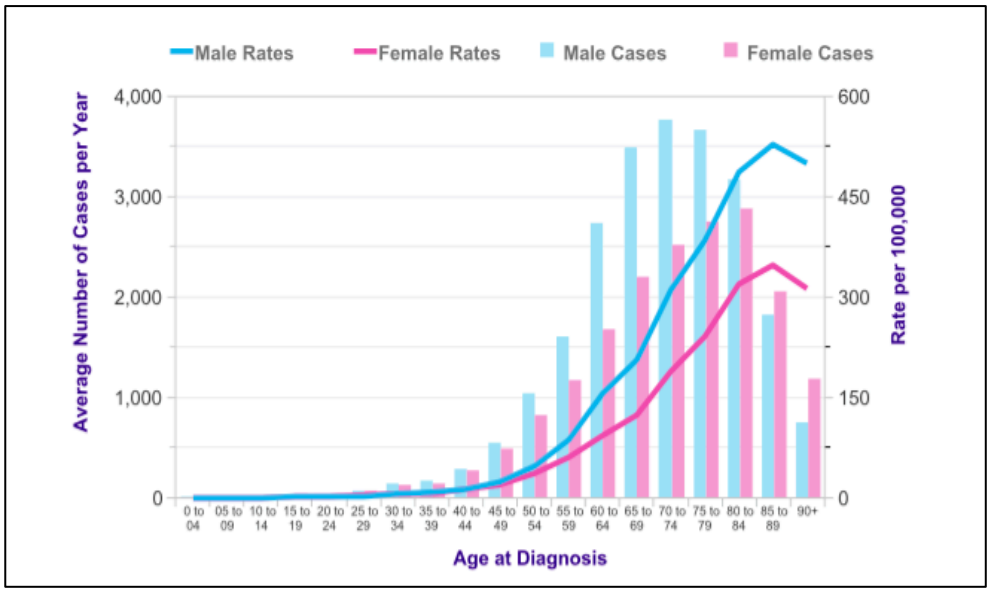

Figure 1.1 Average number of new cases of colorectal cancer per year and age specific incidence rates per 100,000 population, UK, 2012-2014

(Cancer Research UK, http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-One, Accessed March 2017)

Due to our ageing population, national screening programmes and improved diagnostic techniques, a greater number of older people are now being diagnosed with CRCa. However older people are not surviving the disease as well as their younger counterparts. The 5 year survival rate from diagnosis of bowel cancer between 2009 and 2013 was 67.5% for 60-69 year old men and 45.5% for 80-99 year old men. This illustrates an increased burden of this disease in an ageing population (Cancer Research UK, 2017). In general terms, due to improvements in health screening and perioperative care, mortality from CRCa in all populations is decreasing over time. Indeed, the England and Wales age standardised 5 year survival rates for men with CRCa have increased from 24% in the early 1970s to 59% in 2010-11 (Cancer Research UK, 2017). Overall CRCa incidence is increasing over time but this is mirrored by improved survival rates. Age is a significant factor in reduced survival from colorectal cancer and efforts to improve outcomes in elderly CRCa patients should be investigated.

1.2 Surgery for colorectal cancer

Although temporary symptom improvement for CRCa can be achieved with chemotherapy, radiotherapy and other palliative techniques such as stenting the only definitive cure for CRCa is surgical excision. This surgery can be associated with significant morbidity and in the elderly this risk is heightened. The national bowel cancer audit calculates the 90 day postoperative mortality rate following major resection as 3.8% (ACPGBI, RCSEng, & The NHS Information Centre for Health and Social Care, 2015) this increases to 15% in those over 80 years of age (Morris et al., 2011).

1.2.1 Physiological stresses due to surgery

All major intra-abdominal surgery, including that for bowel cancer, confers risks of morbidity and mortality on patients because of the significant physiological stress on many body systems. This physiological insult of surgery was first investigated by Cuthbertson in the 1930's who demonstrated the catabolic effect of orthopaedic injuries on muscle with maximal loss of nitrogen, sulphur and phosphorus on days 2-6

following injury (David & Cuthbertson, 1930), this stress response has been widely studied ever since (Wilmore, 2002).

Physiological stress does not end at the cessation of surgery but is described as a prolonged ebb and flow phenomena during recovery. It continues into the postoperative period when endocrine induced metabolic responses lead to increased carbohydrate, protein and fat catabolism. Serum glucose increases after surgery due to increased hepatic gluconeogenesis and glycogenolysis as well as decreased use of peripheral glucose. This is driven by decreased pancreatic B cell secretion of insulin and by peripheral insulin resistance (Desborough, 2000; Kehlet, 2011).

Skeletal muscle is broken down under the stimulation of cortisol with the amino acids produced further metabolised for energy or into acute phase proteins (Desborough, 2000).

Activation of the sympathetic (part of the autonomic) nervous system, in response to the physiological stress during and after surgery, is responsible for tachycardia and hypertension secondary to noradrenaline stimulation (Desborough & Hall, 1993).

These physiological demands combined mean that surgical patients require a degree of cardiorespiratory reserve. The greater their reserve the more physiological upset they will be able to withstand.

In addition to metabolic and endocrine changes induced by surgery, surgical trauma also activates inflammatory signalling pathways. This acute phase response limits tissue damage, protects against bacterial infection and activates tissue repair processes (Sheeran & Hall, 1997). The main proteins that mediate and maintain this response are interleukin 1 (IL1), interleukin 6 (IL6) and tumour necrosis factor α (TNFα). The increase in inflammatory markers is proportional to the amount of tissue damage sustained. Laparoscopic surgery is much less likely to produce significant rises in IL1, IL6 and TNFα suggesting that the physiological stress associated with laparoscopic surgery is not as great as with open abdominal surgery (Helmy & Wahby, 1999).

High concentrations of IL6 are negatively inotropic due to its augmentation of calcium flux in the myocardial cells. It also acts as a platelet aggregator. These actions contribute to the increased risk of unstable angina during and after major surgery (Sheeran & Hall, 1997).

These inflammatory responses also affect fluid distribution within the body by reducing the effectiveness of the vascular endothelial surface layer. This allows the movement of fluid from the intravascular space to interstitial spaces. This effective hypovolaemia decreases tissue perfusion and tissue oxygenation and increases the likelihood of post operative organ failure (Strunden, 2011).

Therefore, it follows that people who have better preoperative cardiorespiratory function and fitness should have a greater physiological reserve and be better able to cope with the stress of surgery. Objective evidence for this is described later in this chapter.

1.2.2 Perioperative care in colorectal cancer surgery

Traditional dogmas regarding medical care before and after surgery have largely been surpassed by evidence based enhanced recovery after surgery (ERAS) programmes as outlined in the figure below (Figure 1.2).

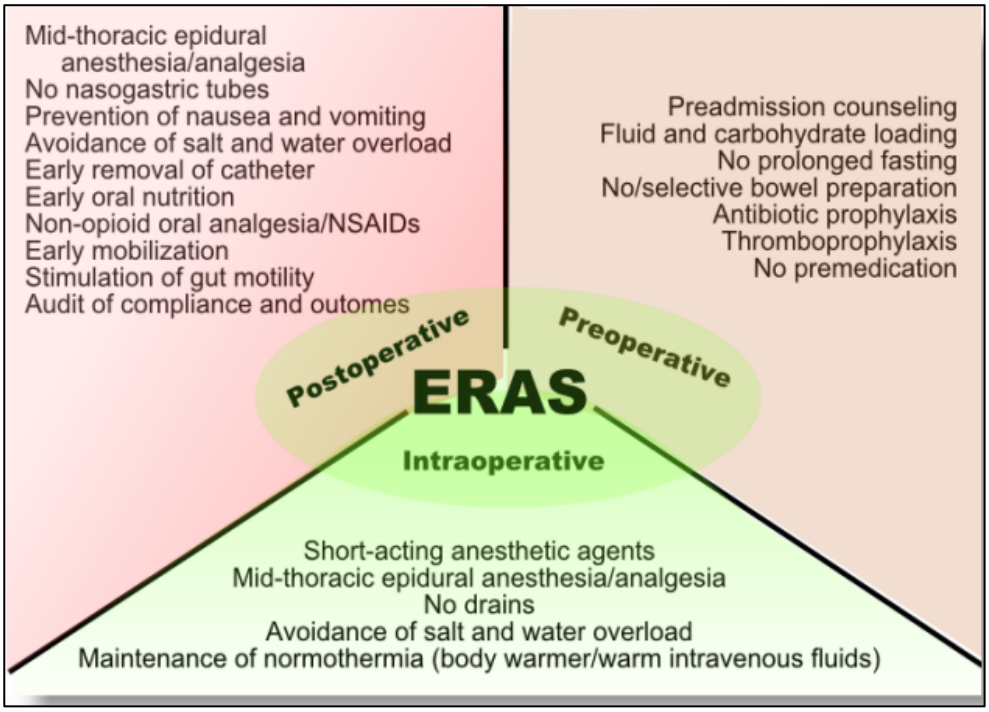

Figure 1.2 Example components of an Enhanced Recovery After Surgery Protocol

(www.erassociety.org/index.php/eras-care-system/eras-protocol, Accessed April 2016)

These pathways aim to reduce the surgical stress and physiological insult to the patient thereby shortening recovery times, reducing complication rates and minimising length of hospital stay. ERAS programmes are composed of preoperative, intra-operative and postoperative components. Preoperative components of ERAS include patient counselling, nutrition, exercise and lifestyle modification. Intraoperative components include venous thromboembolism prophylaxis, augmented anaesthetic protocols and minimally invasive surgical approaches. Postoperatively issues such as early

mobilisation, oral nutrition and adequate pain management are all subject to recommendations by the ERAS Society (Gustafsson et al., 2012). Reviews have found that while ERAS programmes can reduce length of stay in hospital and 30 day morbidity, 30 day readmission to hospital increases and there is no difference in mortality (Walter, 2009).

With regard to exercise, the ERAS Society recommendations state that increasing exercise preoperatively may be of benefit to patients although they note that the evidence level for these interventions is "very low, due to inconsistent data". Although many of the individual ERAS recommendations have been the focus of specific research, exercise recommendations have not been extensively examined, especially with regard to preoperative exercise in CRCa. Therefore, the feasibility and effectiveness of preoperative exercise in CRCa requires further investigation.

1.3 Risk stratification for surgery

In the modern surgical era most colorectal cancer surgery takes place within the framework of enhanced recovery programmes aimed at minimising the physiological impact of

surgery on the patient. However, as noted above, major surgery in the 21st century still exposes patients to significant risk, with these risks more evident in the elderly. Moreover, although the risk of postoperative complications does increase with age, it is not only the number of years alive that is an independent risk factor for complications (Khan, 2011; Wydra et al., 2013). There are several other issues that should be discussed in the context of minimising surgical risk in the elderly.

1.3.1 Age and Frailty

A number of physiological conditions that accompany advancing age are independent predictors of adverse surgical outcome (Griffiths & Mehta, 2014). There are many definitions of these frailty syndromes, for example, the "frailty phenotype" encompassing unintentional weight loss, exhaustion, weakness, slow walking speed and low physical activity in those over 65 years. This has been demonstrated to be predictive for increased falls, hospitalisation and likelihood of death (Fried et al., 2001). The relationship between these frailty conditions (rather than the number of years someone has lived) and surgical complications may be due to a lack of

physiological reserve in multiple organ systems. Frailty is commonly assessed by the Edmonton Frail Scale (EFS), a questionnaire incorporating physical, cognitive and functional capability. It is validated for use by non-geriatricians, can be completed in less than 5 minutes (Partridge, 2012; Rolfson, 2006) and is a useful tool which allows risk stratification and identification of potentially modifiable risk factors. It has been used in elderly, medically co-morbid, preoperative populations where low scores were associated with increased post-operative complications, increased length of stay and inability to be discharged home (Dasgupta, 2009). It is also used as an assessment tool within the Proactive care of the Older Patient (POPS) service run by Dr. Dhesi at Guy's and St Thomas' hospital, London. This service has been at the forefront of elderly surgical care in the UK (Harari, 2007). Despite the successful adoption of these tools in specialist centres "surgical frailty" globally remains variably defined and measured (Partridge et al., 2012) and can be hard to quantify.

1.3.2 Cognitive function

Postoperative cognitive disorders (postoperative delirium - a change in mental status characterised by a reduced awareness

of the environment and a disturbance in attention and postoperative cognitive dysfunction – a deterioration in cognition temporally associated with surgery (Deiner & Silverstein, 2009)) are known to increase length of hospital stay, increase risk of adverse long term outcomes and reduce postoperative quality of life (Bickel, 2008). As may be expected these are more common in those with preoperatively documented cognitive disorders. In addition to being assessed by the EFS, mini mental state examinations and geriatric depression scales are frequently used tools for evaluating cognitive function (Bettelli, 2011).

1.3.3 Body composition

Sarcopenia is the age related loss of lean muscle mass, commonly associated with reductions in muscle strength (dynapenia) (Cruz-Jentoft, 2010). Both sarcopenia and dynapenia are established risk factors for disability and death (Mitchell et al., 2012). Specifically in CRCa patients over 65 years old sarcopenia has been shown to increase postoperative length of stay compared to non-sarcopenic controls (20.2±16.9 days vs. 13.1±8.3 days). In the same study infectious complications were significantly higher in

older (greater than 65 years), sarcopenic patients (29.6% vs. 8.8%, p=0.005) (Lieffers, 2012). Furthermore, patients with a higher lean mass have a shorter length of stay following operation than those with a lower lean mass regardless of chronological age (Englesbe et al., 2013). Decreased muscle mass has also been found to be an adverse independent prognostic factor for disease free survival following colorectal cancer resection and sarcopenic obesity found to increase 30 day morbidity and mortality (Malietzis et al., 2016). A recent large meta-analysis of 5267 patients undergoing major abdominal surgery significantly associated sarcopenia with increased major postoperative complications, increased 30 day mortality, reduced 1, 3 and 5 year survival and reduced 1 and 3 year disease-free survival (Jones, 2017).

1.3.4 Functional fitness

In addition to muscle mass and strength "functional fitness" also has implications regarding surgical risk and postoperative recovery. Functional fitness is defined as the physiological capacity to carry out daily tasks safely and without undue fatigue (Santos et al., 2012). Several preoperative screening tests such as "Timed up and go" (Huisman et al., 2014), the

short physical performance battery tests (SPPBT; (Guralnik et al., 1994)) and "6 Minute Walk Test" (Rikli & Jones, 1999) can be used to measure functional fitness. Indeed, "Timed up and go" has been shown to identify twice as many onco-geriatric surgical patients at risk of postoperative complications when compared to ASA (American Society of Anaesthesiology classification) grade alone, a scoring system based purely on degree of pre-existing (acute or chronic) medical co-morbidity (Huisman et al., 2014).

1.3.5 Risk prediction

In addition to the questionnaires or functional physical screening tests outlined above, surgical risk can also be objectively assessed via a variety of preoperative scoring systems. It is important that attempts are made to measure and document the risk attached to surgery at a patient level to allow enhanced perioperative planning and facilitate fully informed discussion regarding patient consent. Such risk prediction tools use a variety of known and/or predicted physiological and operative parameters to calculate an adjusted risk of postoperative morbidity and mortality (Physiological and Operative Severity Score for enUmeration of

Mortality and Morbidity (POSSUM), ACPGBI risk prediction model (www.riskpredication.org.uk), NCEPOD Surgical outcomes risk tool (http://www.sortsurgery.com), American College of Surgeons risk calculator (http://riskcalculator.facs.org/RiskCalculator)). All of these assessments result in an estimated value of risk, as exact risk stratification on an individual level for any medical decision is impossible. However these tools do aid frank discussion with patients about likelihood of postoperative problems and expected outcomes of surgery.

1.3.6 Cardiopulmonary exercise testing

Compared to the complexities of subjectively assessing "surgical frailty", an objective measurement of cardiorespiratory "fitness" can be achieved using cardiopulmonary exercise testing (CPET). CPET can be used in a wide variety of patient subgroups (Weisman et al., 2003), including the elderly, to measure cardiorespiratory function and risk stratify patients prior to surgery. CPET assesses parameters of both cardiac and respiratory performance, such as anaerobic threshold (AT) and maximum oxygen consumption (VO_2 max).

AT is defined as the level of oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms, causing a sustained increase in lactate and metabolic acidosis (Wasserman, 1986a). The nomenclature surrounding AT and the most reliable way of measuring it is debated (Hopker, 2011). Many use a dual methods approach looking at the V slope and ventilatory equivalents together (Palange et al., 2007).

Using the V slope method the AT can be identified as the inflection point on a graph of VCO_2 (carbon dioxide output) against VO_2 (oxygen uptake) during an incremental exercise test where the gradient of the slope increases from 1 (due to the utilization of a mainly carbohydrate diet) to a steeper gradient (representing the evolution of additional CO_2 from the bicarbonate buffering of lactic acid) (Figure 1.3, graph C). Using the ventilatory equivalents method the AT can be identified by the point at which the VE/VO_2 and $P_{ET}O_2$ begin to increase (onset of alveolar hyperventilation with respect to oxygen uptake) whilst the VE/VCO_2 and $P_{ET}CO_2$ remain constant (ventilation remains coupled to CO_2 output) (Figure 1.3, graph A).

VO_2 max is "maximum oxygen uptake attained and measured during an incremental exercise protocol for a specific exercise mode" (Cooper & Storer, 2010). It is defined by the Fick equation as the product of cardiac output and arteriovenous oxygen difference at peak exercise:

$VO_2 \text{ max} = (HR \times SV) \times [C(a\text{-}v)O_2]$

(Where HR is heart rate and SV is stroke volume)

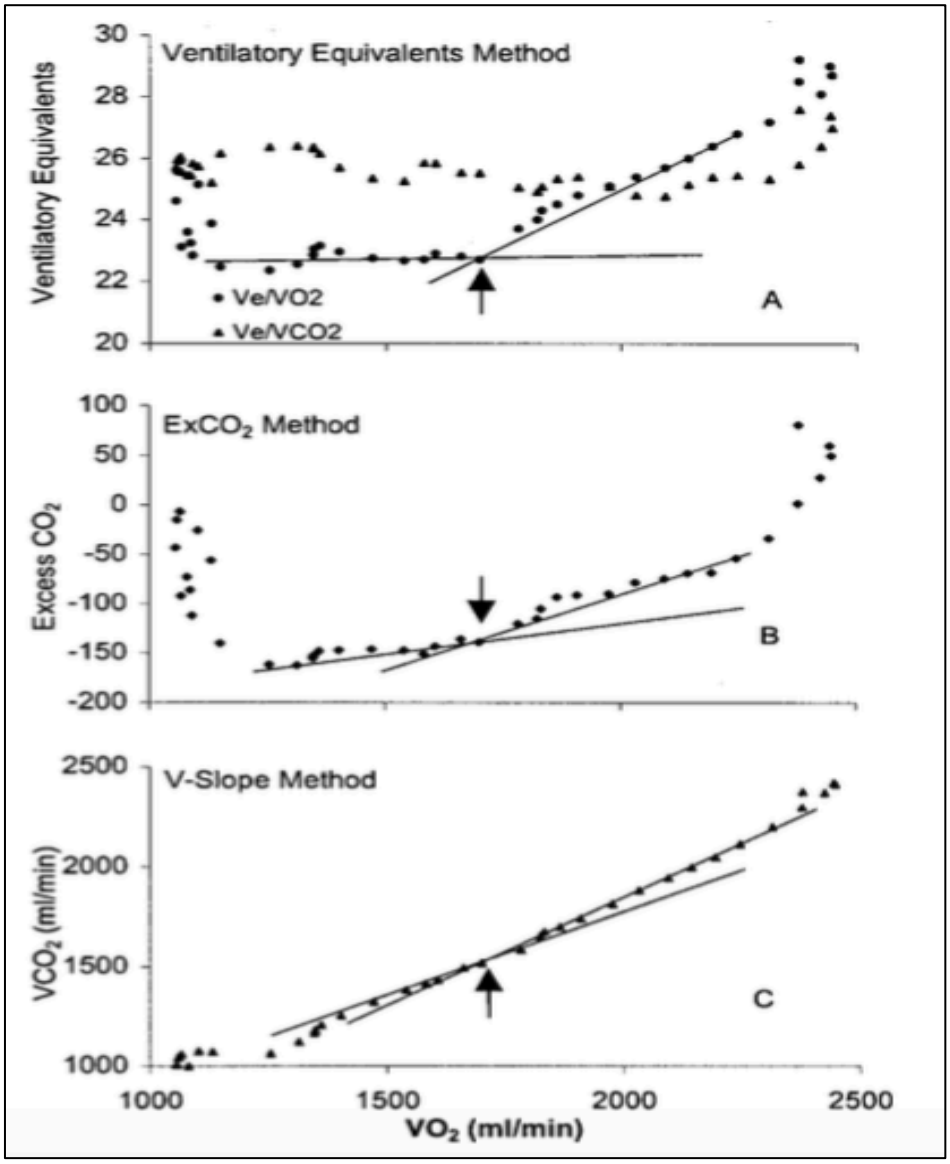

Figure 1.3 Visual determination of AT using a combination of methods. The arrows show the choice of AT in these example graphs from one subject. A. Ventilatory equivalence method: AT is chosen at the time corresponding to the first sustained rise in the ventilatory equivalent of O_2 (VE/VO_2) without a concurrent rise in the ventilatory equivalent of CO_2 (VE/VCO_2). B. Excess CO_2 method: AT is chosen at the time corresponding to the first sustained rise in excess CO_2. C. Modified V-slope method: AT is chosen at the VO_2 value corresponding with the inflection in slope of the VO_2/VCO_2 plot. (Gaskill et al., 2001)

VO_2 max is often referred to as the "gold-standard" measure of cardiorespiratory fitness (Hennis, 2011). It is seen to be a

measure of maximum cardiorespiratory performance; achieved when oxygen uptake (VO_2) plateaus despite increasing work. However, despite its "gold-standard" status the maximal effort required to achieve this level of physical performance is often beyond what is possible for untrained individuals, especially the elderly and those with cardiorespiratory comorbidity (Gibala, 2012). For safety, and to allow more reliable comparisons (either between different groups or before and after intervention), VO_2 peak is commonly used to assess cardiorespiratory function, especially in clinical populations (Balady et al., 2010). VO_2 peak is simply the peak oxygen uptake achieved during a period of graded exercise and is therefore obtainable by all. It has been shown to be a valid indicator of VO_2 max in subjects with normal cardiorespiratory systems (Day, 2003). In clinical practice the use of CPET in risk stratification for CRCa surgery has allowed those at high risk of developing postoperative complications to be identified. CPET assessment is usually employed at the discretion of the operating surgeon and anaesthetist. In some centres it has been shown to give traditionally "high risk" elderly patients (over 80 years) the same postoperative outcomes as low risk elderly patients, by using the CPET results to appropriately assign postoperative care settings (Chan, 2015).

1.4 Fitness and postoperative outcomes

There is good evidence that low cardiorespiratory fitness increases the risk of postoperative complications and morbidity (Levett & Grocott, 2015). The evidence for this in colorectal surgery is described below. There is also evidence that it is possible to improve fitness in some preoperative groups (Dunne et al., 2016), however, the association between improving fitness preoperatively and reducing rates of complications is less well defined. This is true of postoperative complications and more so, postoperative mortality rates. Recent meta-analysis of intra-abdominal surgery suggests that postoperative complications are reduced with improved preoperative fitness but mortality has not been investigated (Moran et al., 2016).

The mechanisms as to how better cardiorespiratory fitness may improve postoperative outcomes are still being investigated. Many studies centre around improved cardiorespiratory reserve as described below. Theories exploring specific organ complications are also being developed, such as exercise decreasing splanchnic blood flow and so pre-conditioning the bowel to low flow during surgery

and the recovery period. This is thought to reduces the frequency of complications such as ileus and anastomotic leak (Knight, 2017).

1.4.1 Colorectal cancer surgery

Specifically investigating patients undergoing major colorectal surgery several CPET variables have been validated to identify those at risk of postoperative mortality and in hospital morbidity. These included AT, VO_2 peak and VE/VCO_2 (West et al., 2016).

Additionally, further studies have quantified cut-off points in variables of preoperative physical fitness; below which postoperative complications are more likely to occur. For example, in rectal cancer surgery an AT and a VO_2 peak less than 10.6 and 18.6 ml/kg/min, respectively were associated with increased morbidity (West, Parry, et al., 2014). Similarly, in colonic surgery, patients with a preoperative AT of 9.9 vs. 11.2ml/kg/min and a VO_2 peak of 15.2 vs. 17.2 ml/kg/min were significantly more likely to have a complication at day 5 postoperatively (West, Lythgoe, et al., 2014). From the same study, those with lower AT values (below these thresholds)

also had a significantly increased length of hospital stay (Figure 1.4).

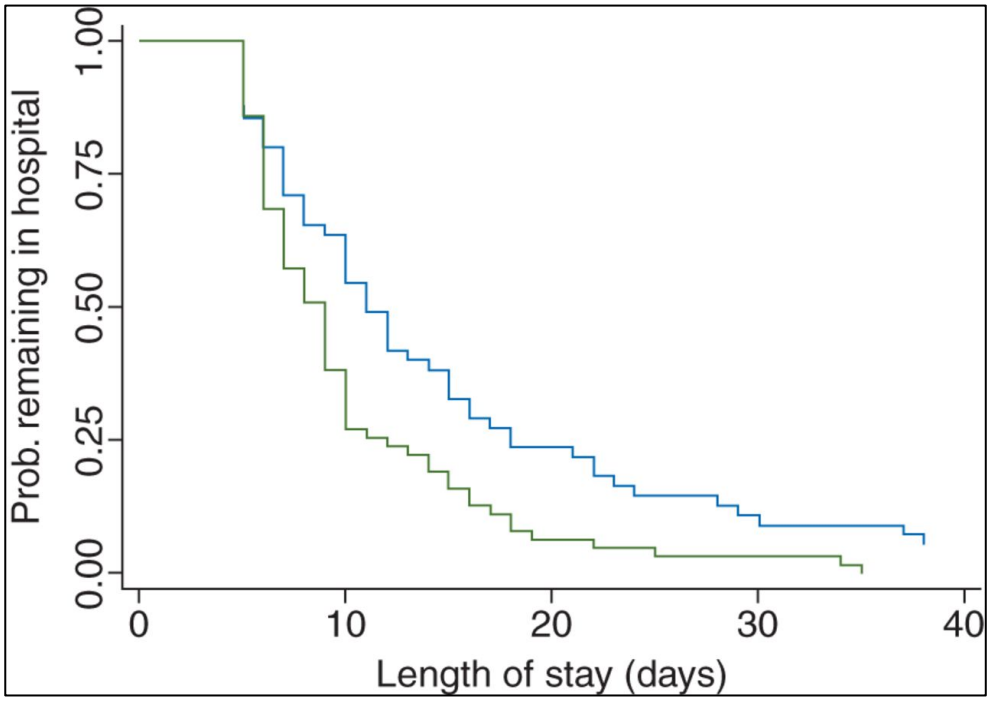

Figure 1.4 Increased cardiorespiratory fitness reduces post-operative length of stay. Kaplan-Meier curve relating oxygen uptake at estimated lactate threshold to length of hospital stay (LOS)

Blue line VO_2 AT at < 10.1.ml/kg/min, green line VO_2 AT > 10.1 ml/kg/min. M. A. West et al. Br. J. Anaesth. 2014;112:665-671. © The Author [2013]. Published by Oxford University Press on behalf of the British Journal of Anaesthesia. All rights reserved.

Adding more evidence to the value of CPET in assessing surgical risk, similar "predictive" values for CPET variables were seen in a large combined group of 847 patients undergoing either major colorectal or urological intra-abdominal surgery. In this group an AT of <10.9 ml/kg/min

was a significant predictor of both all cause in-hospital mortality and 90 day mortality (Wilson, 2010). Likewise in a group of patients undergoing major pancreatic surgery an AT of less than 10 ml/kg/min was associated with a longer hospital stay, increased risk of postoperative fistula and intra-abdominal abscess and a reduced chance of going on to complete adjuvant chemotherapy (Chandrabalan et al., 2013).

1.5 Using exercise to achieve cardiorespiratory fitness

When assessing the feasibility of improving the fitness in CRCa patients prior to operation careful consideration of the amount and type of exercise is required.

The role of "exercise for health" is not a new concept, indeed the father of medicine, Hippocrates, said that "walking is man's best medicine". In 1949 the Scottish epidemiologist Jerry Morris compared the rate of myocardial infarction in bus drivers and bus conductors. He found that the more physically active conductors had a lower incident of heart disease (Morris, 1953). Work in this area has continued to the current day with the American Heart Association producing a scientific

statement in 2016 emphasising the importance of poor cardiorespiratory fitness as a risk factor for all cause and disease specific mortality (Ross et al., 2016).

Despite general acceptance of the health benefits of physical activity, the amount and type of exercise required to achieve an improvement in "fitness" has long been debated. Previous studies suggested that an increase in "free living activity energy expenditure" (above resting metabolic rate) of 287kCal a day was associated with a 32% (HR 0.68, 95% confidence interval 0.48-0.96) lower risk of mortality in community living 70-80 year olds (Manini et al., 2006). More recent work has concluded that a more modest energy expenditure of 1000kCal/week equates to a 20 – 30% reduction in all cause mortality (Myers et al., 2014). There have been studies suggesting that the type of exercise as well as the volume of exercise is important in providing reduction in mortality. The Harvard Alumni Health Study reported a reduced age standardised mortality rate with increasing amount of moderate or vigorous activity taken but not with non-vigorous activity (Lee & Paffenbarger, 2000). Considering minimum levels of physical activity, there appears to be a linear relationship between fitness and health, such that even a

small amount of exercise, whilst maybe not prolonging life, may confer some health benefits. One study demonstrated a reduction in incidence of non-insulin dependant diabetes mellitus with just 40 minutes exercise a week at an intensity of >5.5 METS (i.e. activities such as digging in the garden or chopping wood, METS are measures of the energy cost of physical activities or the ratio of metabolic rate (and therefore the rate of energy consumption) during a specific physical activity to a reference metabolic rate, set by convention to 3.5ml O_2/kg/min) (Lynch, 1996).

Based on guidelines from the World Health Organisation (World Health Organisation, 2010), the Department of Health in the UK and the US Office for Disease Prevention and Health Promotion recommend that both adults (19-64 years) and older adults (65 years and over) perform 150 minutes of moderate intensity exercise or 75 minutes of vigorous activity every week. This activity should be accumulated in bouts of greater than 10 minutes duration (Paterson & Warburton, 2010). In addition, activities to improve strength (exercising the major muscle groups with resistance exercise training (Paterson & Warburton, 2010)) and balance are also encouraged, with advice that sedentary time should be

minimised. This advice has also been endorsed in recent Canadian guidelines "Exercise for people with cancer; a clinical practice guideline" as safe for those undergoing and following cancer treatment (Segal et al., 2017).

1.6 Previous preoperative exercise studies

Investigating the effectiveness of preoperative exercise is not a new idea. A number of studies in different clinical groups have assessed the effect of both traditional (endurance and resistance) and alternative (e.g. inspiratory muscle training) exercise training modes. For example, studies looking at preoperative inspiratory muscle training on postoperative outcomes in patients undergoing both major vascular and cardiac surgery have shown a reduction in length of hospital stay, length of intensive care unit stay and fewer cases of postoperative pneumonia (Arthur, 2000; Hulzebos, 2006).

Recently Dunne et al., successfully completed a high intensity interval training prehabilitation study in patients awaiting liver resections for CRCa metastasis showing an improvement in VO_2 peak of 2ml/kg/min in 4 weeks (Dunne et al., 2016).

A systematic review of preoperative exercise in lung, prostate and abdominal cancers showed benefit in both clinical endpoints and functional outcomes with both resistance and aerobic training. This lead to suggestions from the authors that exercise should be prescribed as an adjuvant therapy in the treatment of these cancers (Singh, 2013).

In further support of this premise, a recent systematic review of 21 studies of preoperative exercise in lung cancer patients showed an increase in exercise capacity and pulmonary function as well as reduced complication rates and length of hospital stay with preoperative exercise (Garcia, 2016). A significant improvement in VO_2 peak has been shown in patients undergoing lung resection for cancer in a mean of 67 days with endurance cycle ergometry training, 5 times per week, with increasing intensity and duration of training sessions over time (Jones et al., 2007). Bobbio et al., also showed an increase in VO_2 max in preoperative lung cancer patients after a period of pulmonary prehabilitation, although this involved a large time commitment of 90 minutes of hospital based exercise (60 minutes cycle ergometry training followed by upper body conditioning with free weights) 5 days a week for 4 weeks (Bobbio et al., 2008).

Preoperative exercise in patients with upper gastrointestinal cancers has also been studied. A Japanese group used a combined strength and aerobic exercise training programme to show a reduction in postoperative complications after a 4 week exercise programme. Although it must be noted that the methodology of this study may be questionable given that only 18 people were included in their exercise group and no power calculation was described to say whether this sample size was adequate. The intervention appeared to be home-based using a variety of methods to achieve aerobic exercise 5-7 times a week, resistance training 1 or 2 times a week and stretching although the details are not well described (Cho et al., 2014).

Most recently a randomised control trial of preoperative exercise in elderly and/or co-morbid patients undergoing major abdominal surgery has been published showing an increase in preoperative cycling endurance and reduction in postoperative complications in the intervention group (Roca, 2017).

A systematic review on exercise during and after cancer treatment for different types of cancer, noted a predominance of studies looking at cardiovascular exercise training in breast cancer patients. It concluded that whilst many studies had

small numbers of participants and were not randomised controlled trials, both physiological and psychological benefits were observed in most studies (Galvão & Newton, 2005). They supported the notion the exercise does have benefit for cancer patients. This was also the conclusion from a large meta-analysis of 34 randomised controlled trials in cancer patients. They found an improvement in both quality of life measures (QoL) and physical fitness following exercise (especially with supervised programmes) both during and after cancer treatment regardless of clinical characteristics and patient demographics (Buffart et al., 2017).

However, despite the promises offered by the above reviews, there remains great heterogeneity between exercise interventions including the type, duration and intensity of exercise. However, the overarching message from the collated evidence is that improved cardiorespiratory fitness increases the likelihood of a complication free surgical journey; with consensus on the best type of exercise regime to achieve this still needed (Carli et al., 2017).

1.7 Previous exercise studies in colorectal cancer patients

1.7.1 Exercise for the primary prevention of colorectal cancer

Specific to CRCa, there is much published epidemiological literature on lack of physical activity as a risk factor for CRCa. Those who have an increased BMI (often linked to sedentary behaviour) (Heinonen et al., 2013), poor diet (low in fibre, high in red meat) and are physically inactive are at an increased risk of developing CRCa (Newton, 2011). Indeed, it has been estimated that 12-14% of colon cancers may be attributable to lack of frequent vigorous exercise (Slattery, 2004). A recent Australian study estimated that 1814 (6.6% of the total incidence) colonic, breast and endometrial cancers in >25 year olds in 2010 were attributable to insufficient physical inactivity, 707 of these were colon cancers (Olsen et al., 2015). Additionally, those with the aforementioned lifestyle risk factors prior to diagnosis have a higher risk of disease specific mortality and all cause mortality following treatment for CRCa (Haydon, 2006). Postulated mechanisms explaining how regular exercise may protect against cancer development and progression include (Harriss et al., 2007; M. Slattery, 2004; Thomas, 2016):

- Improved recruitment, mobilization and activation of immune natural killer cells during exercise (Idorn & Hoiman, 2016).
- Augmented inflammatory response. The level of circulating cytokine IL6 increases in response to exercise, secondary to an increase in its transcription rate. IL6 induces the IL1ra and IL10 cytokines and inhibits TNFα and IL1 production resulting in an anti inflammatory environment (Petersen & Pedersen, 2005). Cancer development is linked to a chronic inflammatory state and so this change in environment has been linked to a reduced risk. The exact mechanisms are still debated (Walsh et al., 2011).
- Effects on insulin and insulin like growth factors. For similar reasons the acute exercise inhibition of TNFα removes the direct inhibitory effect that this cytokine has on insulin signaling (Petersen & Pedersen, 2005) (Ahn et al., 2016). Impaired insulin signaling (or increased insulin resistance) has been shown to increase risk of CRCa development (Berster & Göke, 2008).
- Increased gut motility. Gut transit time is significantly reduced by regular moderate intensity exercise. Possible mechanisms include; change in visceral blood flow,

neuronal, hormonal or mechanical effects (Oettle, 1991). There is an inverse relationship between bowel transit time and development of CRCa which is still under investigation (Slattery & Potter, 2002).

- Decreased obesity. Multiple studies have shown an increased risk of CRCa with increasing BMI, relative risks of up to 3.4 have been reported (Gunter & Leitzmann, 2006).

1.7.2 Preoperative exercise in colorectal cancer

Our published systematic review of exercise in the preoperative period in CRCa patients forms chapter 2 of this thesis. In brief 8 studies were reviewed including 5 randomised control trials (RCT) with exercise programmes lasting 2 – 6 weeks with a minimum of 30 minutes of exercise 3 times a week. Only 2 studies looked at CPET variables as their primary outcome.

A study from West et al., looked at patients having neoadjuvant chemoradiotherapy (NACRT) for rectal cancer, they demonstrated a reduction in fitness during NACRT in both groups. They went on to show the group who underwent preoperative exercise training between the end of NACRT and

surgery regained their baseline fitness whereas the control group remained at a reduced fitness level up to the time of surgery (West, 2014).

Kim et al., showed improved physiological efficiency as lower oxygen consumption at a given workload after exercise training (Kim, 2009). Their intervention was home-based cycle ergometry aerobic training with increasing intensity and duration over 3 weeks. Five studies looked at functional outcomes including the 6-minute walk test; two of these found a significant improvement in this test with exercise training. Little difference was found in any study with regard to postoperative complication rates or length of hospital stay. Quality of life measures were assessed in several studies, the results of which suggested a qualitative improvement in QoL with exercise (Boereboom, 2016).

These studies are discussed in more detail in chapter 2. This also discusses gaps in the current literature which would be targets for future research work.

A more recent systematic review looking at preoperative exercise studies in CRCa surgical patients over 60 years old included studies up to January 2016. They analysed 5 studies (all of which were included in our systematic review) and concluded that preoperative exercise is a means of enhancing

preoperative patient condition but that the quality of the studies done to date was poor (Bruns et al., 2015). Again more recently Singh's group studied 19 rectal cancer patients using a moderate intensity and weight training programme and showed maintenance of pretreatment muscle mass with exercise despite neoadjuvant therapy (Singh et al., 2017).

1.7.3 Exercise during chemotherapy for colorectal cancer

Despite the conclusion that preoperative exercise can enhance preoperative patient condition in CRCa, there is sparse evidence for a benefit of exercise intervention during neoadjuvant or adjuvant chemotherapy specifically in colorectal cancer. The majority of studies have used mixed patient groups with various cancer diagnoses, limiting the applicability of the results to specific types of cancer (Adamsen et al., 2009; Adamsen, 2003). Exercise does have proven benefit in reducing fatigue and increasing physical functioning during adjuvant chemotherapy in a 12 week combined aerobic and resistance training programme (Kuan-Yin, 2014). Additionally increased daily physical activity levels (assessed via questionnaire) have been shown in low intensity aerobic exercise groups undergoing adjuvant chemotherapy (Backman

et al., 2014). In a group of cancer patients undergoing chemotherapy, which did include CRCa patients with a mean age of 40 years, Adamsen et al., showed a significant increase in VO_2 max with a 6 week multidimensional programme including aerobic exercise, resistance training, relaxation techniques and massage (Adamsen et al., 2003).

As mentioned previously exercise training can also recover fitness to pre-chemotherapy baseline levels following NACRT for rectal cancer (West, 2014). Recently Morielli et al. published a study of 18 patients looking at exercise during NACRT for rectal cancer. They showed that their exercise program (50 minutes of moderate intensity aerobic exercise 3 times a week) was feasible and safe. Although not powered to assess improvements in fitness outcomes, their results suggested that exercise mitigated against some of the losses in fitness during NACRT, and that fitness was improved following the treatment due to the exercise intervention. In addition to increases in fitness, patients in this study reported that QoL outcomes decreased during NACRT and improved again with exercise prior to surgery once NACRT had finished (Morielli et al., 2016).

1.7.4 Postoperative exercise in colorectal cancer

There are very few studies documenting the effect of exercise interventions in the immediate postoperative period in CRCa patients. A study from Houberg at al., included a 90 day exercise intervention starting at day 1 postoperatively and found no difference in measures of physical function compared to a group who did not exercise; although the exercise group did report reduced fatigue (Houborg, 2006).

Three randomised controlled trials have reported fitness outcomes when assessing exercise in patients during the first few months following CRCa treatment. Work from Bourke et al. assessed 18 CRCa patients (mean age 69 years) and reported an increase in aerobic exercise tolerance after a 12 week exercise and diet programme (Bourke et al., 2011). Similarly, Pinto et al. recruited 46 CRCa patients (mean age 57 years) and found a significant increase in estimated VO_2 peak, compared to a control group, in those who completed a moderate intensity, home-based exercise programme (Pinto, 2013). In contrast to the results of these two studies, Courneya et al studied a larger cohort of 93 CRCa patients (mean age 60 years) and showed no difference in quality of life or fitness measures following a moderate intensity home based exercise programme (Courneya et al., 2003). These

contentious results suggest that further work is needed in this area to fully define any benefit of postoperative exercise on physical fitness/function in CRCa patients.

Interestingly, in a recent reanalysis of results from their previous studies, Carli's group have shown a greater improvement in functional fitness, as measured by improvement in the 6 minute walk test, in their preoperative exercise group compared to the change seen in their postoperative exercise group. This suggests that the preoperative period may be the most effective time to target with exercise for improvement in fitness (Minnella, 2017).

1.7.5 Exercise to prevent recurrent colorectal cancer

Despite the lack of consistent results in the studies outlined above, many studies have focused on exercise in CRCa patients during the survivorship period, following the end of adjuvant oncological treatment. Reduction in mortality with exercise has been shown in CRCa as well as other cancer types such as breast cancer (Courneya et al., 2008; Holmes, 2014). Indeed, a recent meta-analysis has shown that those who exercise regularly either before or after their diagnosis of

CRCa had a lower CRCa specific mortality and lower all cause mortality (Je, 2013).

A systematic review showed good evidence for the use of physical activity after adjuvant cancer treatment (e.g. following postoperative chemotherapy) with a low risk of adverse events (Speck, 2010). Additionally, work from Denlinger et al., showed a decreased recurrence risk as well as improved QoL and cardiovascular fitness with exercise in colon cancer survivors (Denlinger & Engstrom, 2011). Physical activity appears to reduce the risk of colorectal cancer recurrence in those who are disease free 6 months after the end of their adjuvant therapy. There was no significant difference in baseline performance status in these patients and the more activity they took after their treatment the lower the risk of recurrent disease with a dose-dependent relationship apparent between 3 and 26.9 (metabolic equivalents) MET-hours/week (Meyerhardt et al., 2006) (Figure 1.5).

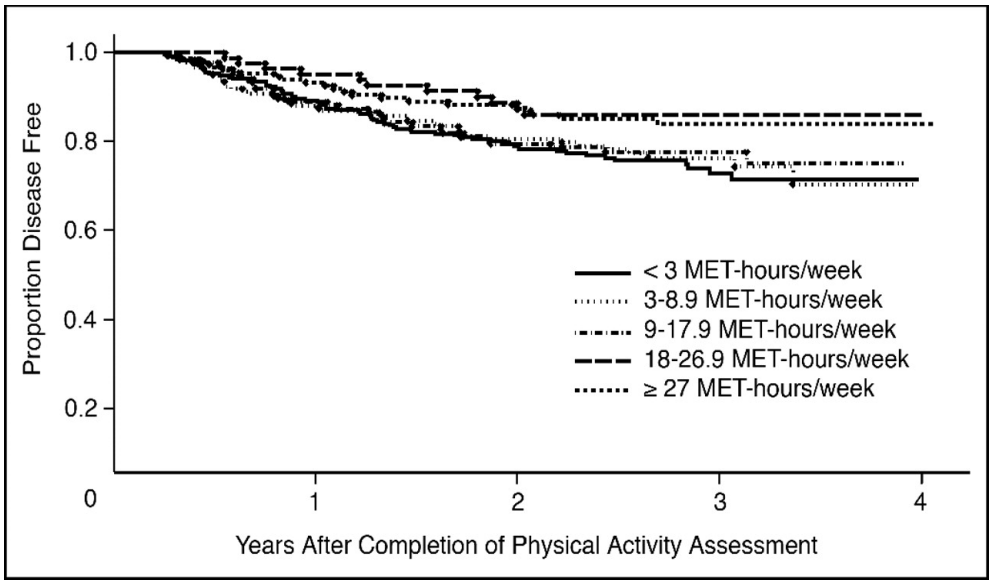

Figure 1.5 Disease free survival following colorectal cancer resection increases with increased reported physical activity (Jeffrey A. Meyerhardt et al. JCO 2006;24:3535-3541, ©2006 by American Society of Clinical Oncology)

1.8 Timing of colorectal cancer surgery in the UK

One of the challenges in improving the fitness of patients before cancer surgery is the limited time frame available. NHS providers are expected to offer first definitive treatment within 31 days from the decision to treat a cancer and 62 days from urgent referral by the general practitioner (Figure 1.6).

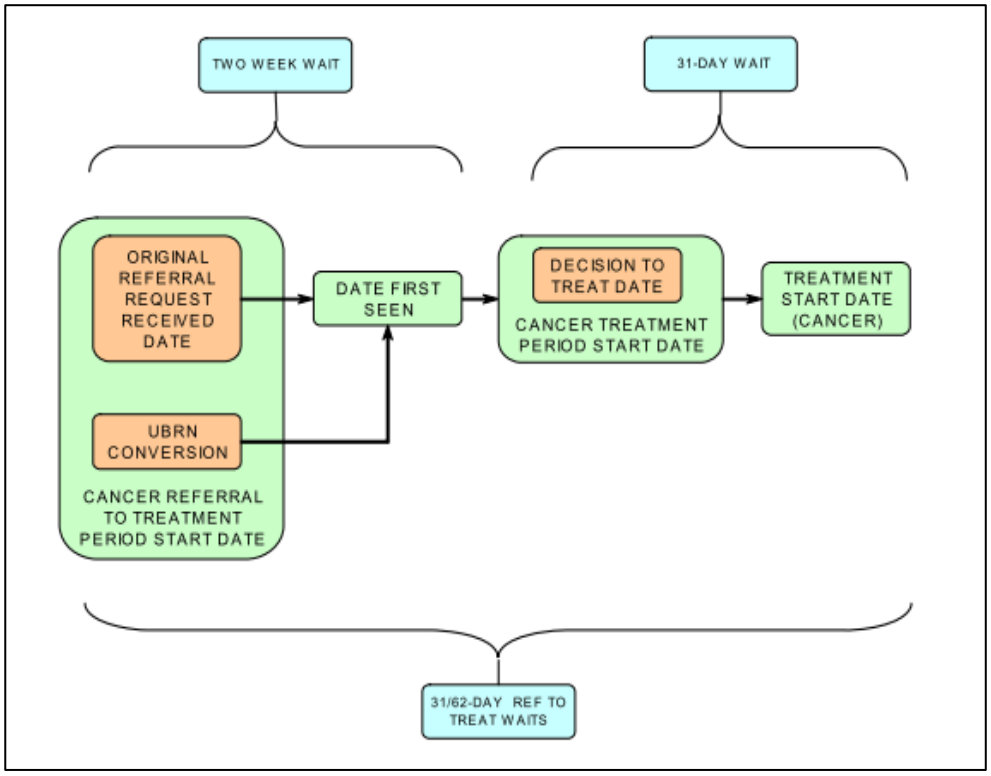

Figure 1.6 UK National Health Service timeline for urgent referrals from general practitioners for suspected cancer (Cancer Waiting Times: A Guide. National Cancer Action Team. http://systems.hscic.gov.uk/ssd/cancerwaiting/cwtguide7-0.pdf. Accessed April 2016)

Many exercise programmes require a longer time frame than this to show improvement, previously reported exercise training programmes in preoperative colorectal cancer patients have lasted between 25 and 186 days (Boereboom et al., 2016). However, any exercise training programme intended to improve the fitness of cancer patients must not delay their potentially curative treatment and so must be feasible, effective and acceptable within this 31 day time frame

(National Cancer Action Team & National Cancer Intelligence Network, 2007).

1.9 Physiological adaptations to exercise

As outlined in the previous sections we have long known the benefits of exercise, Marcus Cicero, in 65 BC, reportedly said "It is exercise alone that supports the spirits and keeps the mind in vigor." Robust scientific research into the health benefits of exercise started in the 1940's (Morris et al., 1953). More recent evidence has supported the use of exercise in cancer patients (Dunne et al., 2016; Tew et al., 2014; West, 2014). However, despite this wealth of supporting literature, the nature of the physiological changes that occur with exercise are multifactorial and in some cases debatable. A detailed review of the physiological changes occurring in response to exercise is outside the remit of this thesis. It must also be noted that the responses to exercise training vary greatly between resistance and endurance training programmes and also between individuals (National Center for Chronic Disease Prevention and Health Promotion CDC, 1999). A summary of the physiological adaptations occurring with different types of exercise is shown below (Table 1.1).

	EET	**RET**	**HIT**
Cardiovascular adaptations			
Cardiac muscle hypertrophy	✔✔ §	✔ §	✔✔***
Increased stroke volume	✔✔ §	✗ +	✔✔¶
Reduced resting heart rate	✔✔ §	✔ ⌫	✔✔⌘
Increased cardiac output at near maximal work rates	✔✔ §	✗ +	✔✔¶
Increased plasma volume	✔✔ §	✗*	?
Improved autonomic tone	✔✔ §	✗ ⇧	?
Decreased resting systolic and diastolic blood pressure	✔✔ §	✗ ⌫	✔✔⌘
Respiratory adaptations			
Increased maximal oxygen uptake	✔✔ §	✗ §	✔✔⌘
Increased ventilation (tidal volume and respiratory rate)	✔✔ §	✔§	✔✔§
Musculoskeletal adaptations			
Increased muscle hypertrophy	✗ § (slow twitch fibres)	✔✔ § (fast twitch fibres)	✔ ⓘ (fast twitch fibres)
Increased bone mass	✔≙	✔✔ ≙	?
Metabolic adaptations			
Aerobic metabolic pathway up-regulation	✔✔ §	✗ §	✔✔°
Anaerobic metabolic pathway up-regulation	✗ §	✔ §	✔**
Increased oxidative capacity of muscle	✔✔ °	✗ §	✔✔°
Improved glucose and insulin sensitivity	✔✔⋆	✔∞	✔⋆

Table 1.1 Comparison of physiological changes with different exercise modalities. EET endurance exercise training, RET resistance exercise training, HIT high intensity interval training

✔ small effect, ✔✔ large effect, ✗ no effect, ? not well studied

§(McArdle, Katch, & Katch, 1996), ¶(Fontana, Betschon, Boutellier, & Toigo, 2011), +(Stohr et al., 2017), ⌘ (R. B. Batacan, Duncan, Dalbo, Tucker, & Fenning, 2017), ⌫ (Morra et al., 2014), ⇧(Collier et al., 2009), ⓘ (Laughlin & Roseguini, 2008), ⏏ (Russo, 2009), °(Burgomaster et al., 2008), ⋆(McGarrah, Slentz, & Kraus, 2016) , ∞ (Tresierras & Balady, 2009), *(Collins, Hill, Cureton, & DeMello, 1986), **(Macdougall et al., 1998), ***(Saadatnia, Ebrahim, & Rashidlamir, 2016)

1.10 Exercise modalities

1.10.1 Resistance exercise training

Resistance exercise training (RET) programs involve moving or maintaining an external load (Fleck & Kraemer, 2014). There are three common types of RET: isometric, isotonic and isokinetic. Negating the need for specialist equipment, isometric is the most common form of RET, usually comprising both the eccentric (lengthening) and concentric (shortening) contraction phases (although these phases can be isolated and performed independently with appropriate equipment (American College of Sports Medicine, 2009)). RET has been used with good effect to improve many facets of health most notably muscle strength and body composition (muscle mass). Independent of age, RET increases strength and improves QoL (Benton & Schlairet, 2012). Specifically in the elderly, RET can

be used to minimise the progression of, or reverse both sarcopenia and dynapenia (the age-associated losses in muscle mass and function, respectively (Mitchell et al., 2012)), in addition to reducing fat mass (Geirsdottir et al., 2012; Treuth & Ryan, 1994) and preventing falls and subsequent fractures (Carter, 2001).

RET is not usually implemented with a view to increase maximal oxygen uptake or improve lipid profiles (Hurley & Roth, 2000), although it has been shown that leg-based RET increased VO_2 max as measured on a stationary leg, but not arm, cycle ergometer, suggesting this increase is due to the peripheral and not central adaptations that combine to elicit increases in cardiorespiratory performance (Frontera, 1990).

RET is more commonly used to improve muscle strength (Folland & Williams, 2007) and cause muscle fibre hypertrophy (Fry, 2004).

A major limitation of strength training programmes, in addition to the lack of evidence for improvements in cardiorespiratory fitness, is that they are often longterm programmes lasting up to 24 months and are therefore unsuitable as a preoperative tool in CRCa patients. Emerging evidence has however shown that physiological adaptation to RET does predominate in the early phases of these exercise programmes (weeks 0-3 (Brook

et al., 2016)), so although RET remains unsuitable as a sole means of improving preoperative fitness in CRCa patients, it may have potential to work alongside a training method which is known to improve cardiorespiratory fitness.

1.10.2 Endurance exercise training

Endurance exercise training (EET) aims to improve the cardiac and respiratory responses to exercise by involving large muscle groups in dynamic activities that result in substantial increased heart rate and energy expenditure (Howley, 2001). Swimming, cycling, rowing and running are typical activities used to perform EET. As with high intensity RET (Kumar et al., 2009) it has been shown that, although older people start from a lower baseline, they get similar absolute increases in VO_2 with EET compared to younger people (Meredith et al., 1989). Makrides et al, showed a 38% increase (1.60 +/- 0.073 to 2.21 +/- 0.073 (SE) l/min) in VO_2 peak in a group of 60-70 year olds, over a period of 12 weeks, greater than the 29% increase (2.54 +/- 0.141 to 3.26 +/- 0.181 l/min) in the young subjects (20-30 years).

In addition to improvement in VO_2 max, EET programmes lasting 12-24 weeks have consistently elicited reductions in

blood pressure, cardiovascular risk factors (Cornelissen, 2009) and exercise capacity (e.g. in patients with chronic pulmonary obstructive disease (COPD) an EET group showed a 33.6 ± 20.6 minute improvement in endurance cycling test at 70% maximum power output compared to a 8.3 ± 15.9 minute increase in a RET trained group ($p<0.001$) (Ortega et al., 2002)).

As with RET the benefits of EET are well documented and accepted, however again similarly to RET, EET often takes several months to show benefit, especially in older people. A meta-analysis has shown a 16% improvement in VO_2 peak with ETT in cohorts of over 60 years in age, the improvement was greater if the training programmes were over 20 weeks duration (Huang, 2005).

1.10.3 High intensity interval training

One relatively recently 're-discovered' alternative to RET and EET is high intensity interval training (HIT; also referred to as HIIT). Commonplace in elite sport settings, HIT is characterised by short bursts of high effort cardiovascular exercise interspersed with periods rest or low effort exercise. A precise, global definition of HIT is difficult to agree as many

studies vary the intensity and duration of the intervals so for purpose of this thesis the specific details of exercise regimes have been included where possible. HIT has been shown to improve time trial performance, peak power output and VO_2 peak in already highly trained endurance cyclists (Billat, 2001; Laursen, 2005; Weston, 1997). A recent meta-analysis has shown both short-term (<12 weeks) and long-term HIT improves VO_2 max in obese and normal weight populations and improves a variety of other markers of cardiometabolic health in the obese group (Batacan, 2017).

Traditional HIT involving Wingate-type exercise is characterised by 30 second intervals of supramaximal exercise on a cycle ergometer against a constant resistance (Bar-Or, 1987). This, very demanding training regime, has been deemed not to be either safe, tolerable or appealing for some people without substantive training pedigree (Biddle & Batterham, 2015; Gibala et al., 2012). In the 1980's Ready et al., first assessed a programme of reduced exertion HIT which involved 10 intervals of one minute at 110% VO_2 max on cycle ergometers. They found that this format of HIT could elicit significant improvements in VO_2 max (+7.7%), peak post exercise blood lactate (-62.0%), maximum oxygen debt (+19.8%), and duration of cycling to exhaustion (+47.5%)

(Ready, 1981). This mode of HIT then appeared to become relatively dormant in the scientific literature until the early 2000's when Gibala et al. used the Ready protocol to show significant improvements in time trial performance and peak power output (thus the potent stimulus for improving exercise performance) with low volume HIT (10 intervals of 60 seconds at 100% peak power output) (Little, 2010). Recent work has shown significant improvements in VO_2 peak with HIT intervals set at 110% peak power output compared to no improvement at 80% peak power output. In this study increasing the work to 150% showed no additional benefit in VO_2 peak improvement. This adds further evidence for the benefit of reduced exertion HIT which is more achievable for many study populations (Raleigh et al., 2016).

Much literature has explored the effect of HIT on different physiological (and psychological) parameters in different healthy (young vs. old, for example) and co-morbid clinical subgroups (Ciolac, 2012; Moholdt et al., 2009; Molmen-Hansen et al., 2012; Nytrøen et al., 2012).

Despite a significantly lower training time and exercise volume than government recommended levels of exercise (World Health Organisation, 2010) HIT induces comparable increases in skeletal muscle oxidative capacity and metabolic

adaptations (Burgomaster et al., 2008; Gibala et al., 2012). HIT has also been proven to be significantly more effective in increasing VO_2 max and stroke volume (Bacon, 2013; Helgerud, 2007). Indeed, a systematic review by Milanovic et al. found that HIT improved VO_2 max to a greater extent than endurance training in healthy, young to middle aged adults (Milanović, 2015), although this review did use different constructs of HIT. "HIT" can encompass a variety of exercise modalities, timings and intensities and this makes comparison of effects between different studies difficult. As alluded to above, traditional Wingate based HIT (Bar-Or, 1987) is the most intense form of HIT training and may not be tolerated well by exercise naïve individuals. However, the mode of HIT used by our unit and others (5-7 x 1-min high-intensity bouts with 60-90 sec recovery) has shown to be well tolerated in untrained populations whilst also producing similar metabolic adaptations to Wingate protocols (Hood, 2011).

As previously outlined one of the most consistently cited benefits of HIT (based on 7-10, 1 min intervals) is the time-efficiency of each session. In addition, another major advantage of this form of HIT, especially for clinical populations where time is limited, is that physiological improvements appear to happen in a very short time period.

Figure 1.7 illustrates an example of the amount of time and intensity involved in HIT, Wingate HIT and endurance training.

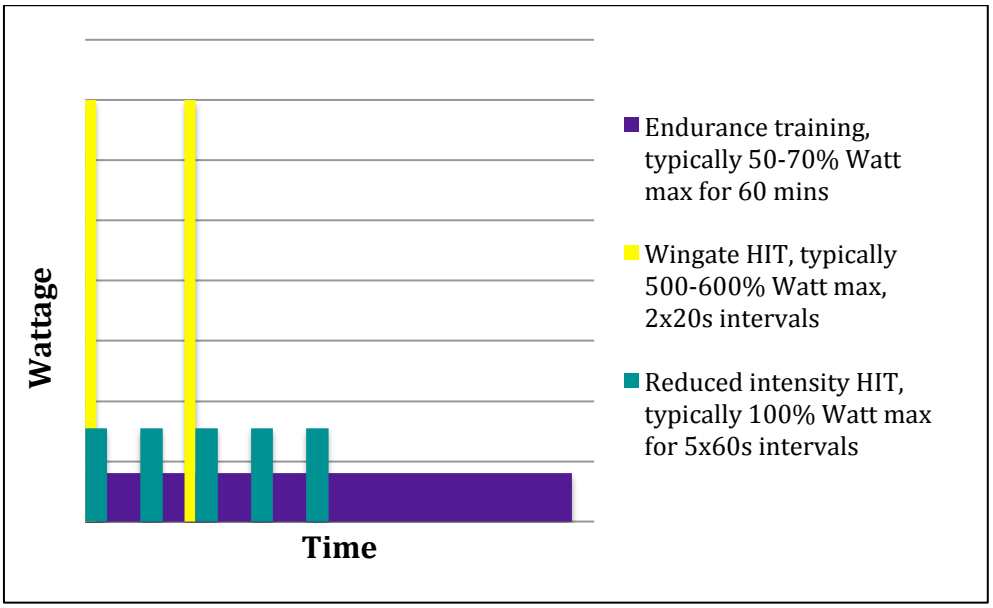

Figure 1.7 Example of time commitment and work intensity comparing typical endurance training, Wingate HIT and reduced intensity HIT protocols

Indeed, studies have shown increases in VO_2 peak after as little as 2 weeks of HIT (Talanian, 2007). Gibala agrees that dramatic improvements in exercise performance are possible after very short HIT regimes. However, when investigating this his group found no improvement in VO_2 max after 2 weeks of HIT. They suggest that peripheral mechanisms i.e. increased muscle oxidative capacity and changes in carbohydrate metabolism (within the muscle) are more important than central adaptations (cardiorespiratory improvements leading

to increased VO_2 max) in the improvement in exercise performance after short term HIT (Gibala et al., 2006).

1.10.4 Mechanisms of improvement due to HIT

The mechanisms that allow HIT to produce significant changes in fitness parameters with limited exercise volume are still being investigated with no consensus yet being reached. Most studies looking at mechanisms of action have recruited young, fit, even athletic, subjects which may preclude their direct translation into clinical cohorts. Allied to difficulties in assessing the effectiveness of HIT *per se* for improving fitness, pinpointing the exact mechanism/s for any improvements is also difficult due to the huge variety in timing, frequency, intensity and duration of HIT regimes. However, both peripheral and central adaptations have been postulated.

1.10.4.1 Peripheral adaptations due to HIT

Peripheral adaptations can be defined as changes that occur within the muscle to improve oxygen utilization when exercising. The exact explanations of these changes are still being investigated although up regulation of enzyme pathways

involved in the production of energy within mitochondria appear to be a unifying theme (Gibala, 2009).

A significant trigger for the improvements due to HIT appear to be the near instant generation of peak power output (Hazell, 2010) with a suggestion that myoglobin can be reloaded with oxygen during the rest intervals of a HIT session and so glycolysis and oxidative phosphorylation during the high intensity intervals can be more efficiently fuelled.

McCartney's early work discussed the repeated attempts to produce maximum power as a stimulus for increased glycolysis and oxidative phosphorylation and the use of alternative energy sources such as free fatty acid oxidation (McCartney et al., 1986).

In 1998 MacDougall noted an increase in the maximal activity of markers of both glycolytic and oxidative enzyme pathways in muscle following HIT (Macdougall et al., 1998) with Burgomaster's work in 2005 supporting this explanation (Burgomaster, 2005). These studies showed an increase in the activity of hexokinase, phosphofructokinase (glycolytic enzymes) and malate dehydrogenase, succinate dehydrogenase and citrate synthase (oxidative enzymes).

Further support for the notion of HIT-induced increases in mitochondrial enzyme capacity was shown by Little et al.,

(Little et al., 2010), showing up regulation of peroxisome proliferator-activated receptor ϒ co-activator 1α (PGC-1α), an important co-activator in coordinating the mitochondrial response (Figure 1.8). This was also shown in a 6 week training study, whereby both EET and HIT (with 3 hours less time commitment per week) increased skeletal mitochondrial protein content, lipid oxidation and protein content of PGC-1α to a similar extent (Burgomaster et al., 2008).

Due to the up regulation of similar enzyme pathways to EET, physiological changes with HIT appear to follow a pattern similar to EET (Gibala & McGee, 2008). However, although traditionally RET is associated with increased muscle mass there is some evidence for increased muscle mass with HIT (Boereboom, 2016; Osawa, 2014), suggesting that HIT may also be able to elicit the health-based and functional improvements more commonly associated with RET.

Recently Little et al. have shown that training intensity primarily regulates increases in mitochondrial respiration and protein content. In their study, groups performed either sprint training (4-10 intervals of 30 seconds at 200% peak power output), HIT (4-7 intervals of 4 minutes at 90% peak power output) or continuous training (20-36 minutes at 65% peak

power output) over 4 weeks. Changes in mitochondrial protein content (PGC-1a, p53, and PHF20) were only seen after the most intensive sprint training, with these changes more strongly associated with changes in mitochondrial respiration than protein content (Granata, 2016).

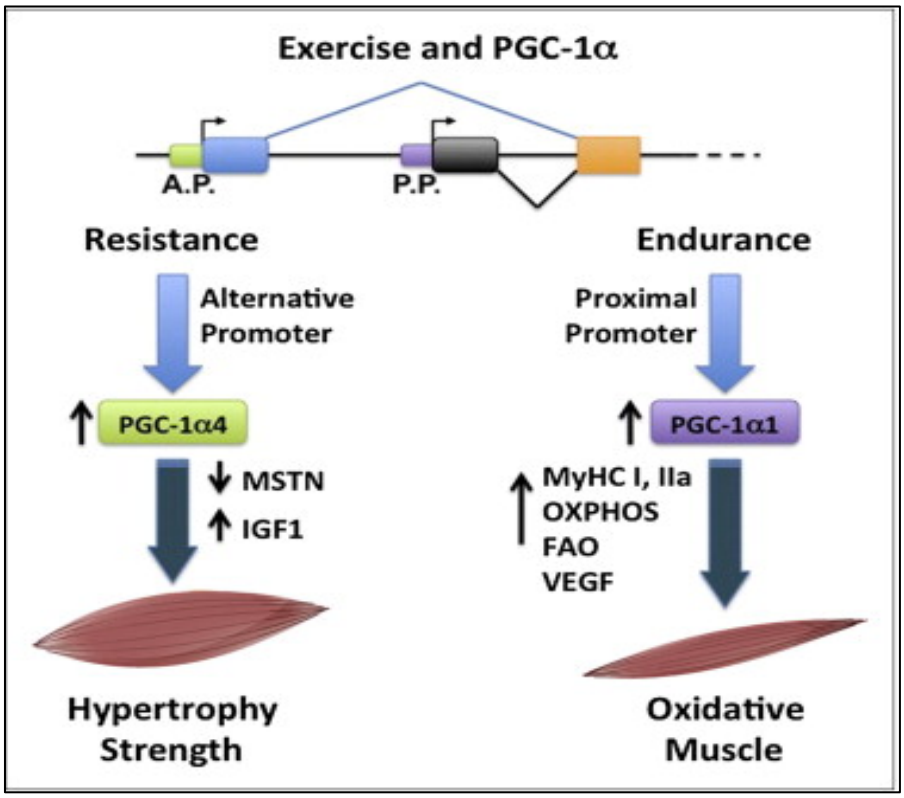

Figure 1.8 Intracellular factors that influence exercise training response

A.P. Alternative promoter, P.P. Proximal promoter, PGC Peroxisome proliferator-activated receptor gamma, MSTN is gene encoding myostatin, IGF insulin like growth factor, MyHC myosin heavy chain, OXPHOS oxidative phosphorylation, FAO fatty acid oxidation, VEGF vascular endothelial growth factor *(www.exercisemed.org/research-blog/what-determines-the-trainin.html. Accessed April 2016*(Ruas et al., 2012) *)*

Adding more complexity to the study of mechanisms for HIT-induced improvements in fitness, trained athletes and recreationally active young people do not show the same changes in oxidative enzyme pathways as older individuals or sedentary young men (Gibala et al., 2006; Laursen & Jenkins, 2002). In these athletically trained groups an increased skeletal muscle buffering capacity is thought to play a more important role in performance improvement (Weston, 1997). High concentration of H^+ ions is an inhibitory environment to the function of enzyme PFK (Spriet, 1995), an improved ability to deal with H^+ ions within the muscle would allow increased activity of PFK and therefore a higher glycolytic yield of ATP and energy for exercise.

Continuing on a cellular level there has been much work done on the effects of exercise and glucose metabolism. Generally both aerobic, resistance and combination exercise training programmes have been shown to improve glycaemic control irrespective of any weight loss due to the exercise (Boulé, 2001; Umpierre et al., 2011). HIT has been shown to have superior benefits at reducing HbA1c (glycated haemoglobin – a measure of blood glucose control over the preceding 8-12 weeks), fasting glucose and insulin resistance when compared to continuous training and control groups (Jelleyman et al.,

2015). The cellular mechanisms responsible for these beneficial changes are still being investigated but much work centres around the improvement in peripheral insulin sensitivity with exercise (Henriksen, 2002). Up regulation of several causative metabolic pathways in the glucose transport system including those affecting the GLUT4 transporter and skeletal muscle glucose uptake following HIT have been shown (Etgen, 1997; Etgen, 1993). Reduction in insulin resistance and improved glycaemic control are known to reduce morbidity and mortality in those with impaired glucose tolerance and type 2 diabetes (Kim, 2013).

1.10.4.2 Central adaptations to HIT

Central adaptations can be defined as changes that affect the delivery of oxygen to exercising muscles (Laursen & Jenkins, 2002) and are commonly associated with changes to the cardiovascular and/or respiratory systems (Gielen, 2010; Mckenzie, 2012).

Documented cardiovascular changes secondary to HIT have included decreased resting heart rate, increased stroke volume, decreased left ventricular ejection time, decreased systolic, diastolic and mean arterial blood pressure and

decreased forearm vascular resistance. These changes have been seen in healthy individuals after 12 weeks training (Heydari, 2013). Other investigated changes include increased left ventricular wall thickness (Pluim, 2000) and increased stroke volume (Rowell, 1993; Vella & Robergs, 2005). Additionally, in a group of patients with established post infarct heart failure, central adaptations to HIT have included improved: left ventricular ejection fraction, stroke volume, mitral annual excursion, ejection velocity and systolic mitral annular velocity, all measured on echocardiogram. These improvements were specific to HIT and not seen in the moderate continuous training arm of the study who undertook 47 minutes of walking at 70-75% peak heart rate three times a week for 12 weeks (Wisløff, 2007). All of these adaptations are suggestive of improved cardiac response to the increased demands imposed by HIT.

Exploring a different component of the cardiovascular system, Rakobowchuk et al. examined changes in vascular structure and function with HIT and found a significant improvement in popliteal artery endothelial function and distensibility but no change in carotid artery distensibility. This was explained by local alterations in vascular wall structure, and/or alterations in vascular tone although changes in basal (non-stimulated)

sympathetic tone was also thought to have influenced the findings (Rakobowchuk et al., 2008). In a systematic review of 7 papers exploring the effects of HIT vs. moderate intensity continuous training Ramos et al. concluded that flow mediated dilation (FMD) of the brachial artery was better improved with HIT compared to moderate intensity continuous exercise (Ramos, 2015). FMD is an index of vascular endothelial function. Typically a blood pressure cuff is inflated to a supra-systolic pressure and then the artery diameter monitored for changes in size when the blood flow returns using doppler ultrasound. The shear forces from the returning blood flow induce production of the vasodilating substance nitric oxide from the vascular endothelium (Harris, 2010). FMD has been shown to correlate well with invasive measures of coronary artery endothelial function and gives an insight into the state of atheroma formation within vessels (Raitakari & Celermajer, 2000).

Likely allied to improvements in vascular function, improvements in blood pressure (Bp) have been seen with HIT (Kessler, 2012). Indeed it is likely that central adaptations explain a 9% drop in systolic blood pressure (SBp) after 6 weeks HIT in 60-70 year olds (Adamson & Lorimer, 2014).

Whilst neither a truly central or peripheral adaptation to HIT change in plasma volume has been postulated as a mechanism behind the adaptations that are seen during this type of exercise. The theory is that HIT causes a sudden accumulation of metabolites in the intramyocellular compartment, this induces an osmotic shift of water out of the vascular compartment, dropping the plasma volume. The extra fluid load on the myocytes (osmotic swelling) has been thought to be responsible for cellular remodelling and perhaps the adaptations seen with HIT (R. S. Metcalfe et al., 2015).

1.11 HIT in specific populations

1.11.1 HIT as a performance enhancing training tool

As outlined in previous sections HIT has been used to enhance physical performance in athletic populations for a number of years (Laursen, 2010). Indeed, the review article by Laursen et al. suggested that in trained athletes improvements in endurance performance can only be achieved through HIT (Laursen & Jenkins, 2002); a statement on which consensus has not been reached. His later papers suggest that a polarized training programme involving both HIT (10-15% training time) and low intensity, high volume training (85 –

90% training time) maybe the optimum regime to improve performance in intense exercise athletes (Laursen, 2010). In young, healthy participants HIT can also achieve significant improvements in VO_2 max, O_2 pulse and power output, all of which can be achieved with less onerous time commitment (than traditional EET) in short time periods (6 HIT sessions over 2-3 weeks) (Astorino, 2012).

1.11.2 HIT in clinical populations

HIT has shown benefit for clinical populations. For example, Ciolac et al. showed that HIT had superior benefits over continuous moderate intensity training in both preventing and controlling hypertension in people at familial risk of, or people diagnosed with, hypertension (Ciolac, 2012). In a meta-analysis of 472 patients with coronary artery disease HIT showed a greater improvement in VO_2 peak than continuous moderate intensity exercise (Liou, 2016). HIT has also been shown to better decrease the length of time spent in hyperglycaemic episodes, and the level of postprandial hyperglycaemia in type 2 diabetics when compared to endurance training (Gillen, 2012).

It is not only the immediate results of HIT that have been shown to be more effective than alternative forms of exercise training. Moholdt et al. has shown that HIT not only improves VO_2 peak in patients who have undergone coronary artery bypass grafting, but that the effect lasts much longer than the improvement seen with moderate continuous training (Moholdt et al., 2009).

Some people have questioned the safety of HIT in patient groups and those with significant co-morbidities (Levinger et al., 2015). Reassuringly the risk of significant cardiac event during HIT in those initially presenting with chest pain has been reported as 1 in 10,000 (Myers, 2000). Over and above proving the safety of HIT in those with coronary artery disease Warburton et al. has shown clinical benefit of HIT over continuous training, including reduced incidence of angina and ischaemic ECG changes (Warburton et al., 2005). Likewise Wisloff et al. showed an increase in VO_2 max in elderly (mean age 76 years) heart failure patients after a 12 week HIT programme (Wisløff, 2007).

Studies such as this one have led researchers studying medical conditions, in which exercise has traditionally been discouraged, to look at HIT as a means to improve fitness. Indeed, a Scandinavian study looking at cardiac transplant

recipients from 3 months to 1 year following surgery is currently underway, comparing the effect of 85-95% peak effort HIT intervals with continuous training on change in VO_2 peak (Nytrøen et al., 2016). This group have safely completed HIT studies in this patient cohort in the past (Nytrøen et al., 2012).

In keeping with this work on chronic cardiovascular disease patients, those with chronic obstructive pulmonary disease have also shown similar or greater training benefit from HIT compared with continuous training. Although the exercise intensity was much higher in the HIT group (20 minutes of 30 second intervals at 100% peak work rate vs. 40 minutes continuous at 50% peak work rate, twice a week for 12 weeks), the length of time spent training was significantly less (Vogiatzis, 2002).

Although evidence for HIT in the preoperative CRCa population awaiting curative resection is limited, HIT has been used in other preoperative groups. Dunne et al. used HIT in those awaiting liver resection for CRCa metastases (median age 62 years) and demonstrated a 2ml/kg/min increase in VO_2 peak after 4 weeks of 3 sessions per week (Dunne et al., 2016).

Taken together, these studies and associated reviews (Batacan et al., 2017; De Brandt et al., 2016; Xie, Yan, Cai, & Li, 2017)

document both the benefit and safety of HIT in multiple common chronic diseases.

1.11.3 HIT in the elderly

To date there have been few studies on Wingate-style HIT (with short bursts of supramaximal exercise intensity) in the elderly (defined as over 65 years for the purpose of this thesis) and those published have usually been of a longer duration than would be available to older people preparing for surgery. In healthy, older adults (63±5 years) Ahmaidi et al., showed an increase of 26% in AT and 20% in VO_2 max after 12 weeks of HIT using a training intensity set just below the anaerobic threshold (Ahmaidi et al., 1998). Similarly, Pichot et al., showed an increase of 18% in VO_2 max after 14 weeks of HIT training at 85% heart rate maximum (Pichot et al., 2005). With 9 weeks of HIT at the 2nd ventilatory threshold Lepretre et al., showed a 15% increase in VO_2 peak (Lepretre et al., 2009). The modalities of these programmes were varied, with differing definitions of intensity, and also differences in repetition number (4 to 9 intervals) and duration (1 to 10 minutes) making them difficult to compare. In a population with known frailty (mean age 83 years) but no specific co-

morbidities, Binder et al., showed significant improvements in VO_2 max using a combination of both EET and HIT, but these changes occurred over a 9 month period (Binder et al., 2002).

More recently Wingate-style HIT studies in the elderly have been explored. In a letter to Journal of the American Geriatrics Society in 2014 Adamson and Lorimer describe an 8% improvement in VO_2 max with 6 second all out sprint cycling intervals (against 7% body weight) over 6 weeks in a group of 65 year olds (Adamson & Lorimer, 2014). As outlined above, the majority of HIT studies in older people have tended to be of lower (yet still significant) work intensity for slightly longer duration (Knowles, 2015). For example, 8 weeks HIT at 85-95% VO_2 max with 7 repetitions of 2 minute intervals in 12 healthy 68 year olds gave a significant increase of 2.7 ml/kg/min VO_2 max (Bruseghini et al., 2015). These studies show that, although emphasis must always be on participant safety, it is important and possible to prescribe HIT at an exercise intensity that will deliver maximum gains in the shortest time frame possible.

1.11.4 HIT in colorectal cancer patients

As outlined in previous sections, HIT has been used in many varied clinical groups and in the elderly with a view to improving different aspects of physical function and fitness, but there has been little work on HIT in preoperative CRCa patients in whom surgery is their primary treatment. This may be due to the limited time available from 'decision to treat' to surgery. Reviews have suggested that individually prescribed and supervised HIT may be a safe and effective means of exercise therapy preoperatively (Weston, 2016). However, to our knowledge there is no published data available on short duration HIT, that complies with national cancer management timelines, in a solely preoperative CRCa patient group.

1.12 Thesis synopsis

CRCa is a common condition that can only be cured with surgery. Surgical intervention in the population where CRCa is most prevalent carries significant risk of morbidity and death. HIT is an exciting novel strategy with the potential to improve the physical fitness of CRCa patients, reducing the risks of surgery and improving clinical outcome for these patients.

This thesis explores the possibility of using a HIT program, compliant with national cancer management timelines, to

improve the fitness of patients prior to their cancer surgery. The first study investigates whether preoperative fitness is seen as an important issue by the UK colorectal cancer surgical community. The second study investigates feasibility and efficacy of HIT in a healthy population, age-matched to those commonly diagnosed with CRCa, and the third study evaluates the same HIT programme in a group of preoperative CRCa patients.

1.13 **Thesis aims**

The aims of this work are to:

- Review the current published research literature investigating exercise in preoperative colorectal cancer patients (Systematic review - Chapter 2).

- Investigate the perceived need for exercise programmes in the preoperative period for CRCa patients, and the willingness of expert clinicians treating this group to engage in exercise as a treatment adjunct (Delphi study - Chapter 3).

- Investigate the efficacy and feasibility of a 31 day HIT exercise programme, compliant with national cancer management timelines, to improve the cardiorespiratory fitness of older, healthy volunteers age-matched to those most commonly presenting for curative CRCa surgery (Healthy volunteer study – Chapter 4).

- Investigate the efficacy and feasibility of a HIT exercise programme, to improve the cardiorespiratory fitness of preoperative CRCa patients within 31 days before curative CRCa surgery (Cancer patient study – Chapter 5).

Taken together, these aims will determine the effectiveness and feasibility of HIT in preoperative CRCa patients (Figure 1.9).

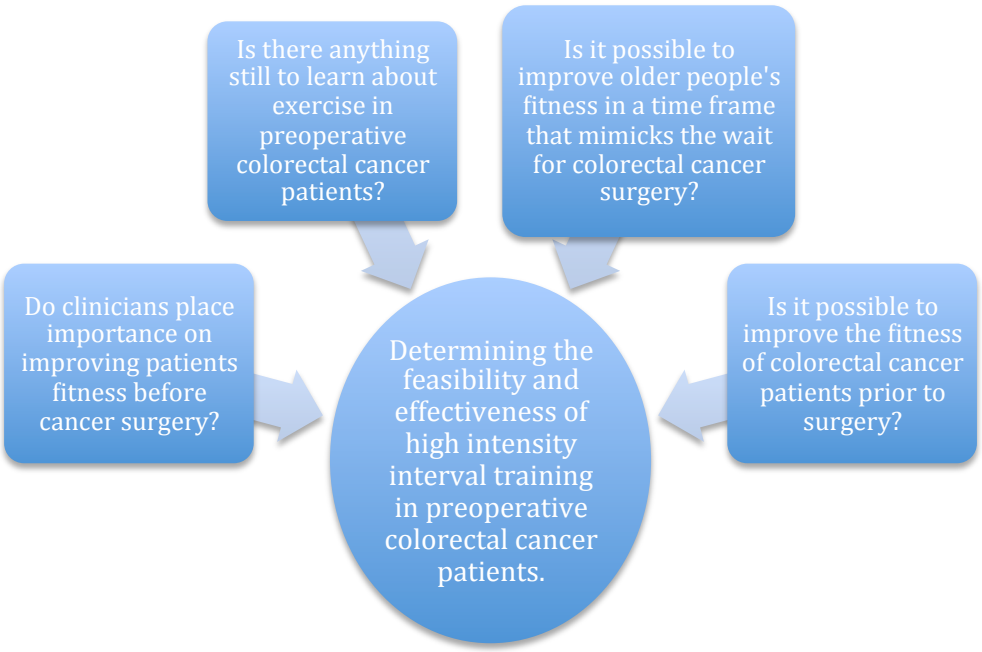

Figure 1.9 Thesis aims

2 Systematic review of preoperative exercise in colorectal cancer patients

2.1 Introduction

As described above there are many points along the cancer pathway when physical fitness plays an important role, from primary prevention to prolonged survivorship. A body of population-based, epidemiological research concludes that increases in exercise are associated with a reduction in the primary risk of developing CRCa (Harriss et al., 2007) and can improve survival after colorectal cancer treatment (Haydon et al., 2006).

However, in contrast to the wealth of research literature indicating that exercise following cancer treatment confers a reduction in mortality (Courneya et al., 2008), decreased risk of disease recurrence and improved quality of life (Denlinger & Engstrom, 2011), currently there is only limited evidence supporting the benefit of exercise during the active phase of surgical and oncological management of CRCa (Kuan-Yin et al., 2014).

Again, as mentioned previously there are time limits imposed on the management of cancer in the UK. This limits the time available to improve cardiorespiratory fitness preoperatively

(treatment for cancer must start within 31 days of the decision to treat (National Cancer Action Team & National Cancer Intelligence Network, 2007)). The time pressure experienced in the UK and internationally may well contribute to the lack of quality research and subsequent evidence base supporting the use of exercise treatments in the period between decision to treat and surgery for CRCa. Given however, that recent work has shown that those with improved cardiorespiratory fitness have lower rates of mortality and complications following CRCa surgery (West, Lythgoe et al., 2014; West, Parry et al., 2014), this time period provides an opportunity to improve cardiorespiratory fitness before surgery, with the possibility of reducing perioperative risk and improving postoperative outcome.

In 2014, a meta-analysis evaluated the effect of exercise training in CRCa patients (Cramer, 2014) through all stages of the treatment pathway. This meta-analysis included studies published until the end of 2012 and found only three RCTs for inclusion, all reporting effects of training only in patients who had completed CRCa treatment. They found no evidence of exercise improving short-term quality of life or fatigue. There was strong evidence for short-term improvements of physical fitness after aerobic exercise compared with controls. Given

that no studies reported survival rates or safety data and all evidence was weak they did not feel that they could recommend that exercise interventions become part of routine practice. Since this review, there have been several investigations of exercise training programmes in the preoperative cancer patient. Consequently there is a need to revisit the evidence supporting the use of preoperative exercise interventions in this patient group.

Given emerging data regarding exercise prehabilitation and the lack of definitive, large-scale, high quality research in this area, this review aims to examine the current evidence base for preoperative exercise in CRCa patients.

2.2 **Methods**

2.2.1 Study design and participants

This review was registered on the PROSPERO database prior to the literature search (registration number CRD42014015556). PRISMA guidelines for systematic reviews were followed (Moher, 2009). Studies were included if they were randomised or cohort studies involving any type of exercise in the preoperative period in adults awaiting curative resection for their primary colorectal cancer. Studies with control groups

who did no exercise and those with pre and post exercise intervention measurements but no control group were included. Exclusion criteria included studies investigating solely respiratory muscle training, postoperative exercise and studies investigating exercise prior to palliative surgery.

2.2.2 Systematic literature search

A clinical librarian performed the literature search. Articles were searched without language or date restriction (published up until 12th November 2014). MEDLINE, EMBASE, CINAHL, AMED and BNI databases were searched. The Cochrane Library was searched for evidence based reviews and Dynamed, PEMSoft and NICE Guidance for clinical guidelines. Clinicaltrials.gov website was searched for relevant unpublished studies. Reference lists of the identified primary studies (including previous review articles) were hand-searched for further studies.

Medical subject headings (MeSH) were used including the terms 'NEOPLASMS', 'COLORECTAL NEOPLASMS', 'COLORECTAL SURGERY', 'PREOPERATIVE CARE' and 'EXERCISE'. Free-text words included 'exercise' and 'pre AND operative'. Abstracts of identified studies were screened by

two researchers independently. Full text versions of potentially eligible studies were retrieved. These were assessed independently by two researchers against the inclusion/exclusion criteria and agreement was reached by consensus.

2.2.3 Outcomes

Outcomes included postoperative mortality, postoperative length of hospital stay, postoperative complications, CPET variables assessing cardiorespiratory fitness, markers of functional fitness, quality of life measures, tumour recurrence, changes in tumour biology and biochemical inflammatory markers.

2.2.4 Data extraction

Data regarding study characteristics were extracted onto an electronic database. Risk of bias was assessed independently by two researchers using the Newcastle Ottawa Quality Assessment scale for cohort studies (Wells et al., 2000) and the Cochrane tool for assessing risk of bias (Higgins et al., 2011) for randomised controlled trials. Discrepancies were resolved by consensus.

2.2.5 Data synthesis

Due to significant clinical heterogeneity in the type of exercise interventions, meta-analysis was deemed inappropriate. There was heterogeneity in the nature of the colorectal pathology, additional aspects of prehabilitation (e.g. diet modification), control group interventions and duration of exercise training performed.

2.3 **Results**

2.3.1 Description of included and excluded studies

Nine studies were identified and underwent full text review (Burke et al., 2013; Carli et al., 2010; Dronkers et al., 2010; Gillis, 2014; Kim et al., 2009; Li et al., 2013; Mayo et al., 2011; Timmerman et al., 2011; West, 2014). One hundred and twenty two studies were identified from the initial literature search and twenty one from hand-searching the study references and through other sources. No further studies were identified from searching clinical trial databases for unpublished studies.

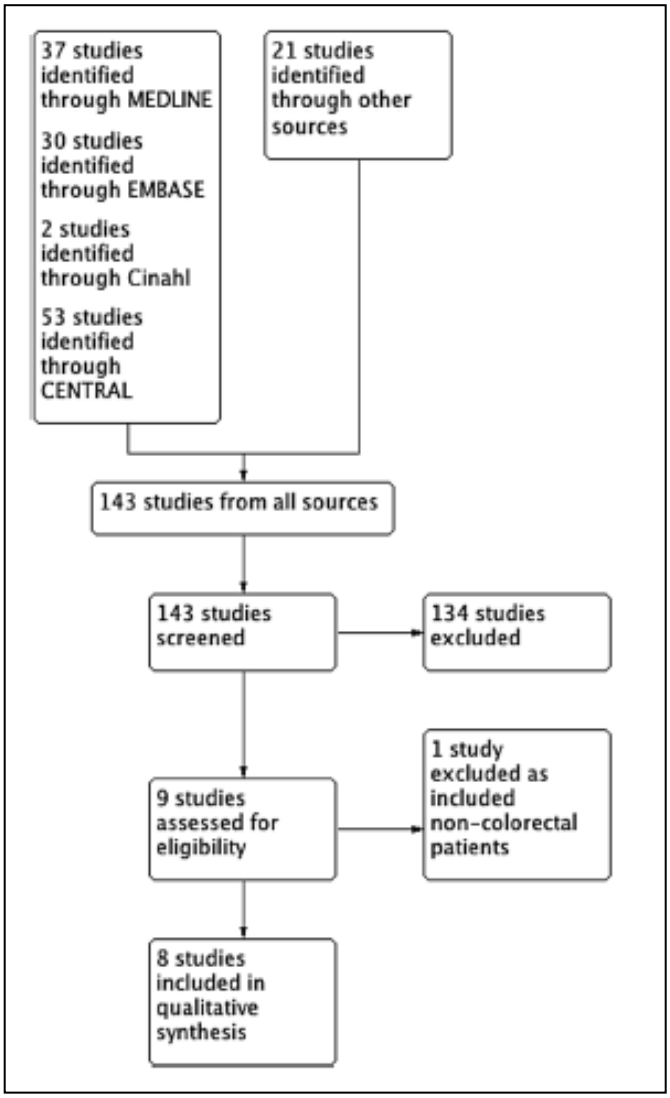

Figure 2.1 PRISMA flowchart of included and excluded studies in the systematic review

One hundred and thirty four studies were excluded as they were duplicate publications or did not adhere to inclusion criteria. Nine studies underwent full text review and one of these studies was excluded as it included non-colorectal cancer patients (Timmerman et al., 2011). Therefore, eight studies were included in the qualitative synthesis.

Information on the characteristics of the included studies is shown below (Table 2.1). The majority of the current work on exercise in preoperative colorectal cancer patients has been undertaken by groups at McGill University in Canada and between Aintree and Southampton in the UK and has been published in the last 5 years. Mayo et al. (Mayo et al., 2011) was a data re-analysis of Carli et al. (Carli et al., 2010). Burke et al. (Burke et al., 2013) used a subsection of patients enrolled in the West study (West, 2014).

Author	**Gillis *et al.* 2014**	**Burke *et al.* 2013**	**Li *et al.* 2013**
Country	Canada	UK	Canada
Study design	RCT	Cohort	Cohort
Sample size	77	10	87
Gender	48M: 29F	3M: 7F	51M: 36F
Mean age (years)	66	58	67
Pathology	Non-metastatic colorectal cancer	Locally advanced rectal cancer, completed NACRT	Non-metastatic colorectal cancer
Intervention	4 weeks preoperative exercise +8 weeks post-operative exercise (at home, 3*week, 50min session, resistance and aerobic (walk, jog, cycle, swim)) vs. 8 weeks post-operative exercise only	Cycle interval training, in-hospital, 3*week, 30min sessions	Aerobic exercise 3*week (walk/aerobic exercise machine), 30min sessions, resistance exercises, at home
Duration of exercise	25 days	6 weeks	33 days
Additional intervention	Whey protein, psychological support for anxiety	Nil	Whey protein, psychological support for anxiety
Adherence	78% in preoperative group	98%	45%
Primary outcomes	Functional walking capacity, 6MWT@ 8 weeks post-operatively	Lived experience of QoL @preoperative compared to baseline	Function walking capacity, 6MWT@ 8 weeks post-operatively
Secondary outcomes	Self reported activity, QoL, anxiety, depression, complications	Nil	Self reported activity, QoL, complications

Author	**Mayo *et al.* 2011**	**Kim *et al.* 2009**	**West *et al.* 2015**
Country	Canada	Canada	UK
Study design	RCT	RCT	Non randomised interventional
Sample size	133	21	35
Gender	65M: 68F	13M: 8F	23M: 12F
Mean age (years)	61	60	68
Pathology	Non-metastatic colorectal cancer or benign colorectal pathology	Non-metastatic colorectal cancer or benign colorectal pathology	Locally advanced, resectable rectal cancer, completed NACRT
Intervention	Bike/strength group - At home, 30min daily at 50% maximum heart rate on bike (increasing) plus 15min weights 3*week. Walk/breathing group- 30min walking daily, 5min breathing exercises daily	Moderate intensity cycling, 30 min sessions, 7*week, at home	In hospital, 40min interval training on bikes, 3*week
Duration of exercise	38 days	3.8 weeks	6 weeks
Additional intervention	Nil	Nil	Nil
Adherence	16%	74%	96%
Primary outcomes	6MWT	CPET variables, submax. CPET variables, 6MWT	AT
Secondary outcomes	HADS, complications QoL	Nil	Number of steps, VO_2 peak

Author	**Carli *et al.* 2010**	**Dronkers *et al.* 2010**
Country	Canada	Netherlands
Study design	RCT	RCT
Sample size	113	42
Gender	65M: 68F	35M: 7F
Mean age (years)	61	70
Pathology	Non-metastatic colorectal cancer or benign colorectal pathology	Colon cancer
Intervention	Bike/strength group - At home, 30min daily at 50% maximum heart rate on bike (increasing) plus 15min weights 3*week. Walk/breathing group- 30min walking daily, 5min breathing exercises daily	Exercise group- In hospital, 60 min, 2*week, breathing exercises, resistance training, inspiratory muscle training, aerobic exercise (walk/cycle), plus 30min walking a day at home. Control group - home, 30min walking a day and breathing exercises
Duration of exercise	43 days	2.5 weeks
Additional intervention	Nil	Breathing techniques
Adherence	16%	95% in training group
Primary outcomes	6MWT	Inspiratory muscle endurance, derived max. aerobic capacity, strength from chair rise time
Secondary outcomes	HADS, complications	Post-operative complications

Table 2.1 Characteristics of included studies

M Male, F Female, 6MWT six minute walk test, QoL quality of life, HADS Hospital anxiety and depression score, RCT randomised controlled trial, CPET cardiopulmonary exercise test, AT anaerobic threshold, VO_2 peak oxygen uptake

2.3.2 Quality assessment of included studies

All studies were at high risk of bias due to the impracticalities of blinding participants and exercise providers to the exercise interventions (Figure 2.2). Several studies blinded those interpreting the outcomes of the exercise intervention and thus reduced the risk of bias in this regard. Accepting the difficulties in blinding participants, five of the six studies assessed using the Cochrane tool for assessing risk of bias had one or more other domains assessed as at high risk of bias. Both West et al. (West, 2014) and Kim et al. (Kim et al., 2009) had significant baseline differences between the exercise and control groups. In several domains across the studies there was not enough methodological detail to assess risk of bias accurately. Gillis et al. (Gillis et al., 2014) was at low risk of bias (accepting the lack of blinding of the participants).

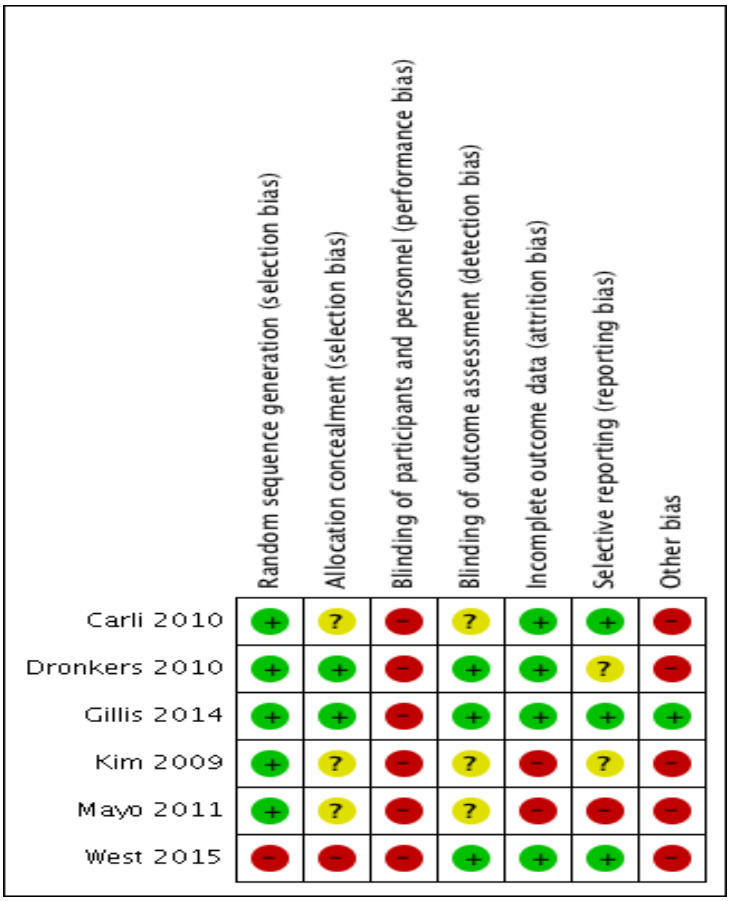

Figure 2.2 Risk of bias of included studies

2.3.3 Description of interventions and compliance

Gillis et al. (Gillis et al., 2014) used a total-body exercise prescription, which consisted of 50 minutes of home-based exercise (unsupervised) for 3 days per week. Exercise involved 20 minutes of any aerobic activity that achieved the target heart rate and 20 minutes of resistance training (using major muscle groups). In addition to exercise, participants were given a dietary intervention (including a protein supplement) and a psychologist instructed participants on relaxation techniques.

Compliance with the intervention was 78%. West et al. (West, 2014) used a supervised in-hospital intervention over a 6 week period with 3 sessions per week. The exercise consisted of 40 minutes on a cycle ergometer with each participant's exercise programme adjusted according to their CPET results. Compliance was high at 96%. Burke et al. (Burke et al., 2013) used the same intervention as West et al. (West, 2014).

Li et al. (Li et al., 2013) asked participants to walk or use any "aerobic" exercise machine for 30 minutes, 3 times per week at half the calculated maximal heart rate in addition to resistance exercises. Participants were also given dietary advice (and protein supplementation) and a session from a psychologist to learn anxiety-reducing techniques. Full compliance with the intervention was 45%. Carli et al. (Carli et al., 2010) used two intervention groups. The first group underwent cycling and strength training. Participants were instructed to exercise at 50% maximal heart rate increasing by 10% each week and weight/resistance training 3 times per week. The other group were encouraged to walk daily for 30 minutes and perform deep breathing exercises. Full compliance was only 16% in the cycle/strengthening group. Mayo et al. (Mayo et al., 2011) used the same intervention as Carli et al. (Carli et al., 2010).

Kim et al. (Kim et al., 2009) used a 4 week aerobic exercise programme which was customised for each participant based on heart rate reserve and rating of perceived exertion (RPE), compliance was 74%. Dronkers et al. (Dronkers et al., 2010) had participants exercise twice per week over a 2-4 week period in an outpatient department. Each session lasted 60 minutes, was supervised and involved a warm up, lower extremity resistance training, inspiratory muscle training, aerobic training, functional activities and a cool down. Participants also followed a home-based programme that involved walking or cycling for 30 minutes per day and inspiratory muscle training. Attendance at the supervised sessions was 97%.

2.3.4 Postoperative outcomes

No studies reported postoperative mortality. However, five studies reported postoperative surgical complications as a secondary outcome. Carli et al. (Carli et al., 2010) recorded Clavien-Dindo grades of postoperative complications (22/56 patients in the bike/strength group and 18/54 patients in the walk/breath group; p=0.56). Gillis et al. (Gillis et al., 2014) reported no difference in 30 day complications between those exercising preoperatively and those exercising postoperatively (12/38 patients in preoperative exercise group and 17/39 in the

postoperative exercise group, p=0.28). Li et al. (Li et al., 2013) also reported no difference in postoperative complications (15/42 of the preoperative exercise group and 20/45 of the control group; p=0.67). Dronkers et al. (Dronkers et al., 2010) reported similar findings of no significant differences in post-operative complications with preoperative exercise (9/22 and 8/20 in the control group experienced a postoperative complication; p=0.65).

In terms of length of stay, Carli et al. (Carli et al., 2010) found a longer mean length of stay in the bike/strengthening group (11.9 days and 6.6 days in the walk/breathing group). Dronkers et al. (Dronkers et al., 2010) found a reduction in length of stay in the preoperative exercise group; however, this was not statistically significant (16.2 days and 21.6 days in the control group; p=0.31). Similarly, Gillis et al. (Gillis et al., 2014) found no difference in median length of stay in the preoperative exercise group (4 days, and 4 days in the postoperative exercise group; p=0.81). In addition, Li et al. (Li et al., 2013) found no difference in median length of stay (4 and 4 days; p=0.71).

2.3.5 Functional outcomes

The primary end point of five of the included studies was improvement in functional exercise capacity based on the 6-minute walk test (6MWT). Gillis et al. (Gillis et al., 2014) demonstrated a 25.2m increase in 6MWT in their prehabilitation group compared to a 16.4m decrease in those who did no preoperative exercise ($p<0.001$). Interestingly, at 8 weeks post-surgery, on average, the prehabilitation group had recovered to their baseline walking times and those who did no preoperative exercise remained below baseline. Li et al. (Li et al., 2013) also showed a significant improvement of 42m in 6MWT with prehabilitation and again this improvement in functional fitness over the control group persisted at 4 ($p=0.01$) and 8 weeks postoperatively ($p<0.01$).

Two studies did not show any improvement in functional fitness with prehabilitation. Kim et al. (Kim et al., 2009) showed no difference between their prehabilitation and control group with respect to improvement in 6MWT, the groups improved by 31m and 27m respectively (p value not given). Carli et al. (Carli et al., 2010) found the bike/strength group had a decrease in 6MWT of 10.6m ($p=0.148$) and the walk/breath group an increase of 8.7m ($p=0.203$), neither of these changes were significant. From the same data, Mayo et al. (Mayo et al., 2011)

looked at the group who completed the prehabilitation phase of the study (52% bike/strength training and 48% walk/breath training). These data showed that 33% of the prehabilitation group improved their 6MWT regardless of their exercise regime, 38% did not change and 29% decreased their 6MWT. Unsurprisingly, those who deteriorated in the prehabilitation phase had significantly lower postoperative 6MWT compared to their baseline.

2.3.6 Cardiorespiratory physiology outcomes

Two studies reported cardiopulmonary exercise test variables e.g. sub-maximal oxygen uptake (VO_2), anaerobic threshold (AT) and peak oxygen uptake (VO_2 peak) as their primary outcome. Kim et al. (Kim et al., 2009) reported a significant reduction of 2ml/kg/min (13%, $p>0.05$) in submaximal oxygen uptake at a given submaximal workload after prehabilitation using a home based cycling exercise programme in less than 4 weeks. This was explained as an improvement in physiological efficiency at submaximal workloads following training, giving an improved physiological reserve. West et al. (West, 2014) evaluated patients undergoing neoadjuvant chemoradiotherapy (NACRT) for locally advanced rectal tumours and showed a significant decrease in AT (-1.91ml/kg/min, $p<0.001$) and VO_2

peak (-2.52ml/kg/min, p<0.001). The exercise group then regained their cardiorespiratory fitness over a 6 week exercise programme, prior to surgery (AT +2.12ml/kg/min, p<0.001) whilst the control group continued to decline (AT -0.65ml/kg/min, p=0.204). This difference between the groups increased over the following 8 weeks (prior to surgery).

Dronkers et al. (Dronkers et al., 2010) used the Physical Work Capacity 170 algorithm to derive maximum aerobic capacity (VO_2 max) from power output at known heart rates during exercise. They found no change in this measurement following exercise training with a preoperative VO_2 max of 27.6ml/kg/min and 32.9ml/kg/min in the intervention and control groups respectively (p=0.16).

2.3.7 Quality of life outcomes

Burke et al. (Burke et al., 2013) reported quality of life measures as their primary outcome showing qualitative improvements in sense of vitality, positive attitude, social connections and sense of purpose following preoperative exercise training. Hermeneutic (the theory of text/interview interpretation) phenomenological methodology was used in this study to allow focus on patient's personal accounts of the study intervention rather than generic quality of life questionnaires.

Four studies (Carli et al., 2010; Gillis et al., 2014; Li et al., 2013; Mayo et al., 2011) also reported quality of life outcome measures. Gillis et al. (Gillis et al., 2014) found no difference between the prehabilitation and control group in any domains of the Short Form 36 Health Survey (SF-36) (73.5 and 72.6 respectively; adjusted p=0.47) or Hospital Anxiety and Depression Scale (HADS) (in the anxiety domain before surgery, the prehabilitation group and control group scored 5.6 and 5.9 respectively; p=0.33). The exercise group had higher SF-36 scores compared with the control group in Li et al. (Li et al., 2013), although this difference was apparent at baseline and did not change with exercise intervention, e.g. in the general health domain before surgery, the prehabilitation and control groups scored 75 and 69 respectively (p=0.16).

Mayo et al. (Mayo et al., 2011) noted that patients who had an improved 6MWT with preoperative exercise also reported significant improvements in mental health, vitality and self-perceived health. Carli et al. (Carli et al., 2010) showed a significant reduction in HADS depression scores between baseline and surgery in those undergoing bike/strength training (4.0 to 3.2; p=0.05) but not in those in the walk/breath group (3.6 to 3.4; p=0.7).

2.3.8 Other outcomes

There was no investigation into colorectal cancer recurrence in the included studies. Tumour biology in response to preoperative exercise was also not investigated.

2.4 Discussion

This systematic review complements other recently published, more general review papers and meta-analyses on perioperative exercise by focusing solely on preoperative exercise in colorectal cancer patients. The current published evidence is mainly limited to work from three centres. Despite the heterogeneous nature of the exercise interventions used in the included studies, this review demonstrates that it is possible to improve the functional fitness of colorectal cancer patients preoperatively, with an increase in 6MWT of between 4m and 42m in intervention groups compared to controls. To put this in context other studies have quoted a mean preoperative 6MWT of 480 ±90m with acceptable postoperative recovery defined as a 6MWT tests within 20m of this and poor recovery defined as a 6MWT greater than 20m below baseline. In this study the 6MWT was shown to have moderately strong, significant, negative correlation with postoperative length of stay following colorectal cancer resection (Moriello, 2008).

The evidence for the feasibility of objectively improving cardio-respiratory fitness (as shown by increased VO_2 peak or AT) using exercise prior to surgery is thus far limited. The recently published study by West et al. (West, 2014) provides the best available current evidence to support the hypothesis that exercise training can improve objective measures of cardiorespiratory performance. However, their intervention took place over a 6 week period and had significant risk of bias due to lack of adequate randomisation resulting in imbalances in baseline characteristics.

From a clinical perspective, there is no evidence that improvements in physical performance translate into an improvement in postoperative outcomes. However, we believe that current studies are underpowered to adequately detect differences in this outcome. In order to demonstrate a statistically significant reduction of 10% in the absolute incidence of postoperative complications (44% from the rehabilitation only arm of Gillis study), studies would need to recruit around 400 participants with an alpha of 0.05 and a power of 0.80. These data currently do not exist. Moreover, no study reported postoperative mortality as an outcome. Similarly, there is limited evidence to show improvements in

quality of life measures following preoperative exercise in colorectal cancer patients.

These findings are in line with a recent meta-analysis (Cramer et al., 2014), which found evidence of short-term improvements in physical fitness but no associated evidence for improved survival. This meta-analysis included multiple cancer types and exercise interventions at many stages of the treatment pathway. Another review published a year before (O'Doherty, 2013) evaluated exercise prior to surgery and found evidence that preoperative aerobic exercise training was feasible, safe and improved one measure of physical fitness. There was data from only one study to show reduced length of postoperative stay. In contrast to these, a review published in the same year (Santa Mina et al., 2013) evaluated exercise prehabilitation prior to a variety of surgical procedures including orthopaedic joint replacements, cardiac surgery and resections for intra-abdominal and thoracic malignancies. They concluded that there was evidence of reduced length of hospital stay and reduced postoperative complications following preoperative exercise interventions. However, poor methodology and high risk of bias was apparent in the studies they included in their review.

Preoperative exercise is limited by national targets requiring CRCa surgery to be performed within one month (National

Cancer Action Team & National Cancer Intelligence Network, 2007). This limits the time window in which to improve physical fitness. The exercise duration in the studies in this review ranged from 17 to 43 days with only 3 studies providing exercise intervention within the 31 day decision-to-treatment target. Once time for screening and exercise assessment is included it is likely that the only study that could be performed with in the current NHS set up is the protocol described by Dronkers (Dronkers et al., 2010).

Colorectal cancer patients are often over 60 years old at diagnosis (Greenlee, 2001), this has implications for improving physical fitness prior to surgery as patient factors such as lower baseline functional status, co-morbidity (such as ischemic heart disease or osteoarthritis limiting exercise tolerance) and reduced muscle mass may affect their ability to undergo exercise programmes. Although recent research suggests there is consensus among surgeons that even very elderly patients can have their physical fitness improved prior to surgery (Boereboom, 2015), it remains to be seen if such patients can benefit from such interventions. However, nearly all of the included studies in this review had a mean age above 60 years old which maintains the external validity of our findings. Unfortunately, due to clinical heterogeneity in the exercise

programmes included in this review, it is difficult to suggest any specific exercise programme, which has implications for the design of future trials in the area. The lack of any objective data that indicates that preoperative exercise improves clinical outcomes means our review cannot recommend that exercise interventions be introduced into routine clinical practice.

The studies included within this review are highly heterogeneous in terms of exercise interventions studied and compliance with these programmes. This limits the comparisons and makes recommending one programme over another problematic. Gillis et al. (Gillis et al., 2014) used home-based interventions, which have advantages over supervised sessions, as they require less staff resources. However, compliance was only 78% in this study. Kim et al. (Kim et al., 2009) also used a home-based intervention and achieved similar compliance rates (74%). Conversely, West et al. (West, 2014) and Dronkers et al. (Dronkers et al., 2010) used a supervised in-hospital programme that both achieved high compliance rates of 96-97%. Clearly, the effectiveness of any exercise programme is determined by both the effectiveness of the intervention in question and the compliance of participants undergoing the intervention. Therefore, future studies should investigate which

forms of exercise interventions can deliver both improvements in physical fitness and achieve high rates of compliance.

There are several limitations with this review. The heterogeneous nature of the studies with regard to exercise interventions and outcome measures makes direct comparisons and meta-analysis problematic. Some of the domains used to assess internal validity are unclear from the study manuscripts. Therefore, some of the studies may be at a higher risk of bias than is apparent. Many of the underlying studies were at high risk for some domains, especially in regards to imbalances in baseline characteristics; this introduces selection bias, which may cloud interpretation of our results. Although only two of the studies we included were observational, the included interventional studies were mainly at high risk of bias, which would downgrade any evidence derived from these studies. When considering the higher quality evidence, only one randomized study (Gillis et al., 2014) received low risk of bias for most domains (excluding blinding). This study showed improvements in functional outcomes but no differences in post-operative complications. Finally, additional interventions such as dietary supplements may confound interpreting direct benefits from exercise.

In terms of future research studies, these should focus on what type of exercise programmes can achieve improvements in physical fitness within a suitable time period that corresponds to cancer treatment timelines (<31 days in the UK). This will be the major limitation of introducing exercise programmes into clinical practice and future studies should ensure interventions are delivered within this period. Indeed, the study by West et al. (West, 2014) used a 6 week programme, which would be difficult to implement due to these national targets for treatment. In addition, future programmes need to be tolerable to the specific demographic of patients that undergo CRCa surgery (>60 years old) and investigate whether such programmes are suitable and effective for even older cohorts of patients (>75 years old). As previously discussed, an important aspect of whether such programmes will be effective in clinical practice will be overall compliance rates and which interventions can achieve the highest rates of compliance. Results from our review suggest in-hospital programmes may achieve higher rates of compliance.

Ultimately, large randomised controlled trials are required to improve the internal validity of current findings. Although blinding of interventions would be difficult, adequate randomisation, allocation concealment and blinding of outcome

assessment are possible in order to improve internal validity. In addition, studies should report both per-protocol results (to help assess how the exercise intervention can work when adhered to) and intention to treat analysis (as those who are non-compliant are more likely to have poor outcomes). Furthermore, they would need to be adequately powered to ensure they can detect differences in postoperative outcomes. Moreover, future clinical trials need to evaluate clinically relevant outcomes such as postoperative complications and mortality if preoperative exercise interventions are to become standard clinical practice in patients undergoing CRCa resection.

In conclusion, the current evidence on preoperative exercise for colorectal cancer patients is limited by a lack of adequately powered, clinically relevant outcomes, heterogeneous interventions and risk of bias issues in the conduct of the studies published thus far. Whilst there is some evidence that preoperative exercise can improve both measures of physical fitness and functional fitness, there is no evidence that this in turn improves postoperative outcomes.

3 Forming a consensus opinion on exercise prehabilitation in preoperative colorectal cancer patients: a multiphase Delphi study

3.1 Introduction

As described in chapter 1 there is evidence that having a higher VO_2 peak or AT (i.e. being more fit) decreases the risk of postoperative complications and morbidity across several surgical specialities (Chandrabalan et al., 2013; Ross et al., 2016; West, 2014; Wilson et al., 2010). There is also published work showing that exercise prehabilitation in colorectal cancer patients is effective in improving preoperative fitness (West, 2014). However, as alluded to in the previous discussion section (chapter 2.4) there is still no definitive evidence to prove the link that using preoperative exercise to improve preoperative fitness improves postoperative outcomes. Furthermore, there is no consensus within the UK surgical community regarding the benefits of preoperative exercise, which modality of exercise is best, which patient populations would benefit from exercise, the possible risks involved and how to practically deliver exercise

interventions. In the published literature, there is no definitive guidance on preoperative exercise before surgery for CRCa.

Enhanced Recovery After Surgery (ERAS) Society guidelines suggest that increasing exercise preoperatively may be of benefit but gives no detail on amount, type or duration of exercise (Gustafsson et al., 2012). In the general population, there are many published guidelines recommending the amount of exercise to be taken by healthy individuals, but these do not relate specifically to CRCa patients (World Health Organisation, 2010).

If the current belief, that preoperative exercise is an effective way of reducing surgical morbidity, is correct, we must develop a way of accepting exercise into routine surgical preoperative care. Changing routine practice would require the involvement of stakeholders such as consultant colorectal surgeons, among others, in developing these exercise programmes. To facilitate this change the first step would be to review the opinions of these professionals on preoperative exercise. This study aimed to establish a consensus of expert opinion from consultant colorectal surgeons on the role of preoperative exercise training for surgical patients with CRCa.

3.2 Delphi methodology

Delphi methodology is widely used in health care to establish consensus on clinical issues (Wesley, 2009). The Delphi technique is an iterative process rooted in structured and repeated communication of specific statements that are revised and/or rejected according to expert responses to refine opinion on a topic until a pre-agreed level of consensus is reached. An expert panel scores a bank of statements relating to the topic on an agree/disagree Likert scale. Scores are accepted or rejected if consensus level is reached, and scores and remaining statements are recirculated either in original form or with revision of the statements to encourage consensus. The process is repeated for a given number of iterations, or until all statements have been accepted/rejected and consensus established. At the conclusion of a Delphi study, a set of statements agreed upon by an expert panel is produced.

3.3 Materials and methods

3.3.1 Study design

We conducted a three-round electronic Delphi study using email invitations and a web-based survey tool (Bristol Online Surveys,

University of Bristol, http://survey.bris.ac.uk). It was completed between April 2014 and November 2014. The study was granted ethical approval by the University of Nottingham Medical School Ethics Committee (C10042014 SoM MSGEM).

3.3.2 Participants

Practicing consultant colorectal surgeons were recruited by an email invitation. Invitations were sent to surgeons from units spread across the UK and included both those working in teaching hospitals and district general hospitals. Those who registered their interest were sent a participant information sheet. Informed, written consent was obtained from all individual participants included in the study.

3.3.3 Electronic surveys

Via e-mail, participants were invited to score an online survey instrument that considered the nature and form of exercise prehabilitation for colorectal surgery. The survey was organised to consider five broad areas:

- Potential benefits of improved cardiorespiratory performance

- Prehabilitation
- Intended users
- Risk management
- Practical application

Statements were constructed to best reflect a range of pertinent issues and topics. Scoring was based on a five point (strongly agree, agree, neither agree nor disagree, disagree and strongly disagree) Likert scale; free-text boxes enabled participants to make further comment on their scoring and to contextualise their responses.

The survey instrument was scored on three separate occasions with the purpose of establishing consensus upon both general principles and specific aspects of prehabilitation for colorectal cancer surgery. Between scoring rounds, all participants received feedback of whole group responses; this feedback did not identify individual participants or their scores. Following each scoring round, specific statements were revised prior to rescoring to support the process of finding consensus.

Prior to the questionnaires being distributed, a score of 80% (across agree/strongly agree or disagree/strongly disagree categories) was established as a consensus threshold, i.e. where >80% participants agreed, the statement was accepted

to inform prehabilitation programmes; where >80% disagreed the statement was rejected and removed from the process; statements where the 80% threshold was not achieved in either direction were revised and rescored. In each round, participants were given 3 weeks to complete the survey with an e-mail reminder at 2 weeks.

Descriptive statistics for responses were generated after each round of scoring, and free-text comments reviewed to inform the development of subsequent rounds. After each round, statements exceeding the 80% threshold (for agree/disagree) were accepted/rejected and removed from subsequent scoring. When appropriate, remaining statements were revised or reworded in accordance with the free-text comments before being used in the subsequent round. The number of statements decreased in rounds 2 and 3 as statements were accepted or rejected. A final email was sent containing the agreed statements regarding exercise prehabilitation in colorectal cancer surgery patients and those statements on which it was not possible to reach consensus.

3.4 Results

An invitation email was sent to 33 consultant colorectal surgeons. Twenty responded and gave written consent to take part in the study. Responses to the first round survey were received from 19 of 20 participants; these 19 respondents were sent second round surveys. One participant did not receive the second round survey and was withdrawn from the process. Eighteen participants were therefore sent third round surveys, all of whom responded.

The first round survey consisted of 32 statements (Table 3.1). Of these statements, 15 reached the predetermined consensus level of 80% agreement and were accepted as exceeding the consensus threshold. Experts agreed that;

‘‘Improved aerobic performance leads to improved preoperative cardiorespiratory function and better tolerance of the physiological demands of surgery”

‘‘Exercise training could improve aerobic performance’’

‘‘Exercise training could be used to beneficially improve aerobic performance inpatients awaiting elective, laparoscopic, open, malignant and non-malignant surgery” and across all age ranges from 40 to over 80 years old.

In this round of statements it was also agreed that ‘‘Preoperative exercise training programmes would be most useful if capable of improving performance within 31 days” and if they were designed to provide the greatest gain in fitness in the shortest time frame. Ninety-four percent of experts agreed that preoperative exercise training programmes would be supported in their own practice.

The statement ‘‘Preoperative exercise training programmes are likely to risk respiratory complications’’ received greater than 80% disagreement and was removed from the survey. The remaining 16 statements were carried forward into the second-round survey.

Improved aerobic performance leads to…	**Agree n (%)**	**Neither agree or disagree n (%)**	**Disagree n (%)**	**Outcome**
1a. Improved preoperative cardiorespiratory function	19 (100)			**Accept**
1b. Improved preoperative muscle strength	15 (78.9)	3 (15.8)	1 (5.3)	**Round 2**
1c. Improved preoperative mood and wellbeing	15 (78.9)	4 (21.1)		**Round 2**
1d. Better tolerance of the physiological demands of surgery	18 (94.7)	1 (5.3)		**Accept**
1e. Reduced need for intraoperative vasoactive drugs	9 (47.4)	10 (52.6)		**Round 2**
1f. Reduced requirement for HDU/ITU postoperative care	12 (63.2)	7 (36.8)		**Round 2**
1g. Reduced postoperative length of stay in hospital	13 (68.4)	6 (31.6)		**Round 2**
1h. Reduced postoperative time to mobilise	13 (68.5)	6 (31.6)		**Round 2**
2a. Exercise training could improve aerobic performance	19 (100)			**Accept**
2b. Exercise training should be an aspect of preoperative care	15 (79)	3 (15.8)	1 (5.3)	**Round 2**
2c. Preoperative exercise programmes should be designed to improve cardiorespiratory fitness	19 (100)			**Accept**
2d. Preoperative exercise programmes should be designed to improve muscle strength	13 (68.4)	3 (15.8)	3 (15.8)	**Round 2**
2e. Preoperative exercise programmes should be designed to improve balance and flexibility	12 (63.2)	5 (26.3)	2 (10.5)	**Round 2**
Exercise training could be used to beneficially improve aerobic performance in ……	**Agree**	**Neither**	**Disagree**	**Outcome**
3a. Patients awaiting elective (planned) surgery	19 (100)			**Accept**
3b. Patients awaiting urgent (e.g. cancer) surgery	15(79)	2 (10.5)	2 (10.5)	**Round 2**
3c. Patients awaiting emergency surgery	1 (5.3)	4 (21.1)	14 (73.7)	**Round 2**
3d. Patients between 40 and 60 years old awaiting surgery	17 (89.5)	2 (10.5)		**Accept**
3e. Patients between 60 and 80 years old awaiting surgery	18 (94.7)		1 (5.3)	**Accept**
3f. Patients over 80 years old awaiting surgery	17 (89.5)	1 (5.3)	1 (5.3)	**Accept**
3g. Patients awaiting laparoscopic surgery	18 (94.7)		1 (5.3)	**Accept**
3h. Patients awaiting open surgery	18 (94.7)		1 (5.3)	**Accept**
3i. Patients with benign pathology	18 (94.7)		1 (5.3)	**Accept**
3j. Patients with malignant pathology	18 (94.7)		1 (5.3)	**Accept**

Preoperative exercise training programmes are likely to risk……	**Agree**	**Neither**	**Disagree**	**Outcome**
4a. Cardiac complications	3 (15.8)	3 (15.8)	13 (68.4)	**Round 2**
4b. Neurological complications	2 (10.5)	3 (15.8)	14 (73.7)	**Round 2**
4c. Respiratory complications		3 (15.8)	16 (84.2)	**Reject**
4d. Musculoskeletal injuries	7 (36.8)	5 (26.3)	7 (36.8)	**Round 2**
Preoperative exercise training programmes……	**Agree**	**Neither**	**Disagree**	**Outcome**
5a. Would be most useful if they improved aerobic performance within the 31 day time frame for cancer surgery	17 (89.4)	1 (5.3)	1 (5.3)	**Accept**
5b. Should be designed to give the greatest gain in fitness in the shortest time frame	18 (94.8)	1 (5.3)		**Accept**
5c. Are already supported by robust evidence of their benefit	3 (15.8)	14 (73.7)	2 (10.6)	**Round 2**
5e. Are deliverable in your hospital	5 (26.4)	8 (42.1)	6 (31.6)	**Round 2**
5d. Would be supported by you in your own practice	18 (94.8)		1 (5.3)	**Accept**

Table 3.1 First round – Statements and responses, statements highlighted in blue were accepted, those highlighted in green were put into round 2 and those highlighted in tan were rejected

At this point, the responses and free-text comments from the first Delphi round were analysed. This led to five questions from the first round being rephrased in an attempt to add clarity to the statements (Table 3.1 Questions 1e, 2d, 3c, 4a and 4b). Additionally, three of the original first round statements were divided into two parts each and reworded in order to aid clarity (Table 3.1 Questions 1f, 2e and 4d). In total, 19 statements were therefore asked in the second round survey.

In the second round survey, six statements were accepted. The

expert panel agreed that ‘‘Improved aerobic performance leads to improved preoperative muscle strength, mood and wellbeing and a reduced postoperative time to mobilisation and length of stay in hospital”. Consensus was also reached that exercise training should be an aspect of preoperative care, and that exercise training could be used to beneficially improve aerobic performance in patients awaiting urgent (cancer) surgery.

Three statements regarding the risks of preoperative training programmes were rejected by the expert panel;

‘‘Preoperative exercise training programmes are likely to risk cardiac complications if the programme is personally tailored and suitable monitored’’

‘‘Preoperative exercise training programmes are likely to risk neurological complications if the programme is personally tailored and suitable monitored’’

‘‘Preoperative exercise training programmes are likely to risk musculoskeletal injuries if a low impact (e.g. cycling/swimming) programme is personally tailored and suitably monitored’’

Consensus was not reached on the remaining 10 statements (Table 3.2).

Improved aerobic performance leads to…	**Agree**	**Neither**	**Disagree**	**Outcome**
1a. Improved preoperative muscle strength	15 (83.3)	2 (11.1)	1 (5.6)	**Accept**
1b. Improved preoperative mood and wellbeing	15 (83.3)	3 (16.7)		**Accept**
1c. Less need for intraoperative vasoactive drugs due to better cardiac performance	8 (44.5)	9 (50)	1 (5.6)	**Round 3**
1d. Reduced requirement for HDU postoperative care (e.g. Epidurals, CVP lines)	6 (33.4)	9 (50)	3 (16.7)	**Round 3**
1e. Reduced requirement for ITU postoperative care (e.g. Organ support)	9 (50)	8 (44.4)	1 (5.6)	**Round 3**
1f. Reduced postoperative length of stay in hospital	16 (88.9)	2 (11.1)		**Accept**
1g. Reduced postoperative time to mobilise	17 (94.4)	1 (5.6)		**Accept**
	Agree	**Neither**	**Disagree**	**Outcome**
2a. Exercise training should be an aspect of preoperative care	17 (94.5)		1 (5.6)	**Accept**
2b. Preoperative exercise programmes should be designed only to improve muscle strength	1 (5.6)	4 (22.2)	13 (72.3)	**Round 3**
2c. Preoperative exercise programmes should be designed to improve balance	14 (77.8)	2 (11.1)	2 (11.1)	**Round 3**
2d. Preoperative exercise programmes should be designed to improve flexibility	10 (55.6)	4 (22.2)	4 (22.2)	**Round 3**
Exercise training could be used to beneficially improve aerobic performance in ……	**Agree**	**Neither**	**Disagree**	**Outcome**
3a. Patients awaiting urgent (e.g. cancer) surgery	15 (83.4)	2 (11.1)	1 (5.6)	**Accept**
3b. Patients awaiting emergency surgery that will be performed within 24 hours	1 (5.6)	4 (22.2)	13 (72.2)	**Round 3**
Preoperative exercise training programmes are likely to risk……	**Agree**	**Neither**	**Disagree**	**Outcome**
4a. Cardiac complications if the programme is personally tailored and suitable monitored	2 (11.1)	1 (5.6)	15 (83.4)	**Reject**
4b. Neurological complications if the programme is personally tailored and suitably monitored		2 (11.1)	16 (88.9)	**Reject**
4c. Musculoskeletal injuries if a high impact (e.g. running) programme is personally tailored and suitably monitored	6 (33.3)	5 (27.8)	7 (38.9)	**Round 3**
4d. Musculoskeletal injuries if a low impact (e.g. cycling/swimming) programme is personally tailored and		2 (11.1)	16 (88.3)	**Reject**

suitably monitored				
Preoperative exercise training programmes……	**Agree**	**Neither**	**Disagree**	**Outcome**
5a. Are already supported by robust evidence of their benefit	2 (11.1)	12 (66.7)	4 (22.2)	**Round 3**
5b. Are deliverable in your hospital	9 (50)	2 (57.8)	4 (22.2)	**Round 3**

Table 3.2 Second round - Statements and responses, statements highlighted in blue were accepted, those highlighted in green were put into round 3 and those highlighted in tan were rejected

At this point, statements and comments were again reassessed. This resulted in four statements being rephrased for the third round of the survey (Table 3.2 Questions 1c, 2b, 3b and 5b). Additionally, two (Table 3.2 Questions 1d and 1e) were consolidated and reworded into one statement (''Improved aerobic performance leads to reduced length of postoperative stay in high dependency unit (HDU)/intensive therapy unit (ITU)''). This resulted in nine statements being asked of the expert panel in the third round (Table 3.3).

Improved aerobic performance leads to…	**Agree**	**Neither**	**Disagree**	**Outcome**
1a. Reduced need for vasoactive drugs due to better cardiac performance	10 (55.6)	7 (38.9)	1 (5.6)	**No consensus reached**
1b. Reduced length of postoperative stay in HDU/ITU	12 (66.7)	5 (27.8)	1 (5.6)	**No consensus reached**
2a. Preoperative exercise programmes should be designed to improve muscle strength only	0	0	18 (100)	**Reject**
2b. Preoperative exercise programmes should be designed to improve balance	13 (72.3)	5 (27.8)	0	**No consensus reached**
2c. Preoperative exercise programmes should be designed to improve flexibility	9 (50)	6 (33.3)	3 (16.7)	**No consensus reached**
Exercise training could be used to beneficially improve aerobic performance in…	**Agree**	**Neither**	**Disagree**	**Outcome**
3a. Patients awaiting emergency surgery within 24 hours of admission	2 (11.1)	0	16 (88.9)	**Reject**
Preoperative exercise training programmes are likely to risk…	**Agree**	**Neither**	**Disagree**	**Outcome**
4a. Musculoskeletal injuries of a high impact (e.g. running) programme is personally tailored and suitably monitored	2 (11.1)	7 (38.9)	9 (50)	**No consensus reached**
Preoperative exercise training programmes…	**Agree**	**Neither**	**Disagree**	**Outcome**
5a. Are already supported by robust evidence of their benefit	3 (16.7)	11 (61.1)	4 (22.2)	**No consensus reached**
5b. Are deliverable in your hospital e.g. a supervised programme of static cycling	12 (66.7)	3 (16.7)	3 (16.7)	**No consensus reached**

Table 3.3 Third round - Statements and responses, no consensus was reached on statements highlighted in yellow, those highlighted in tan were rejected

During the third round, the following two statements were rejected and seven statements did not reach consensus.

‘‘Preoperative exercise programmes should be designed to improve muscle strength only’’

‘‘Exercise training could be used to beneficially improve aerobic

performance in patients awaiting emergency surgery within 24 hours of admission''

In total during the Delphi process, a total of 21 statements achieved the consensus agreement of the expert panel, six statements were rejected by the panel and consensus was not reached on seven statements (Table 3.4).

Statements achieving consensus agreement of the expert group

1. Improved aerobic performance leads to improved preoperative cardiorespiratory function

2. Improved aerobic performance leads to better tolerance of the physiological demands of surgery

3. Improved aerobic performance leads to improved preoperative muscle strength

4. Improved aerobic performance leads to improved preoperative mood and wellbeing

5. Improved aerobic performance leads to reduced postoperative length of stay in hospital

6. Improved aerobic performance leads to reduced postoperative time to mobilise

7. Exercise training could improve aerobic performance

8. Exercise training should be an aspect of preoperative care

9. Preoperative exercise programmes should be designed to improve cardiorespiratory fitness

10. Exercise training could be used to beneficially improve aerobic performance in patients awaiting elective (planned) surgery

11. Exercise training could be used to beneficially improve aerobic performance in patients awaiting urgent (e.g. cancer) surgery

12. Exercise training could be used to beneficially improve aerobic performance in patients between 40 and 60 years old awaiting surgery

13. Exercise training could be used to beneficially improve aerobic performance in patients between 60 and 80 years old awaiting surgery

14. Exercise training could be used to beneficially improve aerobic performance in patients over 80 years old awaiting surgery

15. Exercise training could be used to beneficially improve aerobic performance in patients awaiting laparoscopic surgery

16. Exercise training could be used to beneficially improve aerobic performance in patients awaiting open surgery

17. Exercise training could be used to beneficially improve aerobic performance in patients with benign pathology

18. Exercise training could be used to beneficially improve aerobic performance in patients with malignant pathology

19. Preoperative exercise training programmes would be most useful if they improved aerobic performance within the 31 day time frame allowed for cancer surgery

20. Preoperative exercise training programmes should be designed to give the greatest gain in fitness in the shortest time frame

21. Preoperative exercise training programmes would be supported by you in your own practice

Statements rejected by the expert group

1. Preoperative exercise programmes should be designed to improve muscle strength only

2. Exercise training could be used to beneficially improve aerobic performance in patients awaiting emergency surgery within 24 hours of admission

3. Individually tailored and suitably monitored preoperative exercise training programmes are likely to risk cardiac complications

4. Individually tailored and suitably monitored preoperative exercise training programmes are likely to risk neurological complications

5. Individually tailored and suitably monitored preoperative exercise training programmes are likely to risk respiratory complications

6. Individually tailored and suitably monitored low impact preoperative exercise training programmes are likely to risk musculoskeletal complications

Statements on which no consensus was achieved among the expert group

1. Improved aerobic performance leads to reduced need for intraoperative vasoactive drugs due to better cardiac performance

2. Improved aerobic performance leads to reduced length of HDU/ITU postoperative stay

3. Preoperative exercise programmes should be designed to improve balance

4. Preoperative exercise programmes should be designed to improve flexibility

5. Individually tailored and suitably monitored high impact preoperative exercise training programmes are likely to risk musculoskeletal complications

6. Preoperative exercise training programmes are already supported by robust evidence of their benefit

7. Preoperative exercise training programmes are deliverable in your hospital

Table 3.4 Final results of the Delphi survey showing statements that were accepted as consensus by the expert group, those that were undecided and those that were rejected

3.5 **Discussion**

This Delphi study has produced a collection of statements that might inform the future development of prehabilitation programmes for CRCa surgery patients. These statements have been agreed by an expert group of consultant colorectal surgeons and include agreement on the importance and role of exercise prehabilitation. Such consensus and detail has not been defined previously and will be important to consider in any future introduction of preoperative exercise.

Surgeons agreed that improvement in aerobic capacity has many benefits in the perioperative period and that exercise should be part of a preoperative care package. It was agreed that patients undergoing elective and urgent operations for benign and malignant pathology across several age categories could be involved in preoperative exercise programmes. The expert group would globally support such exercise programmes.

The expert group disagreed that exercise should focus on improving muscle strength only and agreed that the emphasis should be on improving cardiorespiratory (aerobic) capacity. Previous studies using HIT in older people have shown

significant improvements in aerobic capacity in other clinical groups such as lung cancer (Jones et al., 2007) and chronic cardiac disease patients (Moholdt et al., 2009). The drawback with these studies is that improvement in fitness was seen over 6–12 weeks, whereas improvements in fitness in preoperative CRCa patients would need to be evident in a shorter time frame. The group did not agree that preoperative exercise should be used in patients awaiting emergency surgery (defined as taking place less than 24 hours from admission) due to the very limited time available and the acute nature of emergency surgical pathology. They also disagreed that suitably tailored and monitored exercise programmes pose high risk of complications to participants. In HIT studies on patients with known coronary artery disease, there have been very few adverse events reported (Guiraud et al., 2010; Meyer et al., 2012). It seems unlikely that CRCa patients without specific cardiorespiratory comorbidities would be at any higher risk of complications.

No consensus was reached on whether improved aerobic performance would reduce the need for intraoperative vasoactive drugs or length of postoperative stay in critical care wards. There were several free-text comments made during the survey, indicating that use of vasoactive drugs was outside the

expert knowledge of consultant colorectal surgeons, which may explain the lack of agreement in either direction. No consensus was reached regarding the improvement in balance or flexibility, with preoperative exercise, nor the risks of musculoskeletal complications associated with high-impact exercise.

Interestingly, there was no consensus on whether there was currently good evidence of the benefits of preoperative exercise in colorectal cancer patients or whether this type of exercise programme would be deliverable in healthcare institutions at present. As discussed in chapter 2, there is limited published work on preoperative exercise in CRCa patients (Boereboom et al., 2016; O'Doherty et al., 2013) especially in a time frame dictated by the national cancer management timelines. This would explain why even expert surgeons in the field are unconvinced by the strength of current published literature. This evidence gap is addressed by work in the following chapters of this thesis.

A perceived limitation of this Delphi study may be the small number of consultant colorectal surgeons recruited to the study; however, it is well documented that although larger numbers of participants in Delphi studies will increase the reliability of group judgment, these improvements with group sizes above 12–15

participants are small (Murphy et al., 1998).

This work has produced the first consensus agreement amongst an expert group of consultant colorectal surgeons on the importance of preoperative exercise in CRCa patients and the benefits that this exercise may give. It was agreed that a wide range of patients would benefit from preoperative exercise and that surgeons would support exercise programmes in their own institutions. However, it is clear from our results that more evidence is required to support the introduction of timely preoperative exercise interventions.

From this background investigation confirming that preoperative exercise is important, beneficial and well supported this thesis goes on to investigate the feasibility and efficacy of a 31 day HIT exercise programme, compliant with national cancer management timelines, to improve the cardiorespiratory fitness of older, healthy volunteers age-matched to those most commonly presenting for curative CRCa surgery.

4 The feasibility and effectiveness of a 31 day HIT exercise programme, in improving the cardiorespiratory fitness of older, healthy volunteers

4.1 Introduction

As described in chapter 1 there is increasing interest in improving patient's preoperative fitness in an attempt to reduce the risks associated with surgery. In CRCa patients this exercise must be effective in the short time available before an expedient operation, limited by the 31 day time restrictions as described in introduction section 1.8.

This observational cohort study aimed to investigate the feasibility and effectiveness of using a HIT exercise programme to improve the cardiorespiratory fitness of older, healthy volunteers within 31 days. This mimics the time frame between decision to treat and surgery for CRCa patients. This pilot study was designed to assess efficacy, trouble shoot exercise protocols and establish safety and acceptability of HIT in a group analogous to those presenting for surgery, prior to

opening a similar study in cancer patients of similar age and with similar comorbidities.

4.2 Materials and Methods

4.2.1 Study aims

The primary aim of this study was to assess the mean change in VO_2 peak (in ml/kg/min) following HIT.

The secondary aims were;

- Mean change in anaerobic threshold following HIT
- DEXA and USS assessed changes in lean muscle mass and structure following HIT
- Determination of participant compliance and adherence to HIT
- Change in functional ability using short performance battery tests following the HIT
- Quality of life and performance questionnaires to measure subjective outcomes (EQ-5D, IPAQ, DASI)

4.2.2 Experimental design - overview

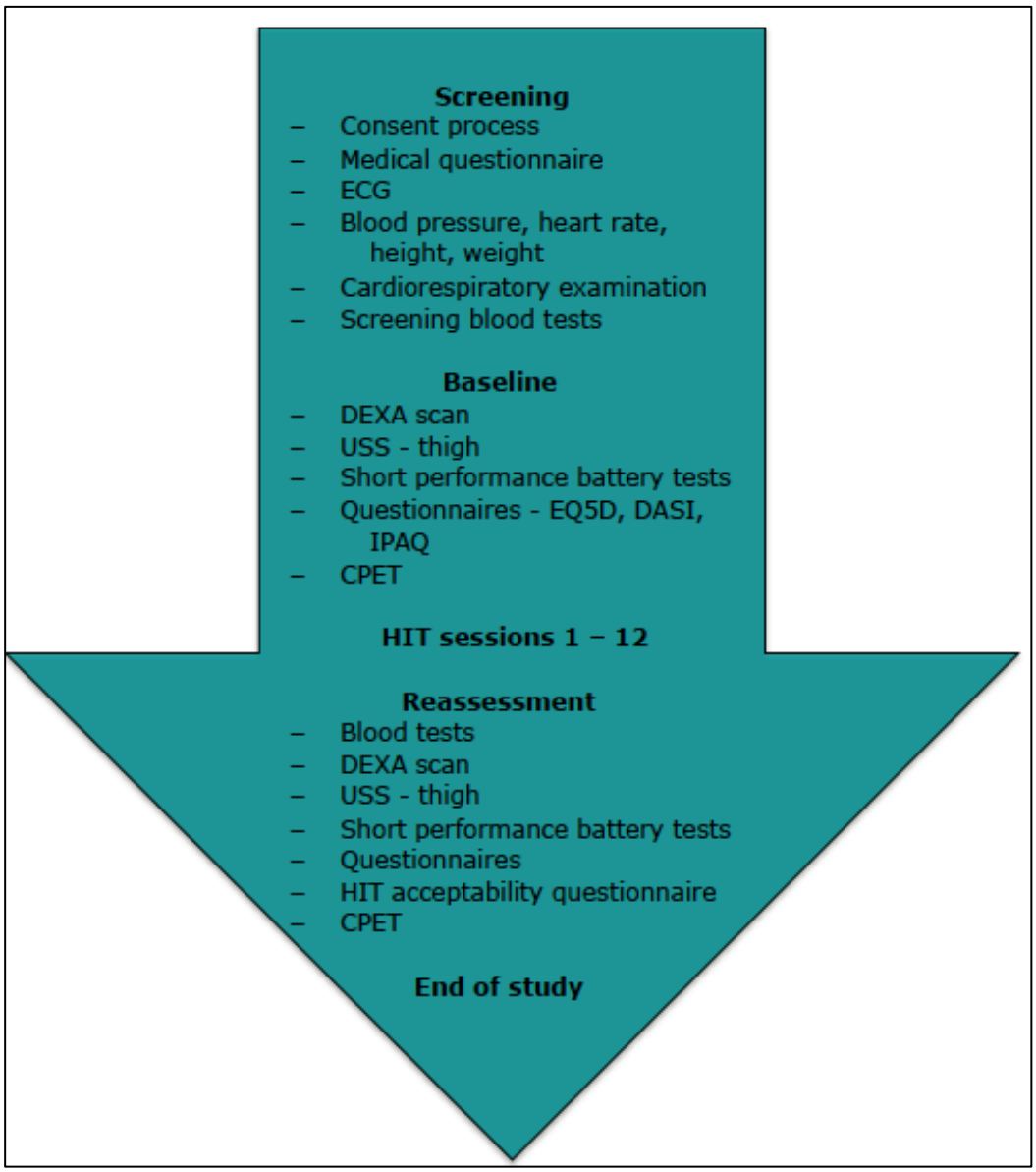

Figure 4.1 Schematic flow diagram of the HIT protocol

4.2.3 Participants

Twenty four volunteers, male and female, between 60 and 75 years old were recruited from demographic data mailings (Royal Mail, UK) and from advertising in the local area. Volunteers were recreationally active. All participants gave written informed consent and completed medical screening including: cardiorespiratory examination, blood sampling for routine haematology and biochemistry profiles, electrocardiogram (ECG), blood pressure and body mass index (BMI) calculation. Subjects were excluded if they displayed evidence of uncontrolled hypertension (blood pressure > 140/100mmHg), significant cardiorespiratory disease or had taken part in another research study in the previous 3 months. The study was approved by the University of Nottingham Medical School Ethics Committee, registered with ClinicalTrials.gov (reference number NCT02167191) and complied with the declaration of Helsinki.

4.2.4 Baseline testing

Following the screening visit participants attended the university medical school exercise physiology laboratory, based at the Royal Derby Hospital, for a baseline testing session. This session consisted of a cardiopulmonary exercise test (CPET) on a cycle ergometer using a 15 W/min ramp protocol (outlined

below). Other measurements taken included:

- Whole-body dual-energy X-ray absorptiometry (DEXA) scan
- Ultrasound scan (US) of vastus lateralis
- Short physical performance battery tests (SPPBT) (Guralnik et al., 1994)
- Functional questionnaires
  - EuroQol 5 Dimensions (EQ5D) (Haywood, Garratt, & Fitzpatrick, 1994)
  - Duke Activity Status Inventory (DASI) (Spanjer et al., 2010)
  - International Physical Activity Questionnaire (IPAQ) (Craig CL, Marshall AL, 2003)

These measurements are described below.

4.2.5 Cardiopulmonary exercise testing

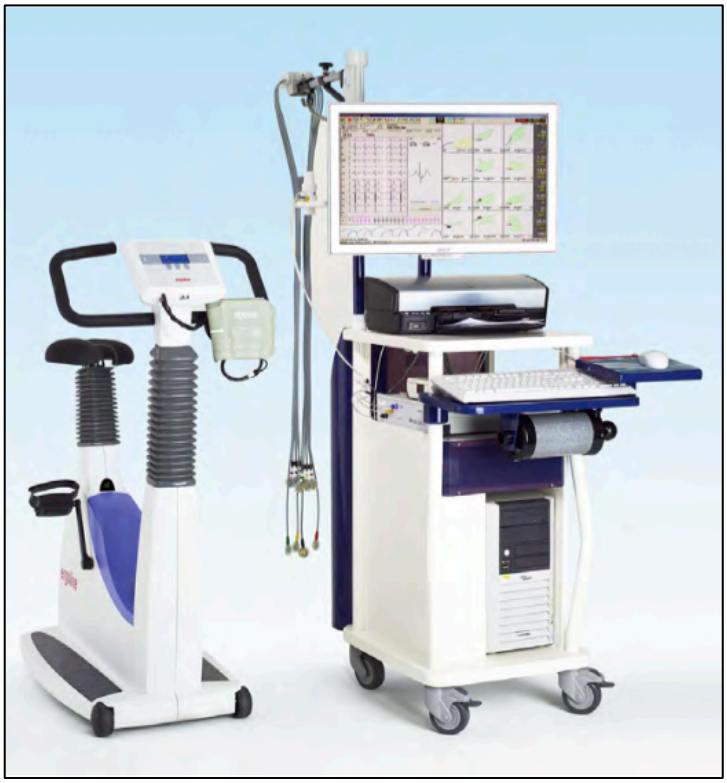

Figure 4.2 Cycle ergometer and metabolic cart similar to those used in the HIT study (www.zan.de/download/Kunden/Manuals/5001006ENG_ZAN600_Operations%20Manual.pdf. Accessed April 2016)

CPET was performed with a Lode Corival cycle ergometer (Lode Corival, Lode, Groningen) and inline gas analysis system (ZAN 680, nSpire Health, Colorado, USA) using a standard 15 W/min ramp protocol (Weisman et al., 2003). Following a 2 min period of unloaded cycling, participants were instructed to maintain a cadence of 50–60 revolutions per minute (rpm) and were verbally encouraged to exercise to 85% or more of predicted maximal heart rate (Max HR=208–(0.7*Age)) and to a respiratory exchange ratio (VCO_2/VO_2) above 1.0. The test was

complete when the participant indicated that they had reached their maximum possible effort, with the time to failure recorded. During all CPET and HIT sessions, participants were monitored with a 12 lead ECG, non-invasive blood pressure monitoring, and pulse oximetry. All sessions were supervised by an advanced life support-trained clinician with termination criteria taken from the ATS statement on CPET (Weisman et al., 2003).

AT (as explained in chapter 1.3.6) is defined as the oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms, causing a sustained increase in lactate and metabolic acidosis (Wasserman, 1986b), was determined by three independent assessors blinded to the participants, using both the V slope (Beaver, 1986) and respiratory equivalents methods (Wasserman, 1978), with the mean of these values used (West, 2011) (Figure 4.3).

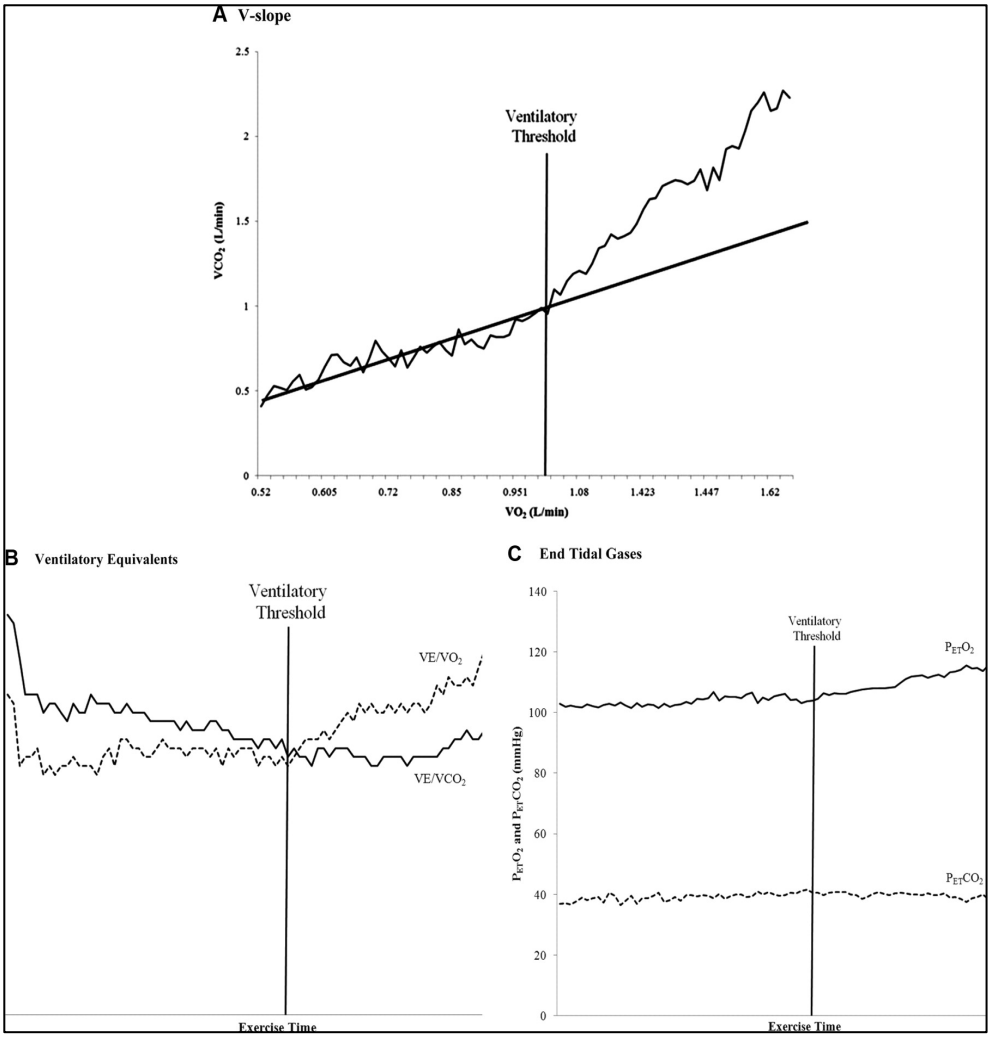

Figure 4.3 Example graphs of the V-slope, ventilatory equivalents and end-tidal methods used for the detection of AT

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4.2.6 Body composition imaging

Whole body DEXA scanning (Lunar Prodigy II, GE Medical Systems, Buckinghamshire, UK) was used to assess body composition and bone mineral density of all participants before and after HIT. DEXA passes two x-ray beams of varying low

energy levels through the body. The amount of x-ray absorbed as it passes through the tissues can be calculated by subtracting the amount appearing at the receiver from the initial amount thus allowing tissues densities to be assessed.

Whole-body mass, lean and fat tissue values were assessed along with specific regions of interest (ROI) for abdominal and leg tissue composition. Abdominal ROI were selected as the region between the lowest visible costovertebral joint and the superior aspect of the iliac crest. Leg ROI were calculated from the greater trochanter of the femur to the joint line of the knee.

Other methods of making these measurements which do not involve x-ray, such as hydrostatic weighing and whole body air displacement plethysmography, are unavailable in our unit and do not allow regional assessment. Moreover, DEXA is more accurate and less affected by diet and hydration than anthropomorphic measurements such as bioelectric impedance testing.

Ultrasound imaging of muscle architecture is a quick, safe, portable, non-invasive technique which involves no exposure to radiation. Muscle thickness, pennation angle and fascicle length have been shown to predict strength and functional capacity in older adults (Selva, 2017).

Sagittal plane US images were taken of the mid-belly of the left vastus lateralis to quantify muscle architecture before and after HIT. Muscle thickness was determined using ImageJ software (Public domain image processing programme, developed by National Institutes for Health, Maryland, USA) based on previously published techniques (Franchi et al., 2014; Reeves, 2004)

4.2.7 Functional fitness and physical activity assessments

An established series of SPPBT combining assessments of balance, gait speed and chair/stand speed (Guralnik et al., 1994) were used as a marker of functional fitness before and after HIT.

Three questionnaires based on physical activity were administered before and after HIT. EQ5D assesses the 5 domains of mobility, self-care, usual activities, pain and anxiety and also contains a 100 point visual analogue scale for general health. It has been validated for use in the general population in England and is used by NICE and the NHS Patient Reported Outcome Measures programme for colorectal cancer (Devlin, 2016; UK Department of Health, 2015) (appendix 8.4.1). IPAQ assesses intensity and volume of physical activity over the preceding 7 days and has been validated in the adult population

in diverse settings (Craig, 2003) (appendix 8.4.2). DASI uses 12 indicators to predict functional activity and can be used to estimate the VO_2 peak and metabolic equivalent of task expenditure of the participant. (MET; ratio of work metabolic rate to standard resting metabolic rate, 1 MET is equivalent to 4.1 kJ/kg/hr (Ainsworth et al., 1995)) It was originally described and validated in healthy adults in 1989 (Hlatky et al., 1989) and had been widely used since, especially in those with physical activity limiting cardiorespiratory disease (appendix 8.4.3).

4.2.8 High intensity interval training regime

Following the baseline testing session participants attended the unit for 12 fully supervised HIT sessions within a 31 day period. The intensity of the HIT intervals was determined from the baseline CPET and by performing an initial assessment session with 60 second intervals at 90, 95, 100, 105, and 110% Watt max (maximum power output achieved during the baseline CPET test). For the remaining 11 sessions participants trained at the load of the highest interval completed during their assessment session

After HIT session 6, and providing that the exercise had been well tolerated, the self rated BORG intensity score was below 8

and the participants were agreeable, the exercise intensity was increased by 10% for the remaining 6 HIT sessions.

Participants cycled for 2 minutes of unloaded warm up, followed by 60 seconds at 110% Watt max (or highest load from the assessment session) and then 90 seconds of unloaded cycling. These intervals were repeated 5 times followed by a 3.5 minute monitored, cool down period (Figure 4.4).

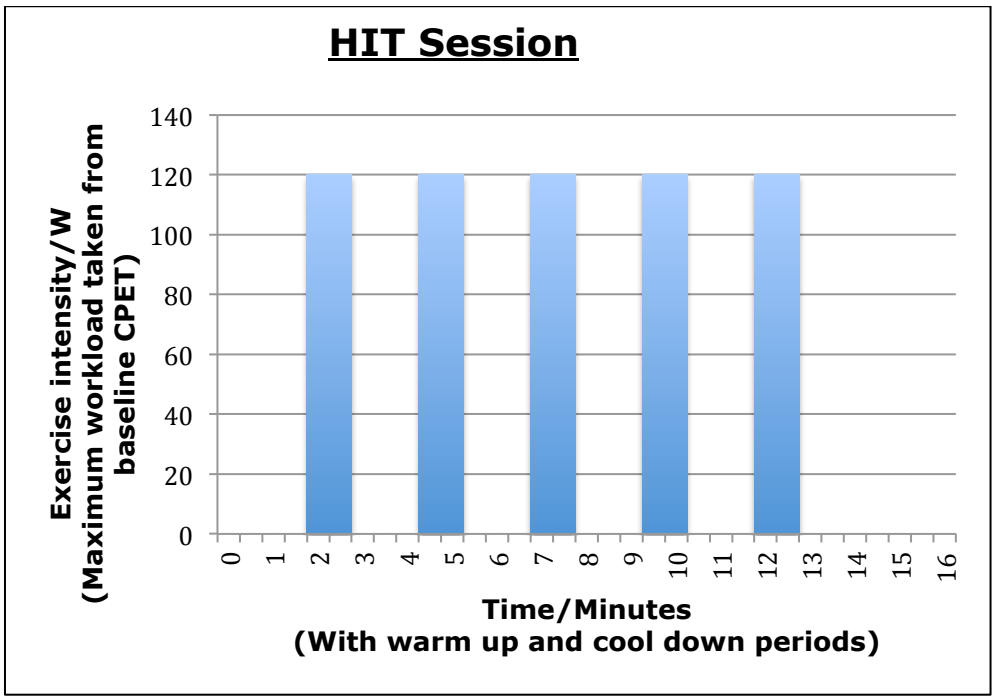


Figure 4.4 Schematic of an example HIT session used in the HIT study

4.2.9 Reassessment

Following 12 HIT sessions a reassessment session took place for all participants. All baseline measurements were repeated. An

in-house questionnaire was used to assess the acceptability of the exercise programme to participants (appendix 8.4.6).

4.2.10 Statistical analysis

A previous similar study in our unit gave a standard deviation of differences in VO_2 max pre and post exercise training as 2.04ml/kg/min (0.16 l/min). Using this data in the nQuery (nQuery, Statistical Solutions Ltd, Cork, Ireland) statistics software package and aiming to detect a mean clinically significant increase in VO_2 peak of 2ml/kg/min, with 95% power and significance at the 5% level, 16 complete data sets were needed. To allow for a 20% drop out rate (similar to other studies in the department) we aimed to recruit 20 individuals.

The value for clinically significant improvement in VO_2 peak was taken from previous similar studies in a different surgical population where improving patient's VO_2 peak by 1.5ml/kg/min would improve the fitness of 30% of their patients over the threshold from high operative risk to low operative risk (Dunne et al., 2016; Dunne et al., 2014).

Normality of data was tested using D'Agostino and Pearson omnibus test. Normal data were expressed as mean ± standard deviation (SD), and nonparametric data as median ±

interquartile range (IQR). Paired Student's t tests were used to test the parametric data, the Wilcoxon matched-pairs signed-rank test was used for nonparametric data. Pearson's correlation was used to explore relationships between changes in vastus lateralis thickness, lean leg mass, and VO_2 peak. GraphPad Prism 6 (San Diego, CA, USA) was used for data analysis with level of significance set at $p < 0.05$.

4.3 Results

4.3.1 Demographics

Twenty-four volunteers began the study and 21 completed (Table 4.1; 8 male and 13 female; 67 (62–73) years; BMI: 26.1 ± 2.9 kg/m^2). Three volunteers were excluded: one failed to reach AT during the reassessment CPET, one suffered claustrophobia in the facemask during the reassessment CPET, and one was withdrawn due to pre-existing paroxysmal atrial fibrillation noted during a HIT session. Participants reported 1.5 ± 1.4 episodes of weekly exercise prior to the start of the study. Mean workload during the HIT intervals was 148 ±44W. There was 100% compliance with the training programme with all participants who successfully completed the baseline and reassessment CPET also completing 12 HIT sessions. The mean duration of the training programme was 28 days (±3.5 days).

Characteristic	Number of participants
Age (range)	66.6 (62-73) years
Gender	8 Male; 13 Female
Previous exercise episodes per week (±SD)	1.5 ±1.4 episodes
Body mass index (±SD)	26.1 ± 2.9 kg/m^2
Comorbidities (number of participants affected)	• Asthma (2) • Hypothyroidism (3) • Hypercholesterolemia (4) • Musculoskeletal disorders (3) • Hypertension (5)
Medication (number of participants affected)	• Inhaled bronchodilators (2) • Thyroxine (3) • Statins (4) • Antihypertensives (5); ○ Calcium channel blocker (1) ○ Diuretics (3) ○ Beta blocker (1) ○ Angiotensin II receptor antagonist (1) ○ ACE inhibitor (1)

Table 4.1 Demographics of HIT participants

4.3.2 Cardiovascular measurement data

There was a significant reduction in both diastolic blood pressure (84 ± 8 vs. 75 ± 14mmHg, p <0.01) and mean arterial pressure (101 ± 8 vs. 93 ± 11mmHg, p <0.01) after HIT (Figure 4.5). Systolic blood pressure was not significantly lower after HIT (134 IQR 14.5 vs. 132 IQR 22.5mmHg, p = 0.11), and resting heart rate was unchanged (67.8 ± 9.6 vs.

68.9 ± 6.7bpm, p = 0.29). There was a significant reduction in submaximal heart rate taken at specific intensities in the reassessment CPET compared to the baseline CPET. This was seen at 25%, 50% and 100% maximum wattage of the baseline CPET (88 ±13 vs. 81 ±8bpm, $p<0.01$, 103 ±15 vs. 98 ±13bpm, $p<0.01$ and 146 ±19 vs. 136 ±19bpm, $p<0.0001$) (Figure 4.6). Haemoglobin was unchanged following HIT (143 ± 10.3 vs. 144.8 ± 11.2g/l, p = 0.56).

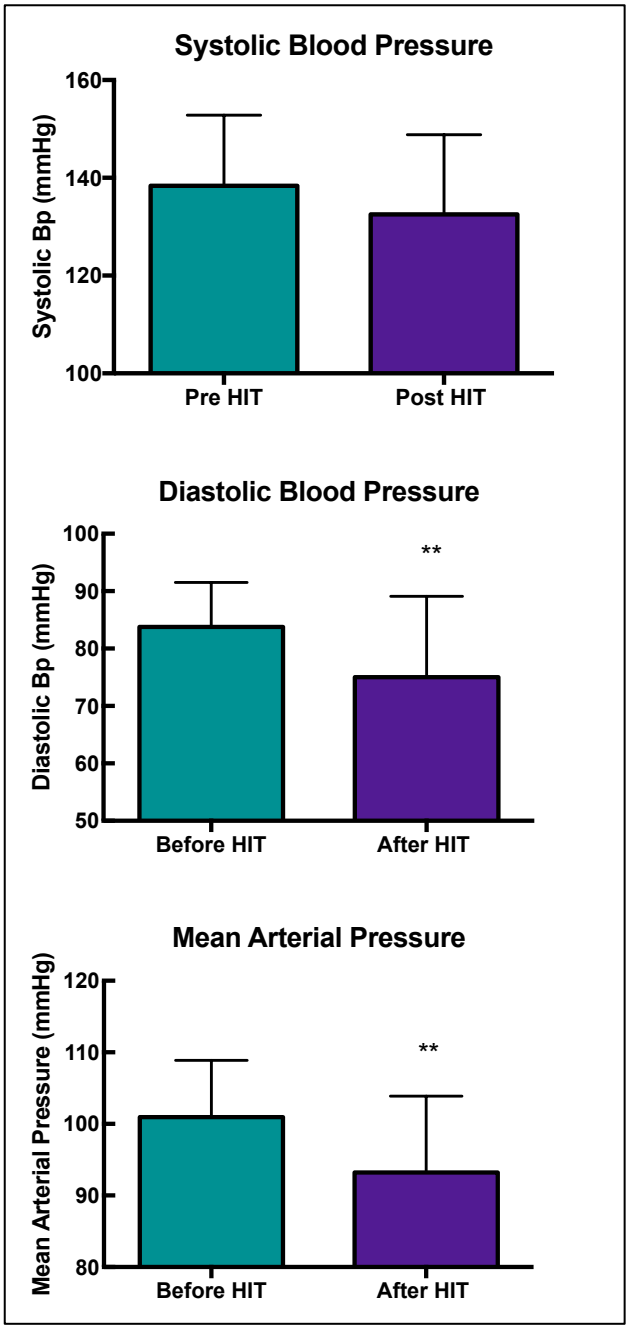


Figure 4.5 Systolic blood pressure, diastolic blood pressure and mean arterial pressure before and after HIT, Values are means ±SD before and after HIT. **p<0.01

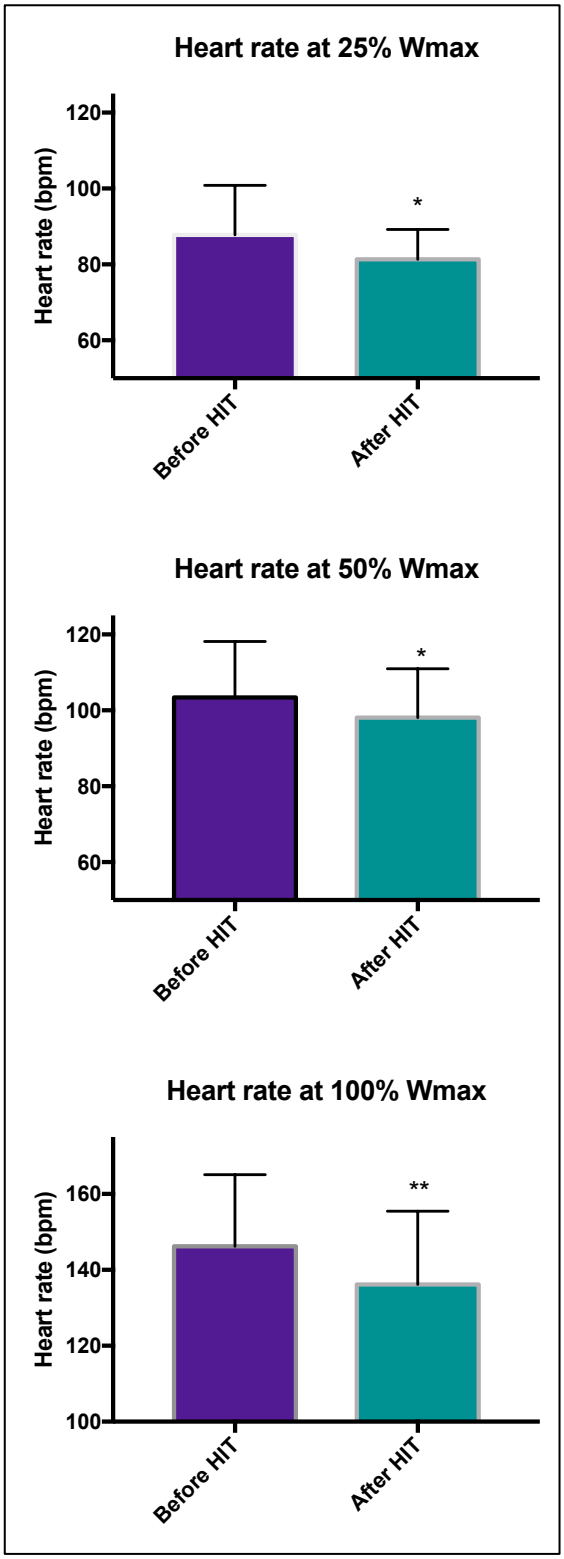


Figure 4.6 Heart rate at % of maximum wattage (of baseline CPET) during the baseline CPET and reassessment CPET, before and after HIT. Values are mean ±SD, *p<0.05, **p<0.01

4.3.3 Cardiorespiratory exercise test data

There was a significant increase in CPET time to failure (737s IQR 95s vs. 772s IQR 155s, $p<0.001$) and CPET wattage at failure (118W IQR 83.5W vs. 142W IQR 85W, $p<0.001$) after HIT. There was a significant increase in VO_2 peak, thus achieving the primary end point of this study, VO_2 peak (23.90 ±4.68 vs. 26.2 ±5.44 ml/kg/min, $p<0.01$, or in absolute values 1.78±0.5 vs. 1.93±0.5 l/min, $p <0.01$) (Figure 4.7). The AT determined by 3 independent assessors was significantly increased (17.86±4.45 vs. 20.21±4.11 ml/kg/min, $p=0.008$, absolute values 1.32±0.46 vs. 1.49 ± 0.45 l/min, $p<0.01$) with coefficient of variation less than 25% between assessors.

Neither VO_2 peak nor AT improvements were correlated with baseline values (Figure 4.8). There was a significant increase in peak O_2 pulse (17.1 ± 3.7 vs. 18.5 ± 3.7 100ml/beat/kg, $p<0.001$) after HIT. Full CPET data are appended in appendix 8.5.1.

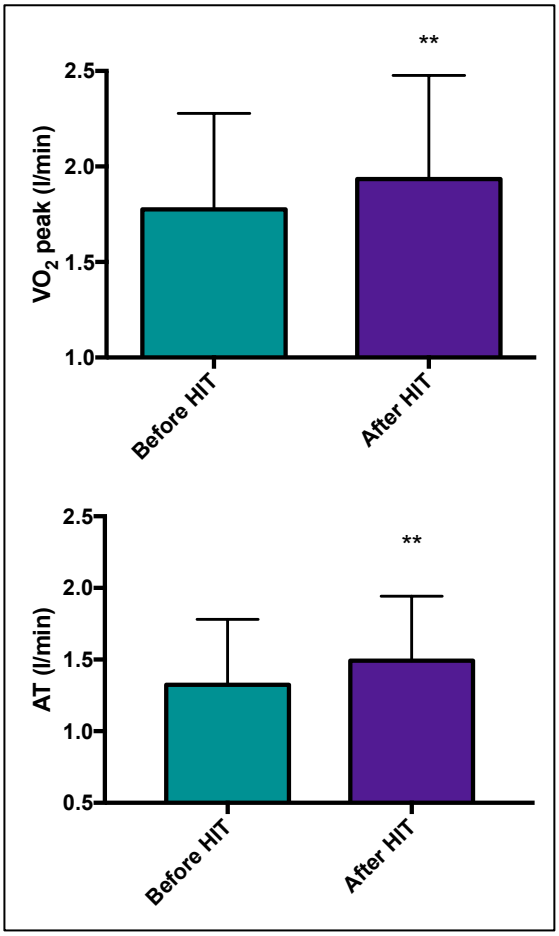


Figure 4.7 VO_2 peak and AT achieved during CPET before and after HIT, values are means ±SD, *p<0.05, **p<0.01

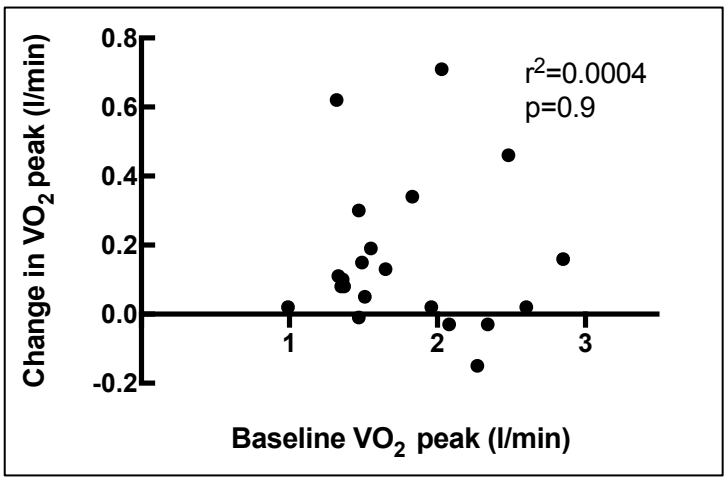


Figure 4.8 Correlation between baseline and improvement in VO_2 peak following HIT

	Before HIT	After HIT	Change	
VO_2 peak (l/min)	1.78 ±0.50	1.93 ±0.54	0.16 ±0.22	p<0.01
VO_2 peak (ml/kg/min)	23.90 ±4.68	26.2 ±5.44	2.30 ±2.84	p<0.01
VO_2 AT (l/min)	1.32 ±0.46	1.49 ±0.45	0.17 ±0.27	p<0.01
VO_2 AT (ml/kg/min)	17.86 ±4.45	20.21 ±4.11	2.35 ±3.63	p<0.01

Table 4.2 CPET variables before and after HIT

There was variation in the improvement in VO_2 peak between individuals, as shown in Figure 4.9.

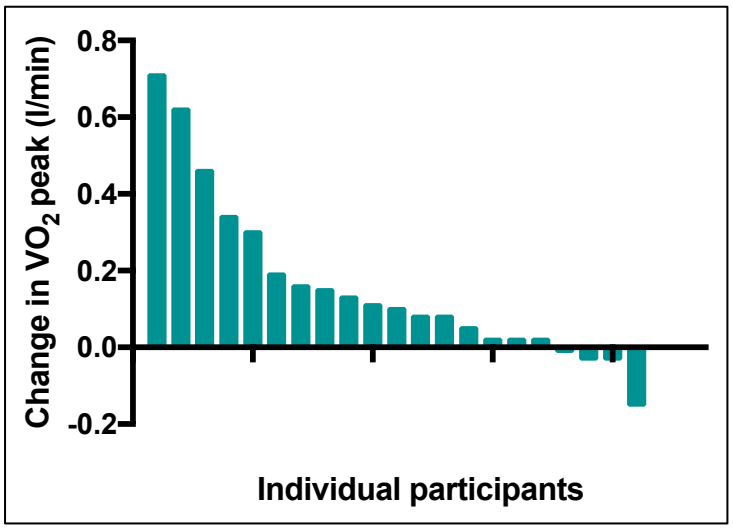


Figure 4.9 Individual participant changes in VO_2 peak following HIT

4.3.4 Body composition data

Due to unavoidable delays in ethics approval for DEXA scanning,

only 15 out of 21 participants had DEXA scans before and after HIT. All participants had US scans before and after HIT. Weight and BMI were unaltered by HIT (BMI 26.1 ± 3 vs. 26.1 ± 3 kg/m^2, p = 0.33). DEXA derived data showed that there was no significant change in total body tissue mass (68490 ± 10503 vs. 68186 ± 10395g, p = 0.19), total body fat mass (23336 ± 7026 vs. 22904 ± 6693g, p = 0.07) or total body lean mass (45154 ± 11142 vs. 45282 ± 11068g, p = 0.67) following HIT. Lean leg mass significantly increased with HIT (4133 ± 1271 vs. 4220 ± 1236g, $p<0.05$) coupled with a significant increase in the thickness of the vastus lateralis muscle (2.04 ± 0.27 vs. 2.17 ± 0.28 cm, $p<0.05$) (Figure 4.10). Abdominal fat mass (2783 ± 938 vs. 2690 ± 913g, $p<0.05$) was significantly reduced following HIT. Parameters of bone mineral density and mineral content were unchanged with HIT.

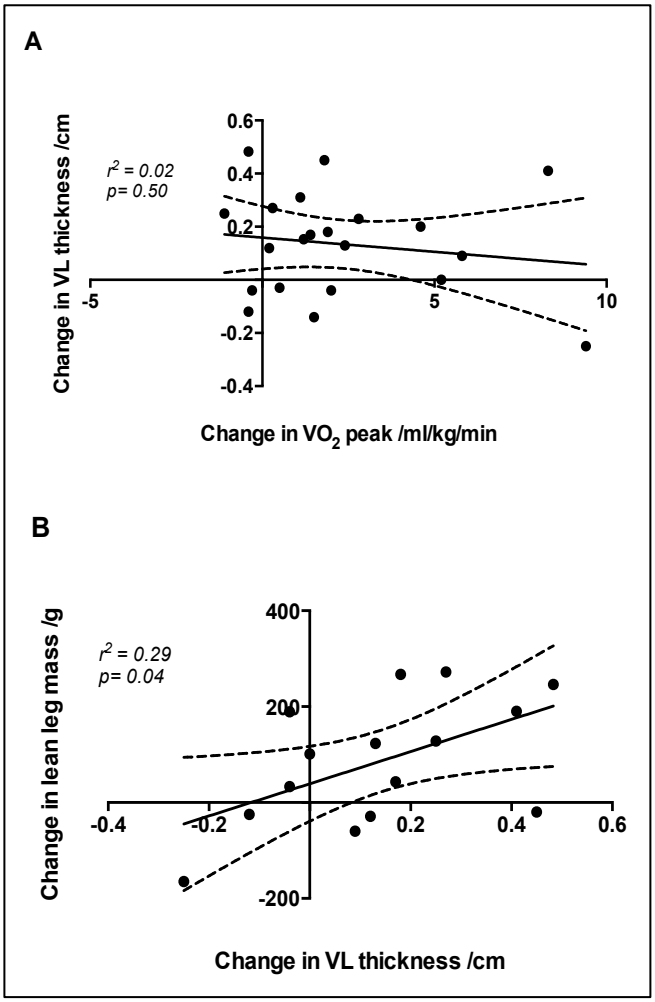


Figure 4.10 Change in lean leg mass with change in VO_2 peak (A) and change in lean leg mass with change in VL thickness (B) following HIT

4.3.5 Functional fitness and physical activity questionnaire data

Scores from the SPPBT, EQ5D (crosswalk score (amalgamation of activity domain scores) and visual analogue scale) and IPAQ were unchanged following HIT. The DASI scores increased following HIT with a subsequent increase in the DASI predicted

VO_2 max (32.4 ml/kg/min (IQR 3.2) vs. 34.6ml/kg/min (IQR 0), p=0.016).

	Before HIT	**After HIT**	**Change**	
SPPBT	11 (IQR 1)	12 (IQR 1)	1	p>0.05
EQ5D crosswalk	1 (IQR 0.076)	1 (IQR 0.163)	0	p>0.05
EQ5D VAS	89% (IQR 18)	90% (IQR 18)	1%	p>0.05
IPAQ	3707±2780	4360±2978	653	p>0.05
DASI	52.9 (IQR 7.5)	58.2 (IQR 0)	5.3	p<0.05

Table 4.3 Results of SPPBT and physical activity questionnaires

4.3.6 Acceptability of HIT

On a five-point Likert scale, the HIT programme was deemed highly acceptable by the majority of participants (Table 4.4).

Comment	**Median Score (Range)** **5 – Strongly agree** **1 –Strongly disagree**
HIT was well explained	5 (4-5)
I enjoyed HIT	5 (4-5)
HIT was a time burden	1 (1-5)
I would recommend HIT to others	5 (4-5)
HIT was more demanding than expected	2 (1-5)
I would do HIT again	5 (4-5)
The travelling involved interfered with my life	1 (1-5)
The physical strain interfered with my life	1 (1-5)
I believe my fitness has improved	5 (3-5)
I would like to have exercised in a group	1 (1-4)
I would like to have exercised at home	1 (1)

Table 4.4 Acceptability of HIT, on a five-point Likert scale

4.4 Discussion

This observational, cohort study showed that it was possible to improve cardiorespiratory fitness in healthy, older people within 31 days using a HIT exercise programme. The regime was safe, acceptable and not associated with any serious medical complications. Improvement in fitness was evidenced by significant improvements in VO_2 peak, AT, time to failure and wattage at failure. Even though the baseline value for these participants was above the threshold for increased postoperative complications in CRCa patients, the ability to improve fitness in a short time frame is encouraging. There is some evidence that those who are less fit at baseline (which maybe the case for many CRCa patients) may demonstrate an even greater improvement in fitness (Weston, 2014), although the lack of correlation between change in VO_2 peak and AT and the corresponding baseline measurements did not support this in the above study.

To our knowledge, this was the first study to assess the efficacy of HIT on cardiorespiratory fitness in healthy, older individuals within the national cancer management timeline. Other groups have reported an improvement in VO_2 peak in healthy older

individuals and those with cardiovascular pathology, but training programmes have lasted 9–14 weeks (Lepretre et al., 2009; Pichot et al., 2005). In 60 year olds following coronary artery bypass grafting, an increase in VO_2 peak from 27 to 30ml/kg/min in 4 weeks was reported, but with a higher training frequency (Moholdt et al., 2009).

It was interesting to note in this study that not all participants saw an improvement in VO_2 peak despite a mean increase in the group. The range of change in VO_2 peak varied between 0.46 and –0.15 l/min (5.8 and -1.1 ml/kg/min). This has implications for preoperative exercise training programmes if this variation in change occurs in cancer patients also. This is further discussed in chapter 5.4.1.

In addition to mean group fitness improvements, we also saw reductions in diastolic and mean arterial blood pressure following HIT. Perioperative high blood pressure increases risk of myocardial ischaemia, dysrhythmias and renal impairment (Kaplan, 2014). This observation is of particular note as several studies report reductions in blood pressure after prolonged duration HIT mirroring the reductions seen following endurance training, suggesting a non-specific effect of exercise training (Iellamo et al., 2014). A recent systematic review agrees with

this showing reductions in diastolic blood pressure with aerobic and resistance training in the region of 2mmHg (or 4mmHg with combined training) in studies lasts several months (Herrod, 2017). However, previous shorter duration HIT regimens in fit individuals have failed to replicate these improvements (Broman, 2006). In contrast we have been able to show significant (and larger magnitude) reductions in blood pressure after just 4 weeks of HIT in our group of participants.

BMI and weight remained unchanged after HIT, despite a significant increase in lean leg mass as evidenced by DEXA and US. These two modalities of imaging muscle mass/thickness showed moderate correlation in measuring the change in muscle mass (r^2 = 0.29, p = 0.04), suggesting that simple ultrasound measurements of vastus lateralis could be used clinically to measure muscle-based changes (Figure 4.10). New ultrasound methods recently developed would give an accurate measure of leg muscle mass (Franchi et al., 2014). Similar HIT protocols in younger age groups have failed to show comparable changes in body composition in the recreationally active (Robinson et al., 2014), but have shown an improvement in body composition in inactive and overweight groups (Gillen, 2013). Although observed increases in lean leg mass may confer an ability to

attain higher VO_2 peak values and explain the increases in time to failure and wattage at failure, we failed to demonstrate a relationship between changes in muscle mass and VO_2 peak (Figure 4.10). This suggests that HIT-induced increases in cardiorespiratory performance observed in this group are not solely attributable to increases in muscle mass.

While quality of life status measured via EQ5D did not improve following HIT, DASI scores did improve, indicating that perceived improvement in functional performance mirrored objectively measured increases in function. Previous work has highlighted the importance of the perception of functional capacity in recovery and time to return to normal activities after surgery documenting a disagreement between these two states in the postoperative patient (Williams, 2014). While engagement with any exercise programme is likely to better inform the perception of functional capacity and minimise this disagreement, patients must be able to engage with the programme for it to be generalisable to the clinical arena. In this study participants found HIT both enjoyable and effective and not a significant burden with regard to time or physical effort. Subjects reported preference towards exercising away from the home and not in a group setting. They did not find the time or travel commitment a particular burden. Psychological

gain or social support gained from attending an exercise programme has been previously reported in an older population (Litt, 2002). An increase in perceived fitness has been shown after exercise training (King, 1989) and self efficacy (an individuals belief in their ability to successfully perform a specific behaviour) is central in adoption and maintenance of exercise programmes (Schutzer & Graves, 2004).

Functional fitness measured by the SPPBT and IPAQ questionnaire was unchanged following HIT. Although validated, these tools maybe too crude to measure any change in this active, older population.

There are limitations to this study: despite demonstrating proof of principle that HIT is well liked, well tolerated and effective in improving fitness in this older group, those who had significant cardiorespiratory comorbidities were excluded from this study (to minimize risk of exercise related complications during this initial feasibility study) and our voluntary recruitment may have created selection bias, only appealing to those individuals already interested in improving their fitness. However, the baseline AT values for this group were comparable to previous exercise studies in our unit falling between controls and colorectal cancer patients (19.7 ±5.81ml/kg/min and 14.4 ±3.23ml/kg/min respectively) (Williams et al., 2014).

It is also difficult to predict precisely how the findings of this study would translate to a group of CRCa patients. It is possible that a patient group would have more co-morbidities and be less likely to exercise regularly; however, this may mean that greater improvements in fitness are seen with HIT.

Recruitment was limited to those between 60 and 75 years to provide a similarly aged cohort to those with the highest incidence of bowel cancer (95% bowel cancer diagnosed in those over 50 years (Cancer Research UK, 2017)). Most major colorectal resections occur in those between 65 and 74 years so a cohort with a mean age of 67 years is representative. As this was a feasibility study, there was no control group or randomisation of participants with the primary objective of this study to assess whether improvements in fitness were possible in the limited time frame in a manner acceptable to the participants.

4.4.1 Conclusion

To summarise the importance of this work, CRCa patients with an AT of less than 10ml/kg/min or a VO_2 peak of less than 17ml/kg/min are significantly more likely to suffer postoperative complications (West, 2014). At present there are no

interventions used to modify this risk factor before surgery. In this study subjects from a similar demographic to those listed for colorectal cancer resection rapidly achieved a significant and clinically meaningful improvement in VO_2 peak within the time limits imposed by the national cancer management timelines. This study provides the foundation for work to assess the effectiveness and acceptability of HIT (described in chapter 5) in a preoperative CRCa population.

5 The feasibility and effectiveness of a short term, HIT exercise programme in improving preoperative cardiorespiratory fitness of colorectal cancer patients

5.1 Introduction

As described in the introduction to this thesis (chapters 1.11.4 – 1.13) this study aims to investigate the feasibility and effectiveness of using a HIT exercise programme to improve the preoperative cardiorespiratory fitness of colorectal cancer patients within 31 days before surgery.

5.2 Materials and methods

5.2.1 Study aims

The primary aim of this study was to assess the mean change in VO_2 peak (in ml/kg/min) following HIT.

The secondary aims were;

- Mean change in anaerobic threshold following HIT

- DEXA and USS assessed changes in lean muscle mass and structure following HIT
- Determination of patient compliance and adherence to HIT
- Change in functional ability using short performance battery tests following the HIT
- Change in quality of life and performance questionnaires, measuring subjective outcomes (EQ-5D, IPAQ, DASI, EORTC QLQ-C30, WEMWB)

5.2.2 Participants

Approval for the study was gained from the NHS Health Research Authority (NRES Committee East Midlands Derby - reference number 14/EM/1311) and Derby Hospitals NHS Foundation Trust research and development department. The study was prospectively registered with ClinicalTrials.gov (reference number NCT02188342) and complied with the declaration of Helsinki.

Participants for this study, named HIT exercise programme in improving preoperative cardiorespiratory fitness of colorectal cancer patients (HITCa), were recruited from colorectal surgery outpatient clinics at Derby Hospitals NHS Foundation Trust. The study was introduced by the usual clinical care team and study information was given to participants during the outpatient clinic

when their cancer management plan was discussed. Patients indicating interest in taking part were contacted by telephone after a cooling off period (usually the following day) to establish whether they still wished to participate in the study and invite them for a screening visit.

It was explained to the potential participant that entry into the trial was entirely voluntary and that their treatment and care would not be affected by their decision. It was also explained that they could withdraw at any time. In the event of their withdrawal it was explained that any data collected so far could not be erased and consent would be sought to use the data in the final analyses where appropriate.

Inclusion criteria for the study were;

- Confirmed colorectal cancer
- Offered curative treatment by the Royal Derby Hospital NHS Foundation Trust Colorectal Cancer Multidisciplinary Team
- 55-75 years of age
- Ability to give informed consent

Exclusion criteria for the HITCa study were;

- Uncontrolled hypertension (BP > 160/100)
- Angina

- Heart failure (class III/IV)
- Cardiac arrthymias
- Right to left cardiac shunt
- Recent cardiac event
- Previous stroke/TIA
- Aneurysm (large vessel or intracranial)
- Severe respiratory disease including pulmonary hypertension
- COPD/asthma with an FEV1 less than 1.5l
- Coagulation disorders
- Scarring disorders
- Neoadjuvant chemo/radiotherapy

- Inability to complete the consent process

Those included in any other research study in the last three months that involved: taking a drug; being paid a disturbance allowance; having an invasive procedure or extensive exposure to ionising radiation, were also excluded.

To improve recruitment into the study and allow more patients to access the preoperative exercise, a protocol amendment was agreed by the ethics committee, modifying the age criteria to allow anyone between 18 and 98 years to be recruited.

Full written and informed consent was taken and medical screening took place as for the HIT study (chapter 4). Along with the screening bloods (full blood count, renal function, liver function, coagulation profile, thyroid function, random glucose and lipid levels) a venous blood sample was taken and stored to allow future gene analysis. This whole blood was stored at -80C in a pax gene tube for analysis once candidate genes have been identified. This sample was stored in compliance with Human Tissue Act 2008.

5.2.3 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was undertaken as in the HIT study (chapter 4.2.5) with AT determined by two independent assessors blinded to the participants, using both the V slope (Beaver et al., 1986) and respiratory equivalents methods (Wasserman, 1978), with the mean of these values used as the value for AT (West et al., 2011).

5.2.4 Body composition imaging

DEXA and USS were undertaken as in chapter 4. As previously whole-body mass, lean and fat tissue values were assessed

along with specific regions of interest (ROI) for abdominal and leg tissue composition.

Sagittal plane US images were taken of the mid-belly of right vastus lateralis to quantify muscle architecture before and after training.

5.2.5 Functional fitness and physical activity assessments

SPPBT were undertaken as in chapter 4.

As well as the EQ5D, IPAQ and DASI questionnaires the cancer patients completed the Warwick-Edinburgh Mental Well-being Scale. This tool was developed and validated for use in the UK in 2007 (Tennant et al., 2007) and has been widely used to evaluate mental wellbeing in a variety of settings (Maheswaran, 2012).

The final questionnaire used in this patient group was the EORTC QLQ-C30. This has been developed to assess quality of life in cancer patients and has a domain specific to colorectal cancer (Sprangers, 1999).

5.2.6 High intensity interval training regime

The HIT regime for the cancer patients was the same as used in the healthy volunteers in chapter 4. Following an initial

assessment session (5 intervals set at 90-110% of the initial CPET maximum wattage) patients cycled 5 intervals of 1 minute each at the maximum wattage achieved during their assessment session. Patients completed up to 4 HIT sessions a week. Patients continued their training until their reassessment session, 2 - 3 days before their surgery date. Patients were excluded from the study for non-compliance if they if they attended fewer than 6 HIT sessions or missed the baseline or reassessment testing session. Improvements in exercise capacity and muscle oxidative potential have previously been shown in 6 sprint interval training sessions but not in single training sessions, this was set as our minimum requirement (Burgomaster et al., 2005; Songsorn et al., 2016).

5.2.7 Reassessment

As in the HIT study the baseline assessments were repeated following the HIT sessions.

5.2.8 Statistical analysis

As in the HIT study a power calculation was performed to detect a mean clinically significant change in VO_2 peak of 2ml/kg/min in paired t tests with 80% power and 5% significance. From the

HIT study the standard deviation of the difference in the pre and post VO_2 peak was 2.8ml/kg/min. Using this data in the nQuery Advisor software the number of complete data sets required was 18. We aimed to recruit 22 individuals in order to achieve 18 complete data sets (assuming a drop out rate of 20%, in keeping with our previous studies).

We again used the D'Agostino and Pearson omnibus test to confirm normal distribution of the data. Normal data were expressed as mean ± standard deviation (SD), and nonparametric data as median ± interquartile range (IQR). Paired Student's t tests were used to test the parametric data, the Wilcoxon matched-pairs signed-rank test was used for nonparametric data. Pearson's correlation was used to explore relationships between changes in vastus lateralis muscle thickness, lean leg mass, VO_2 peak and number of HIT sessions etc. GraphPad Prism 7 (San Diego, CA, USA) was used for data analysis with level of significance set at $p < 0.05$.

5.3 Results

5.3.1 Patient demographics

This study recruited between January 2015 and March 2017 (with a 1 year gap (1 patient recruited) due to maternity leave from February 2015 – February 2016). One hundred and fifty seven patients were approached to take part in the study between February 2016 and March 2017. The outcomes from these patients are detailed in Figure 5.1.

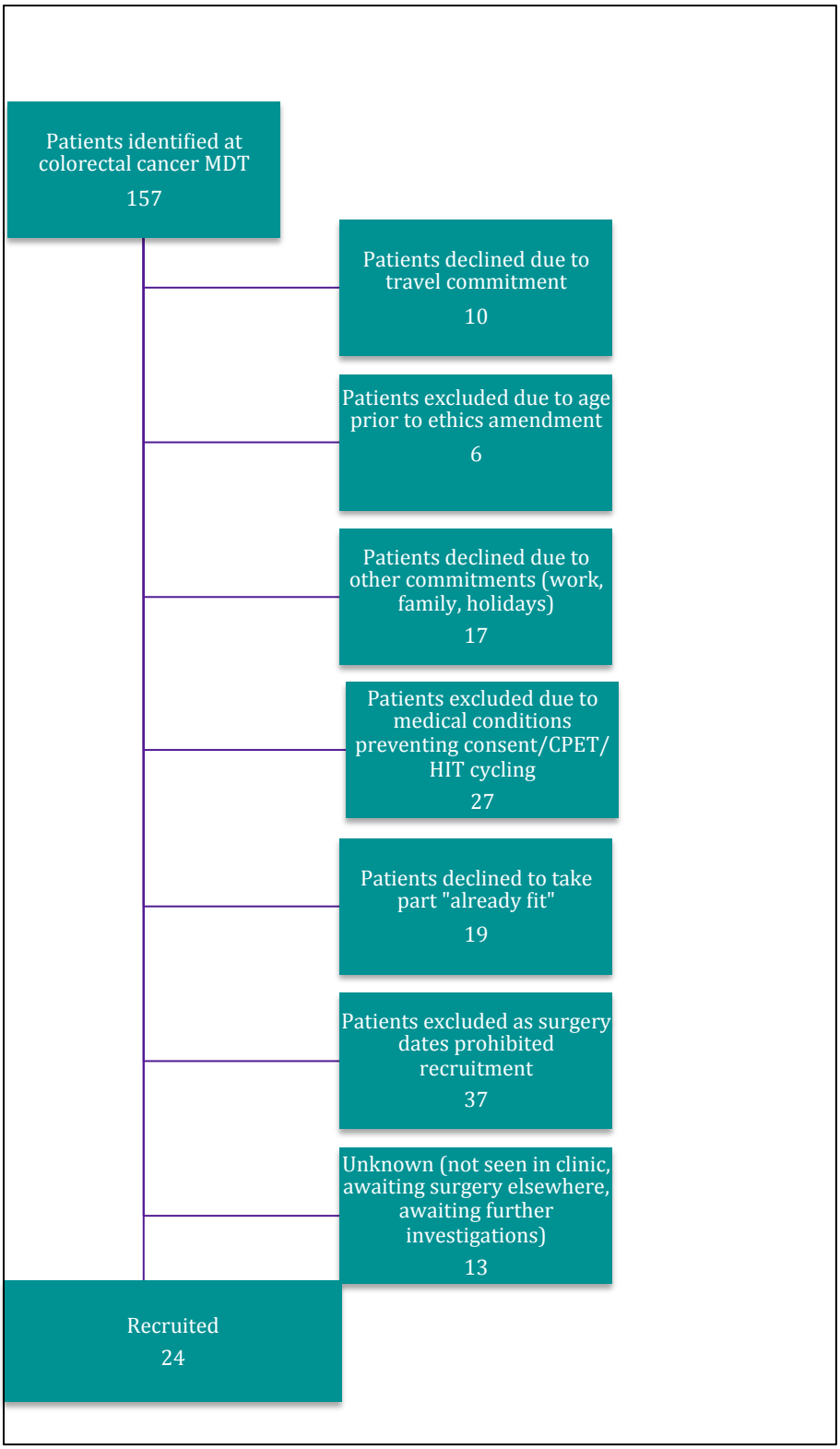


Figure 5.1 Outcomes of patients approached to take part in HITCa study

(MDT multidisciplinary meeting, CPET cardiopulmonary exercise test, HIT high intensity interval training)

Twenty four patients completed the screening process, two were excluded from the study at screening (one due to knee pain preventing cycling and the other due to undiagnosed hypertension). Three patient's operation dates were moved forward after they had started the study not leaving them enough time for them to complete the minimum number (6) of HIT sessions and the reassessment session, they were withdrawn from the study. One patient did not attend for their reassessment visit despite efforts to invite them to complete the study. Eighteen patients completed the study protocol.

The demographic details of the 18 patients who completed the study are summarised in Table 5.1.

Characteristic	Number of participants
Age/years (SD)	67 (±8)
Gender	13M : 5F
BMI (kg/m^2)	29.0 ±4.4
Previous exercise episodes per week	<1 per week (12) 2-3 per week (3) 4-5 per week (2) >5 per week (1)
Comorbidities	• Myocardial infarction (2) • Prior cancer diagnosis (not current CRCa) (2) • Type 2 diabetes (4) • Chronic obstructive pulmonary disease (1) • Psychiatric diagnosis (2) • Controlled hypertension (2) • Musculoskeletal history (inc. joint replacement and spinal surgery) (8)
Medication	• Statin (5) • Isosorbide mononitrate (1) • Inhaled bronchodilator (2) • Warfarin (1) • Metformin (1) • Antihypertensives: o B blocker (5) o Thiazide diuretics (2) o Calcium channel blockers (2) o Angiotensin II receptor antagonists (2) o Loop diuretics (1)
Site of cancer	Right colon (4) Left colon (5) Rectum (9)
ASA	Grade 1 (12) Grade 2 (6)

Cancer T (tumour) stage	T1 or polyp cancer (3) T2 (7) T3 (5) T4 (3)
Post operative N (lymph node) stage	N0 (10) N1 (7) N2 (1)

Table 5.1 Demographic details of HITCa patients (ASA American Society of Anaesthesiologists physical status classification system, 1 Normal healthy patient, 2 Mild systemic disease)

There was no significant change in biochemical markers after HIT (Table 5.2).

	Before HIT	**After HIT**
Haemoglobin (g/L)	141.6 ±18.38	140.5 ±15.47
Haematocrit	0.43 ±0.04	0.42 ±0.04
White cell count (10^9/L)	7.0 ±1.4	7.2 ±1.6
Random glucose (mmol/L)	6.0 ±1.7	6.0 ±1.4
Random total cholesterol (mmol/L)	5.1 ±1.0	4.8 ±0.86

Table 5.2 Biochemical markers in HITCa patients

Patients completed a median of 8 (range 6-14) HIT sessions over a mean of 19 (SD 7) days.

The average training workload was 155W, with all the patients training between 100 and 120% of their baseline Watt max (as determined by CPET).

Three patients had moderate ST depression during training, limiting the training workload (to 100% Watt max) in one of

these patients only. One other patient had their workload limited (to 105% Watt max) due to a minor, self-resolving change in cardiac rhythm.

No patient had his or her training terminated for any clinical reason. There was 100% compliance with the study protocol with all patients undertaking the screening process, baseline testing, minimum number of HIT sessions and reassessment testing.

5.3.2 Cardiovascular measurement data

Despite no change in MAP or diastolic blood pressure (Table 5.3) HIT did elicit a significant reduction in systolic blood pressure (Figure 5.2).

	Before HIT	**After HIT**	**Change**	
Mean systolic blood pressure (mmHg)	152 ±19	142 ±19	-11 ±9.32	p<0.001
Mean diastolic blood pressure (mmHg)	81 ±10	81 ±14	0 ±15.9	p>0.05
Mean arterial pressure (mmHg)	105 ±10	101 ±14	- 4 ±12.0	p>0.05
Resting heart rate (bpm)	75 ±16	75 ±14	0 ±11.5	p>0.05

Table 5.3 Cardiovascular measurement data of HITCa patients

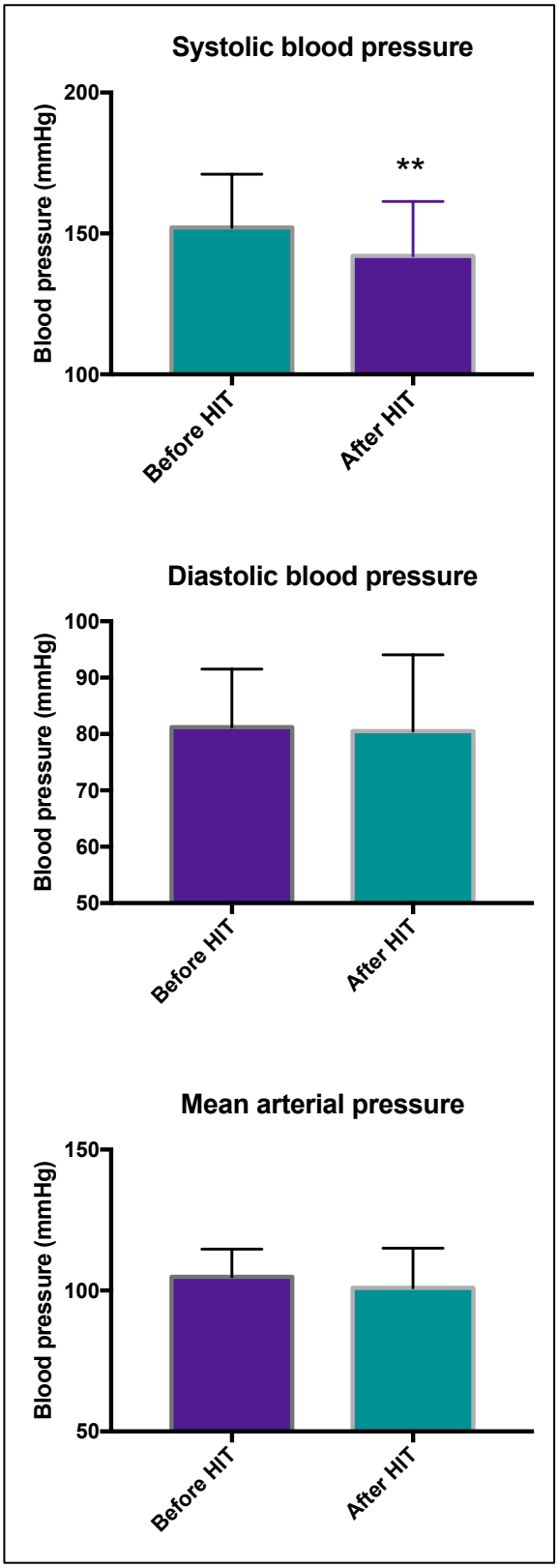


Figure 5.2 Systolic blood pressure, diastolic blood pressure and mean arterial pressure, before and after HIT in CRCa patients, bold lines are mean with SD, ** $p<0.01$

5.3.3 Cardiorespiratory exercise test data

There was no significant change in any CPET derived parameters of cardiorespiratory fitness (absolute VO_2, VO_2 relative to body weight or AT) after HIT (Table 5.4). Full CPET data are appended in appendix 8.5.2.

	Before HIT	**After HIT**	**Change**	
VO_2 peak (l/min)	2.05 ±0.59	2.05 ±0.60	0 ±0.24	p>0.05
VO_2 peak/kg (ml/kg/min)	23.90 ±7.0	24.2 ±7.8	0.34 ±2.58	p>0.05
AT (l/min)	1.20 ±0.29	1.22 ±0.31	0.02 ±0.25	p>0.05
AT (ml/kg/min)	13.99 ±3.39	14.47 ±4.5	0.48 ±2.98	p>0.05

Table 5.4 CPET variables of HITCa patients before and after HIT

There was variation in the change in VO_2 peak on an individual level as shown in Figure 5.3.

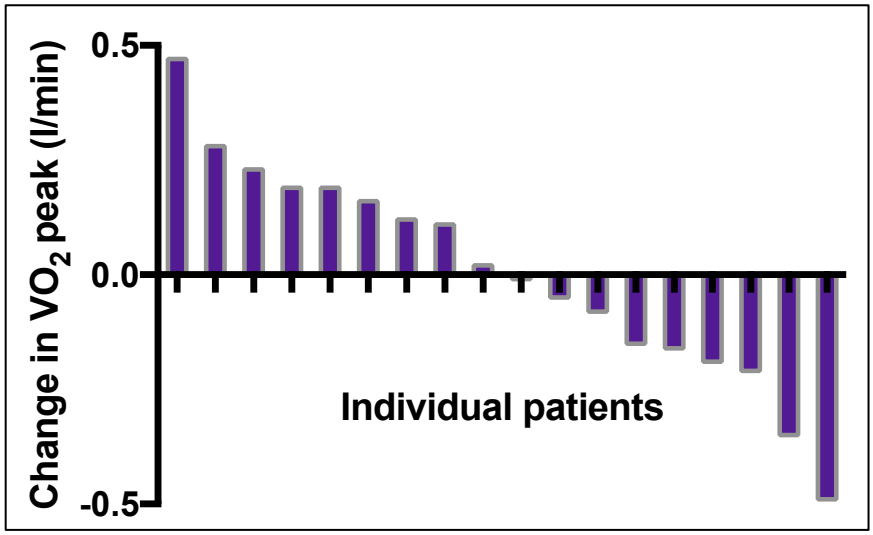


Figure 5.3 Individual change in VO_2 peak following HIT in HITCa patients

In addition to values obtained at, or near to, volitional exhaustion (i.e. the end of the CPET), heart rate and O_2 pulse at 25%, 50% and 100% wattage of the baseline CPET were assessed before and after HIT (Table 5.5 and Table 5.6). Heart rate was significantly lower at all intensities after HIT, but this was not reflected in the O_2 pulse measurements where no significant changes were observed following HIT.

	Before HIT	**After HIT**	**Change**	
HR at 25% Wmax of baseline CPET (bpm)	90 (±19)	86 (±17)	4	p<0.01
HR at 50% Wmax of baseline CPET (bpm)	103 (±19)	98 (±17)	5	p<0.01
HR at 100% Wmax of baseline CPET (bpm)	138 (±22)	130 (±27)	8	p<0.05

Table 5.5 Heart rate at % of maximum wattage (of baseline CPET) during the baseline CPET and reassessment CPET (before and after HIT)

	Before HIT	After HIT	Change	
O_2 pulse at 25% Wmax of baseline CPET	9.94 (±2.3)	9.26 (±2.5)	0.68	p>0.05
O_2 pulse at 50% Wmax of baseline CPET	12.94 (±3.0)	11.92 (±3.13)	0.98	p=0.05
O_2 pulse at 100% Wmax of baseline CPET	14.8 (±2.86)	14.91 (±3.27)	0.11	p>0.05

Table 5.6 O_2 pulse at % of maximum wattage (of baseline CPET) during the baseline CPET and reassessment CPET (before and after HIT)

5.3.4 Exercise performance data

Despite a lack of improvement in the physiological parameters outlined above (chapter 5.3.3), there was a significant increase in time to failure (752 ±93s vs. 789 ±99s, p=0.02) and maximum wattage at failure (142 ±50W vs. 150 ±49W, p=0.007) during the CPET after HIT (Figure 5.4). This suggests that for the same oxygen consumption participants were able to do more work for a longer time.

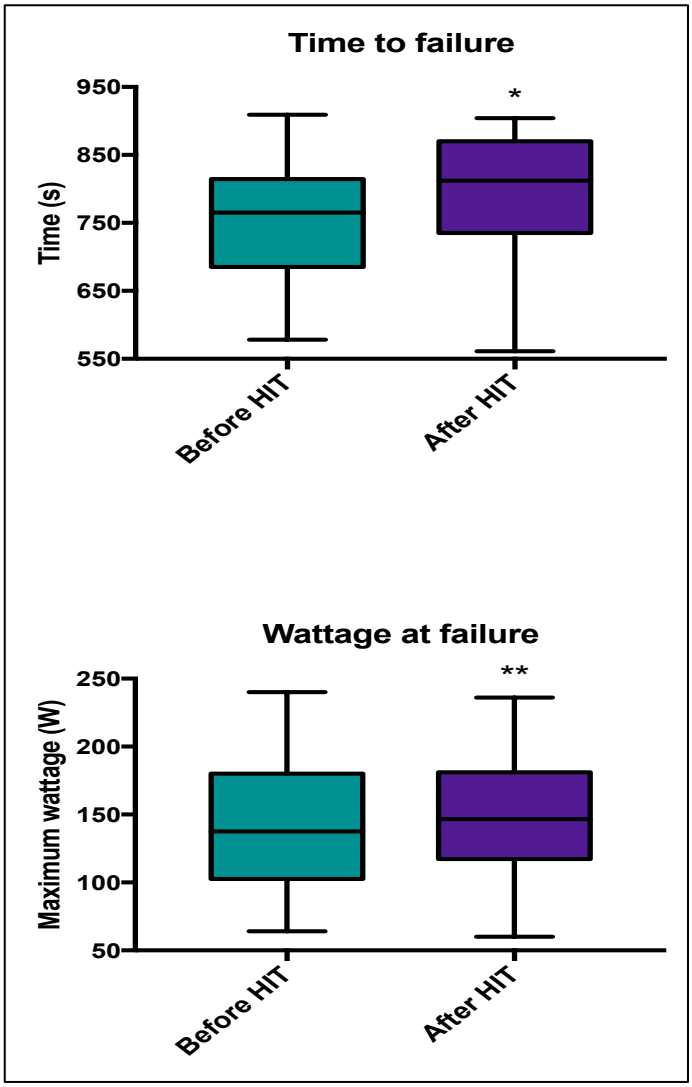


Figure 5.4 Change in time to failure and wattage at failure in HITCa patients following HIT, boxes show median and 25th and 75th percentiles, whiskers show minimum to maximum range, * $p<0.05$, ** $p<0.01$

5.3.5 The effect of HIT duration on improvements in cardiorespiratory fitness

Although there was some variation in the number of HIT sessions completed by each patient (due to factors outwith our control e.g. operation date), there was no significant

relationship between the number of HIT sessions undertaken and the change in VO_2 peak (Figure 5.5) or AT.

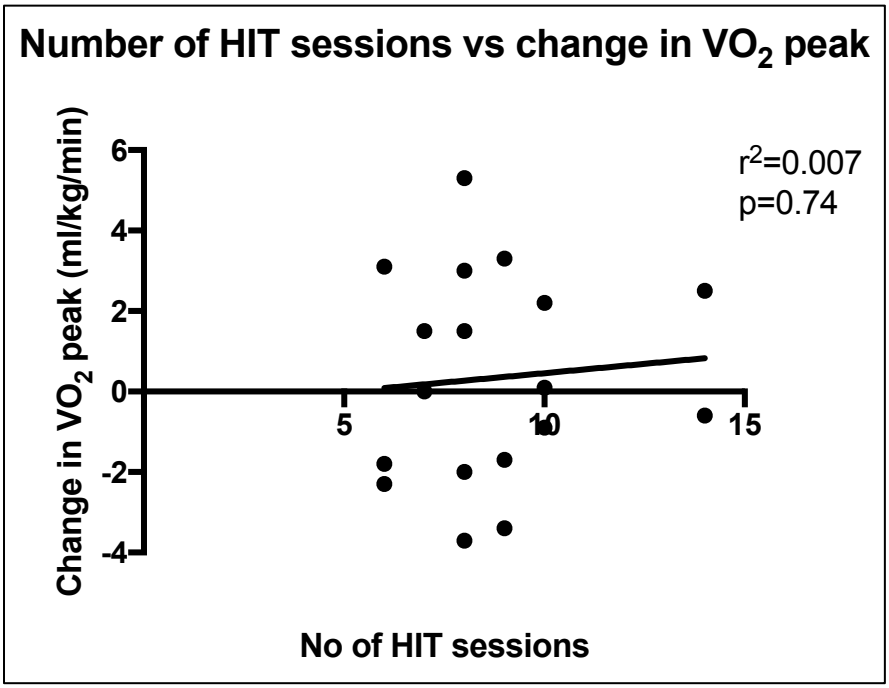


Figure 5.5 Correlation between number of HIT sessions undertaken by HITCa patients and change in VO_2 peak, using linear regression and analysed using Pearson's correlation

5.3.6 The effect of baseline parameters on improvements in cardiorespiratory fitness

There was no significant relationship between baseline VO_2 peak and the HIT induced change in VO_2 peak (Figure 5.6). This was also true for baseline and change in AT (r^2=0.13, p=0.14).

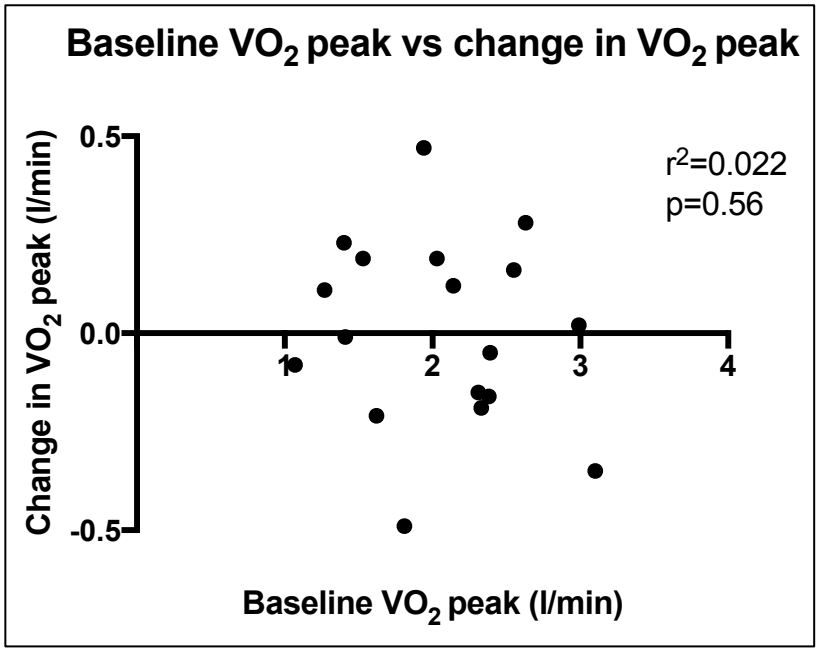


Figure 5.6 Correlation between change in VO_2 peak and baseline VO_2, using Pearson's correlation

Similarly, neither the T (tumour) stage nor the N (node) stage of the tumour affected the response to training in terms of improvement in VO_2 peak (Figure 5.7 and Figure 5.8).

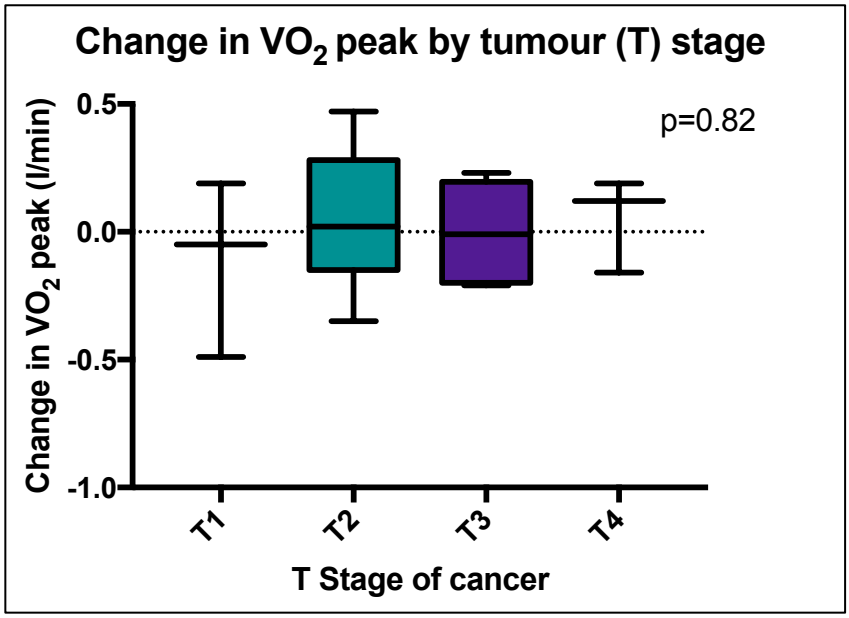


Figure 5.7 Change in VO_2 peak after HIT by tumour (T) stage of cancer in HITCa patients, boxes show median and 25th and 75th percentiles, whiskers show minimum to maximum range

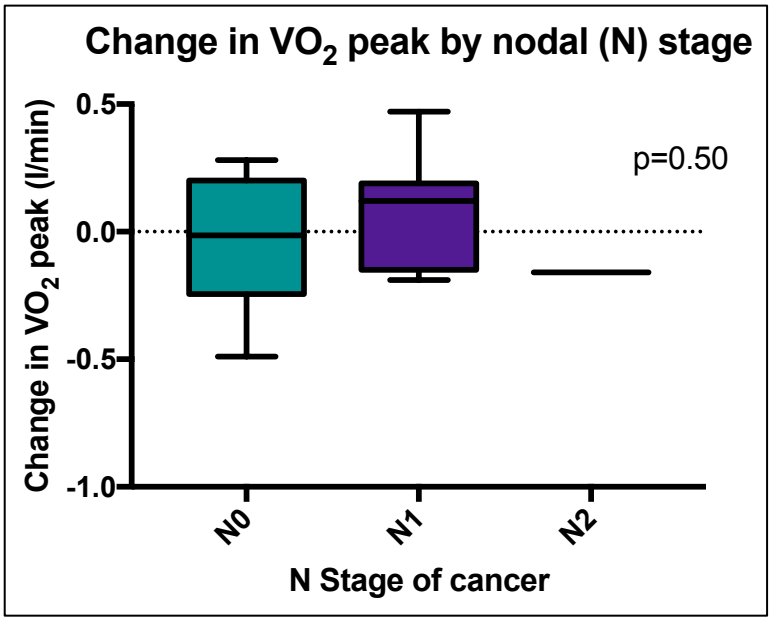


Figure 5.8 Change in VO_2 peak after HIT by nodal (N) stage of cancer in HITCa patients, boxes show median and 25th and 75th percentiles, whiskers show minimum to maximum range (one patient had N2 disease)

5.3.7 Body composition data

There were no significant changes in any body composition parameter (total body fat mass, total body lean mass, trunk fat mass, abdominal fat mass, lean leg mass) measured by DEXA following HIT. Full DEXA data is shown in appendix 8.5.4). The increase in the thickness of the vastus lateralis muscle as assessed via ultrasound just failed to reach statistical significance (1.87 ±0.47cm vs. 2.01 ±0.44cm, p=0.054).

5.3.8 Functional fitness and physical activity questionnaire data

Short performance physical battery tests demonstrated no significant change in physical function following HIT (10.3 ±1.7seconds vs. 10.4 ±1.7seconds, p=0.70). This data is based on analysis of 16 subjects as 1 participant could not complete the baseline tests due to transient leg pain and another participant did not complete the tests at reassessment due to a change in a clinic appointment time follow her reassessment session.

Similarly, as 2 participants failed to complete their quality of life questionnaires after HIT, the following questionnaire results are from the 16 completed datasets (before and after HIT) (Table 5.7). There was a significant improvement in health perception following HIT as indicated by the EQ5D visual analogue scale,

despite no improvement in the EQ5D index score. The IPAQ showed a non-significant change towards an increase in weekly physical activity following HIT. There was no change in DASI or WEMWBS scores after HIT.

	Before HIT	**After HIT**	**Change**	
EQ5D index score	0.926 ±0.083	0.926 ±0.089	0	p>0.05
EQ5D VAS	76 ±13	82 ±10	6	p<0.05
IPAQ (met mins/week)	3810 (IQR 2798)	6594 (IQR 5044)	2784	p>0.05
DASI estimated VO_2 peak (ml/kg/min)	29.6 ±4.5	29.3 ±4.9	-0.3	p>0.05
WEMWBS	60 ±5	60 ±6	0	p>0.05

Table 5.7 Quality of life questionnaire data from HITCa patients

Three additional participants did not return completed EORTC questionnaires after HIT. From the 13 completed datasets there was no significant change in any of the scales of the EORTC 30 or 29 for colorectal cancer symptoms.

5.3.9 Acceptability of HIT

Assessing the acceptability of HIT using a 5-to-1 scoring system (Table 5.8) it was found that patients enjoyed the HIT, they would repeat the programme and recommend it to others. Patients believed that their fitness had improved (assessed prior

to receiving their CPET results) and that the HIT was not too demanding of time or effort. As with the HIT study presented in Chapter 4, patients would not have preferred to exercise at home or in a group.

Comment	**Median Score (Range) 5 – Strongly agree 1–Strongly disagree**
HIT was well explained	5 (4-5)
I enjoyed HIT	5 (4-5)
HIT was a time burden	1 (1-5)
I would recommend HIT to others	5 (4-5)
HIT was more demanding than expected	3 (1-5)
I would do HIT again	5 (4-5)
The travelling involved interfered with my life	1 (1-5)
The physical strain interfered with my life	1 (1-3)
I believe my fitness has improved	5 (3-5)
I would like to have exercised in a group	1 (1-3)
I would like to have exercised at home	1 (1-3)

Table 5.8 Results of acceptability questionnaire for HITCa patients

The questionnaire also allowed free text comments regarding "the most challenging" and "the best" parts of the study.

Comments regarding the most challenging part of the study included;

- "the last HIT interval"

- “the bike”
- “the travelling involved”
- “getting on and off the bike”
- “pushing myself to complete each interval”
- “finding the time”

Comments regarding the best part of the study included;

- “knowing that you have done something to improve yourself for surgery”
- “feeling like you are giving back”
- “a good health screening”
- “knowing that I will be fitter and recover quicker”
- “realising that I can do it”
- “feeling involved and motivated”
- “working with the team”
- “positive impact on mood, self-belief and physical well being”

5.4 **Discussion**

This novel, observational, cohort study demonstrated that there was no significant improvement in cardiorespiratory fitness, as measured by VO_2 peak or AT, in a group of preoperative colorectal cancer patients following a HIT programme that complied with national cancer management timelines. Thus, from this work this intervention cannot be recommended for this group. These patients were however, able to perform more work for a longer period without requiring an increase in oxygen consumption suggesting that they had become more energy efficient following training. In addition, patients were able to exercise more efficiently with lower heart rates at matched workloads. HIT did not induce any significant changes in body composition in this patient cohort. This study suggests that it is safe to use a HIT programme in this population with no notable clinical complications occurring in this study. Importantly, as evidenced by a significantly increased EQ5D VAS, acceptability scores and free text comments, patients enjoyed the HIT and reported a feeling of improved general health following the programme.

Given the improvements in cardiorespiratory fitness seen in our HIT study of healthy age matched participants (Chapter 4) we hypothesised that HIT would elicit improvements in

cardiorespiratory fitness in our colorectal cancer group also, this was not the case. To our knowledge there has been no other research demonstrating an improvement in cardiorespiratory fitness in this patient group within the national cancer management timelines. Dronkers et al., assessed a 6 session preoperative exercise training programme in a similar time frame, but in agreement with our findings showed no improvement in aerobic capacity (Dronkers et al., 2010). Kim et al., trained their colorectal surgery patients for an average of 3.8 weeks, and despite a much higher volume of training (27 sessions), also did not see an improvement in VO_2 peak. They did however find a significant increase in peak power output (Kim et al., 2009). Valkenet et al., used a very short duration moderate intensity training in preoperative gastrointestinal cancer patients and showed an improvement in inspiratory muscle strength only (Valkenet et al., 2016). Most recently Roca et al. did show an improvement in cycling endurance and a reduction in postoperative complications in a group that underwent preoperative high intensity endurance training however these patients had mixed surgical diagnoses (and therefore procedures), data from their CPET tests was not presented and their training lasted a mean of 6 (±2) weeks meaning that their protocol did not comply with national cancer

management timelines (Roca et al., 2017). As none of these studies used HIT as their training modality, it was reasonable to suggest that we may have seen superior improvements using a format of exercise training that has been shown to induce greater changes in fitness in shorter timeframes in healthy groups when compared to continuous moderate intensity exercise training (Gibala et al., 2006).

The possible reasons why we did not see the postulated improvements in cardiorespiratory fitness and therefore must reject our original hypothesis are multiple. Compared to our HIT study in a healthy population (chapter 4) there was a significantly shorter duration of training and therefore fewer HIT sessions. Indeed, we may have seen an improvement in cardiorespiratory fitness if the cancer patients had been able to train for the same amount of time, but this was not possible. The duration of training was limited by the patients scheduled cancer surgery and the frequency of sessions affected by patients personal preference, a minimum of 3 sessions each week was encouraged and achieved by most, although many patients had additional commitments during the preoperative period which training had to be scheduled around. Both of these factors are very difficult to change without adversely affecting study recruitment (i.e. suggesting that patients train every day

or delaying their surgery). These changes would also make the study results less transferable to the clinical setting. Training duration was further limited beyond that imposed by cancer target timelines and patient's personal commitments by the need for study screening, baseline and reassessment testing. These sessions occupied 5-7 days of the total 31 potential days available for training. In addition, the lack of correlation between session number and cardiorespiratory fitness improvements suggests that this was not likely to be the only limiting factor.

It may be that the exercise intensity was not high enough to elicit changes in our timeframe. Very short-term HIT studies (e.g. 2 weeks) have shown changes in VO_2 peak with very small exercise volumes (i.e. total of 15 minutes exercise per study, 6 sessions of 4-6 intervals 30 second sprints per session) in young participants. However, these studies have used "all out" Wingate style HIT with an average wattage around 600-800W at the start of each interval vs. our 100-120% Watt max (mean 155W). Although some studies with Wingate protocols have been performed in older participants, it is unlikely that such intensive regimes would be tolerated, and much less enjoyed, by our patient cohort (Babraj et al., 2009).

Previous work in colorectal cancer patients from our department has shown that AT improves following cancer resection without a change in lean muscle mass or self-reported increase in physical activity (Williams et al., 2014). It is plausible that the reasons for this increase in fitness once the cancer has been resected are conversely responsible for the difficulties in improving fitness whilst the cancer remains in situ. This is supported by work in animal models which has shown that the increased inflammatory load associated with cancer significantly decreases muscle oxidative capacity and alters mitochondrial dynamics (White et al., 2011). In addition, work from our group has shown that muscle protein synthesis in response to anabolic stimuli is blunted in cancer patients, but restored upon resection, further supporting the notion that cancer in situ has the potential to cause metabolic and adaptive disruption (Phillips et al., 2013). If this proposition is correct we may have expected to see a greater improvement in cardiorespiratory fitness in those with an earlier stage cancer (lower T and N stage) and a smaller improvement in VO_2 in those with higher stage cancers. We did not observe this in this study, but the numbers in each stage group were very small and the study was not powered to detect this difference.

In keeping with the lack of change in cardiorespiratory fitness we also observed no significant change in DEXA derived body composition parameters following HIT. This is contrary to the body composition data for the HIT study (chapter 4) where increases in lean leg mass were observed. As above this may be due to the tumour burden suppressing enhanced muscle protein synthesis (a normal adaptation to exercise training (Brook et al., 2016)) and therefore blunting adaptive hypertrophy (Williams et al., 2012). This proposition cannot however be proven by this study as measures of MPS were not made, and despite these differences in DEXA derived data between the two studies, ultrasound-based analysis of vastus lateralis muscle thickness shows similar significant increases in both healthy and cancer cohorts (healthy: 2.04 ±0.27cm before vs. 2.17 ±0.28cm after, p=0.05, cancer: 1.87 ±0.47cm before vs. 2.01 ±0.44cm after, p=0.05).

Another possible explanation for the lack of cardiorespiratory fitness improvement in this study is the frequency of "non-responders" within the study group. As in the healthy volunteer HIT study there was clear variation in the magnitude of change in fitness on an individual level in the colorectal cancer patients. In addition to a lack of mean improvement in fitness as a group, a proportion of patients (9 out of 18) actually showed a

numerical decrease in cardiorespiratory fitness after the HIT programme. This observation was more pronounced than in the healthy group where only 4 out of 21 participants showed no response following training. A lack of increase in fitness following training has been seen in other preoperative colorectal cancer exercise studies (21.5 ±10 vs. 20.9 ±8.7 ml/kg/min VO_2 max) (Kim et al., 2009). It is a recognised phenomenon that some people do not improve their fitness (or indeed muscle mass, the primary adaptive endpoint for resistance exercise training) in response to exercise training. The HERITAGE family study is a large-scale, multicentre study into the genetic influence on exercise response, one of the resulting publications has shown a 5% non-responder rate to exercise (Bouchard et al., 1999). "Non-response" has been investigated for health ((insulin sensitivity (Boule et al., 2005)) and fitness (VO_2 max (Gurd et al., 2016; Timmons et al., 2010)) parameters after endurance exercise training and for muscle hypertrophy after resistance exercise training (Phillips et al., 2013). Relevant to this study, it has recently been shown that the "non-responder" phenomenon also exists when HIT is the exercise stimulus (Phillips et al., 2017). Therefore it may be that a high proportion of "non-responders" were randomly present in this study, or indeed that "non-responders" to exercise are more

likely predisposed to cancer. Other exercise studies in preoperative cancer patients have found a similar non response rate of 50% (Huang, 2015). This second premise may link to the recognition that those who commit to life-long exercise are less likely to develop colorectal cancer (Newton, 2011). Anecdotally we know that those who see improvements are more likely to adhere to exercise training and therefore the "non-responders" may be those least likely to become habitual exercisers. Further investigation is required into the mechanistic basis of heterogeneous exercise adaptation and the frequency of exercise "non-responders" in patient groups. This in turn may be able to inform selection of patients for preoperative exercise based on their likely improvement in fitness.

A further potential explanation for the lack of improvement in cardiorespiratory fitness following HIT in this clinical population may be the medication they were taking. Compared to 1 of the HIT study cohort, 5 out of 18 participants in the cancer cohort were taking beta-blockers which limited their heart rate (and therefore physiological stress (Billeh et al., 2006) response to exercise).

Despite the lack of increase in cardiorespiratory fitness with HIT our patients did become more energy efficient; they were able to cycle to a higher workload and endure a longer CPET during

their reassessment, achieving significantly lower heart rates for a matched workloads after HIT. This improvement in exercise efficiency has been seen previously after moderate intensity exercise training programmes, whereby healthy elderly athletes have significantly lower energy expenditure for a matched power output compared to sedentary elderly participants. The degree of improvement correlated with, and was explained by, an increased mitochondrial volume density and mitochondrial function (maximal ATP production) in elderly athletes (Broskey et al., 2015). This improved efficiency suggests that after HIT our patients were able to conserve energy stores and exert less effort than they had needed to previously. This energy efficiency may be important during the stress of surgery (Desborough, 2000).

In addition to enhanced efficiency, we have also demonstrated HIT induced reductions in systolic blood pressure in this study. This is in keeping with a wealth of literature showing reductions in blood pressure with exercise training, although many of these studies trained people for much longer periods of time (9-12 weeks)(Lepretre et al., 2009; Molmen-Hansen et al., 2012; Skutnik, 2016). HIT studies as short as 2 weeks (6 sessions) in duration have reported improvements in insulin action, cycling performance (time trial) and endurance capacity (Babraj et al.,

2009; Burgomaster et al., 2005; Gibala et al., 2006), but to our knowledge no studies have reported improvements in blood pressure in a preoperative cohort. Reduction in blood pressure may have clinical relevance in the perioperative period; a recent study of 21,720 patients undergoing colorectal surgery gave an odds ratio of 1.6 for postoperative acute renal failure in those with preoperative hypertension (Ramonell et al., 2016). A separate study of over 2 million patients put the odds ratio at 1.14 for hypertension increasing the likelihood of a postoperative myocardial infarction (Moghadamyeghaneh, 2015).

Many of the quality of life questionnaires did not show a change following HIT, this is in keeping with literature demonstrating that health related quality of life (HRQoL) in colorectal cancer patients is comparable to the general population until the disease reaches a palliative stage (Färkkilä et al., 2013). Only the EQ5D VAS, which is the simplest tool to complete, showed a significant improvement in overall "health state". It is difficult to objectively define the psychological benefits that patients get from the HIT programme *per se* although there are likely to be some feelings of improved wellbeing from the exercise alone as this is well documented in many cancer groups with many types of exercise (Mishra et al., 2012). There may also be some

psychological benefit from contact, support and discussion with those facilitating the programme. It is interesting that, although the travel and time commitment may have been a reason not to partake for some individuals, none of those who completed the study would have preferred to exercise in the more convenient location of their own home. This may have been to do with the psychological benefits or perceived superior gains associated with training under supervision in the unit, although the reasons for these preferences were not formally explored in this study. Burke's study questioned advanced rectal cancer patients about their reasons for taking part in preoperative exercise; feelings of camaraderie, control and encouragement were the most frequently mentioned emotional factors (Burke, 2014). Overall it is encouraging for future projects and potential clinical implementation of exercise programmes that this study was well received and enjoyed by those who did it despite the stress of a new cancer diagnosis and impending major surgery.

A limitation of this cohort study is the lack of a control group. This makes it difficult for us to compare the natural progression of cardiorespiratory fitness in the preoperative colorectal cancer population if no exercise been undertaken. Indeed it may be that although we have not shown an improvement in cardiorespiratory fitness or body composition we have negated

declines that would have occurred during this period without training. For example Gillis et al. showed, in a 25 day prehabilitation study, a significant reduction in walking capacity in their preoperative control group (-16m (SD 46m)) (Gillis et al., 2015). In addition, Lieffers et al., showed significant muscle mass wasting in 40% of preoperative colorectal cancer patients (Lieffers et al., 2012). However, Dronkers questions the ethics of a non-exercise control arm when there is such strong supportive evidence in favour of physical activity and improved perioperative outcomes (Dronkers, 2016).

This study was powered for a change in VO_2 peak of 2ml/kg/min, as used in the HIT study and found to be achievable and also used by other groups as a clinically significant improvement with training. To achieve 80% power only 18 participants were required. Based on our results in chapter 5 it can be seen that the standard deviation of difference in VO_2 peak after exercise was less (2.58 ml/kg/min) in the HITCa group than in the non cancer HIT group (2.8 ml/kg/min) and a post hoc power calculation based on the observations in this study consequently lead to a smaller study size of 16 patients required for 80% power. It is reassuring that the study was not undersized based on assumptions made from non-cancer observations. A power of 80% still leaves a 20%

chance of a type II error, but choosing this 4:1 trade off for rejection of the null hypothesis is common practice for studies of this type.

It is our anecdotal experience, that recruitment was easier if the operating surgeon introduced the study. This is in agreement with Kimmick's study who also observed that this was the most important thing in improving recruitment of older people into cancer studies (Kimmick, 2016).

An important strength of this study was its pragmatism. This study was a real reflection of what is possible when working within the confines of the national cancer management timelines in a clinical setting. It was performed in a group of patients representative of the heterogenous colorectal cancer population (i.e. without being highly selective with regards to age, previous fitness, co-morbidities, weight, medications etc.) and in an environment where there is logistical and target driven pressure on time from diagnosis and decision to treat to surgery.

As the curative treatment for colorectal cancer is surgery; any prehabilitation program must aim to improve outcomes from this, without interfering with the patients "journey" to the operating theatre. Ideally in this study all patients would have completed 12 HIT sessions but this was only possible within the

available preoperative time frame in very few. Our pragmatic protocol allowed patients to train for a minimum of 6 sessions so that this study could provide a "real life" model of preoperative exercise and explore results that would also be achievable outside a research setting.

This study has shown that preoperative HIT in colorectal cancer patients can reduce their blood pressure, enhance their energy efficiency, improve their feelings of wellbeing and allow them to both tolerate and enjoy preoperative exercise. However, has not demonstrated that it is possible to significantly improve cardiorespiratory fitness in the limited time available due to national cancer management timelines.

5.4.1 Comparison of HIT in older, healthy volunteers and HIT in preoperative colorectal cancer patients

As discussed in the relevant chapters above we have seen an improvement in cardiorespiratory fitness with 31 days HIT in older, healthy volunteers but have not been able to replicate this improvement in preoperative colorectal cancer patients using the same exercise programme.

The relevant details of the two studies are reviewed in Table 5.9.

	Healthy volunteer study	Preoperative colorectal cancer patient study
Age (range)	66.6 (62 – 73) years	67 (52-77) years
Gender	8M : 13F	13M : 5F
Baseline fitness	13/21 participants <1 exercise episode per week	12/18 patients <1 exercise episode per week
Baseline BMI (kg/m^2)	26.1 ±2.9	29.0 ± 4.4
Cardioresp. Comorbidities	• Asthma (2) • Hypertension (5)	• Myocardial infarction (2) • Chronic obstructive pulmonary disease (1) • Hypertension (2)
Cardioresp. medication	• Inhaled bronchodilators (2) • Antihypertensives: ○ Calcium channel blocker (1) ○ Diuretics (3) ○ Beta blocker (1) ○ Angiotensin II receptor antagonist (1) ○ ACE inhibitor (1)	• Isosorbide mononitrate (1) • Inhaled bronchodilator (2) • Antihypertensives: ○ B blocker (5) ○ Diuretics (3) ○ Calcium channel blockers (2) ○ Angiotensin II receptor antagonists (2)
Duration of training	28 ±3.5 days	19 ±7 days
Number of HIT sessions	12	8 (6 – 14)
Baseline VO_2 (l/min)	1.78 ±0.50	2.05 ±0.59
Reassessment VO_2 (l/min)	1.93 ±0.54	2.05 ±0.60
Change in VO_2 (l/min)	0.16 ±0.22	0 ±0.6
Baseline VO_2 (ml/kg/min)	23.90 ±4.68	23.90 ±7.0
Reassessment VO_2 (ml/kg/min)	26.2 ±5.44	24.2 ±7.8
Change in VO_2 (ml/mg/min)	2.30 ±2.84	0.34 ±2.58

Table 5.9 Comparison of healthy and cancer patient HIT studies

Both the healthy volunteer study and the colorectal cancer patient study were designed to look at changes in cardiorespiratory fitness within the groups following HIT. The

healthy volunteer study was a pilot study for the cancer group to test the acceptability of the protocol and look at changes in fitness in those without disease. They were not intended to be compared to each other however the results of each study are very different and for the purpose of this thesis deserve some comment.

There were baseline differences between the groups which makes any evaluation of changes difficult, there were more men in the cancer group as would be expected from known colorectal cancer incidence statistics (Cancer Research UK, 2017). The effect of gender on improvements in fitness with HIT is still debated with recent studies showing women had a significantly greater improvement in VO_2 peak after 12 weeks of sprint interval training (Bagley et al., 2016) but this has not been reproduced in studies using reduced intensity HIT (more similar to our protocols) which have shown no significant effect of gender (Metcalfe, 2016). The cancer group was also had a significantly higher BMI (26.1 ±2.9 vs. 29.0 ±4.4 kg/m^2, p= 0.025). There was no significant difference in age (p=0.72), baseline exercise habits (p=0.33) or baseline VO_2 peak (p=0.125) between the healthy and cancer groups. Medication and co-morbidities are difficult to compare e.g. fewer of the cancer group had hypertension but as a group they were

prescribed more antihypertensive medications (due to few patients with multiple medications).

The most obvious difference is that the healthy volunteers showed a significant improvement in their fitness whereas the colorectal cancer patients did not. As discussed above in chapter 5.4 the reasons for lack of improvement in the cancer group could be the significantly shorter time available for training and therefore fewer HIT sessions achieved. It may also be because having a cancer in situ makes it more difficult to improve fitness or because there is a greater number of non-responders to exercise in the patient group. This is best illustrated by the graphs of individual change in VO_2 peak, Figure 5.9 and Figure 5.10.

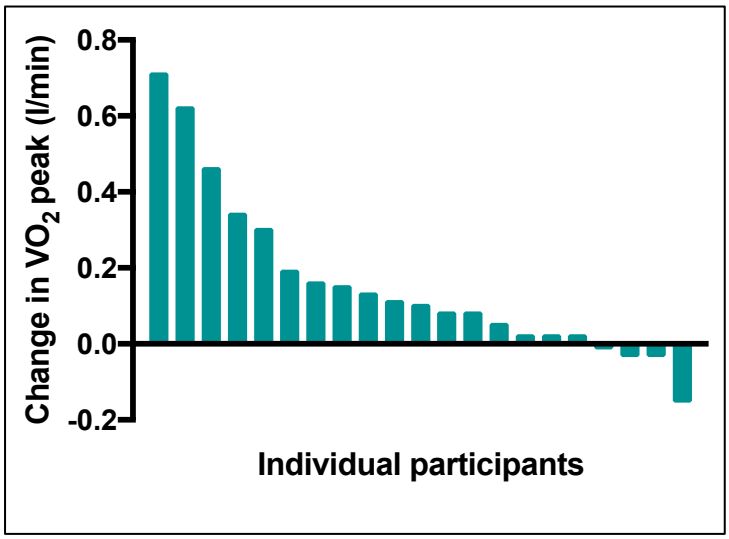


Figure 5.9 Individual changes in VO_2 peak in healthy volunteers

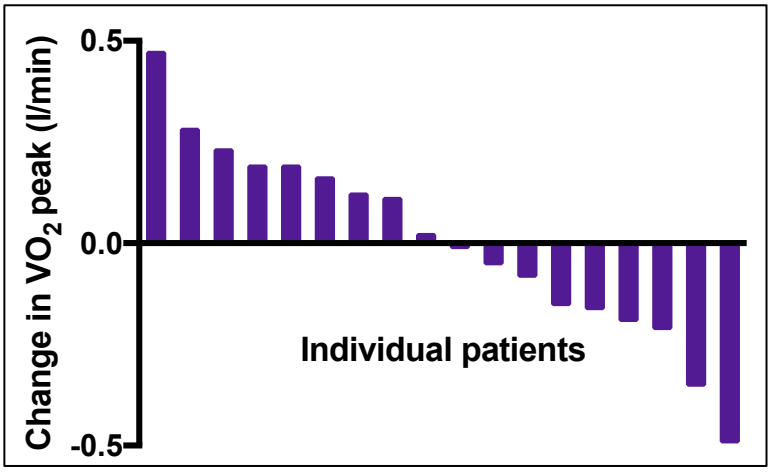


Figure 5.10 Individual changes in VO_2 peak in cancer patients

Again the reasons for these differences are debatable and further large, well-powered clinical studies are required to elucidate these as well as studies investigating the mechanisms responsible for improvement due to HIT which may be lacking in cancer patients.

6 Thesis discussion, overview and future directions

Colorectal cancer is a common and serious health condition cured by surgery. The invasive nature of these operations predispose patients to risks of postoperative complications including death. As our ability to detect cancers and support patients through surgery improves we are operating on an increasingly old patient cohort. Increasing age is often associated with increasing frailty and this increases the risks in the postoperative period.

Preoperative exercise is one method by which patient's fitness for surgery might be improved, by increasing their cardiorespiratory reserve to better equip them for the stress response that major surgery induces.

Studies into preoperative exercise in colorectal cancer patients had previously not been systematically reviewed. The appetite for preoperative exercise within the colorectal surgical professional population treating this group was not known and nor was it known whether it was actually possible to improve fitness in the preoperative time frame in those with colorectal cancer. These questions have been answered in this thesis.

Chapter 2 systematically reviewed the previous evidence for preoperative exercise in colorectal cancer patients and found few studies that showed some improvement in fitness over 25-42 days but that this did not correlate with improvements in postoperative outcomes. The conclusion was that further, well powered, RCTs were required. Studies, currently ongoing, such as PREPARE-ABC (http://www.uea.ac.uk/prepare-abc) are discussed later in this chapter.

Chapter 3 captured the views of a group of consultant colorectal surgeons through a Delphi process, with the outcome that the concept of preoperative exercise was supported but that there was not yet a strong evidence base.

Chapter 4 demonstrated the feasibility and effectiveness of HIT to significantly improve the cardiorespiratory fitness of a group of healthy individuals, aged matched to the colorectal cancer population, within the national cancer management timelines.

However, the application of the same intervention to a group of patients with colorectal cancer did not produce the same improvements and this is shown in chapter 5. This may be because the time available prior to surgery was too short or the intensity of the exercise may not have been high enough to

induce change. It may also be that on a cellular level cancer patients are unable to improve their fitness whilst their cancer remains in situ. Exploring the heterogeneity of adaptation in cancer patients (and the observation of a greater degree of "non-responders") it may be suggested that people who develop colorectal cancer are more likely than others not to respond to exercise. Genetic markers (Bouchard et al., 2015; Phillips, et al., 2013) of potential response to training may allow targeted training interventions, allowing best use of resources, but potentially at the expense of the psychological benefits gained with participation in a preoperative exercise programme.

Despite the lack of improvement in cardiorespiratory fitness our patients benefited from a reduced blood pressure and became more energy efficient during their training. The compliance with the programme was high and they enjoyed the time spent training prior to surgery.

Future investigations need to be focused on the reasons behind the lack of improvement in cardiorespiratory fitness in this patient group. Peripheral (skeletal muscle-based) mechanisms could be further investigated by interrogating pre and post training muscle samples to look at rates of muscle protein synthesis and mitochondrial enzyme activity following training.

The PREPARE-ABC study (Hernon, 2016) plans to evaluate preoperative in-hospital interval aerobic training vs. home moderate intensity training vs. control group in 1146 patients. Their primary objectives are to establish the effectiveness and cost-effectiveness their interventions with regards to short-term recovery outcomes and HRQoL, measured via SF-36, at 12 months. Their study is powered to detect a 25% reduction in postoperative complications and a 3 unit difference in the SF-36 questionnaire (both 90% power, alpha 2.5%) between the control and exercise groups. Hence the much larger number of patients required for this study compared to our work. Recruitment started in November 2016.

Whilst awaiting results of large studies like PREPARE-ABC other options for improving preoperative fitness should be investigated. Home or community based programmes should be encouraged as they require much less NHS resource and would thus be available to a larger proportion of patients. Although, despite the benefit of accessibility, fitness gains in community programs (outside supervised inpatient facilities) are likely to be more modest (Lunt et al., 2014). Also, in our experience, patients preferred to exercise in our unit rather than at home, although home HIT is being further investigated by our research team currently.

If in-hospital training appears to be preferable and more effective then facilities for patients to exercise in the preoperative period would need to be allocated, perhaps by using cardiac rehabilitation units which are more widely available nationally (Hubbard et al., 2016).

If preoperative exercise alone does not show the benefits that had been expected maybe multimodal prehabilitation should be used. There are various studies combining preoperative exercise with nutritional supplementation, lifestyle modifications, comorbid disease optimisation and psychological input which have shown improved functional fitness outcomes postoperatively (Li et al., 2013).

Failing this, if no preoperative optimization methods produce any significant change in postoperative outcomes then the key to reducing postoperative complications may be to operate and remove cancers as quickly as possible. This is, in effect, the current situation in the NHS. The background data as to where the 31 day time limit originated is difficult to ascertain and there is conflicting evidence regarding whether a delay in treatment affects oncological outcomes (Leong & Chapman, 2017). Given that 97% patients in the UK (January – March 2015 (NHS England, 2015)) were treated within 31 days (and currently

much earlier in our institution) there may not be much to be gained from operating a few days earlier.

Sothisrihari et al argue that prehabiliatation should "stop the clock" of the cancer treatment timeline (Sothisrihari et al., 2016) but many feel that there is currently not enough evidence that prehabiliitation improves outcomes to recommend a change in cancer guidelines. Delaying surgery to allow extended prehabilitation (i.e. to ensure improvement in cardiorespiratory fitness) may or may not affect clinical cancer outcomes (Leong & Chapman, 2017).

If patients need to be as fit as possible for surgery and there is not enough time or an appropriate method for improving fitness in the immediate preoperative period our attention must focus on improving fitness in the general population. If everyone engaged in more physical activity they would be "fit for surgery" should the need arise and indeed, there would be less need for surgery, with inactivity and obesity being independent risk factors for colorectal cancer. Changing lifestyle behaviours of a population in this way however, may be easier said than done (Spencer, 2015).

7 References

ACPGBI, RCSEng, & The NHS Information Centre for Health and Social Care. (2015). National Bowel Cancer Audit Report 2015

Adamsen, L., Midtgaard, J., & Madsen, J. K. (2003). Feasibility , physical capacity , and health benefits of a multidimensional exercise program for cancer patients undergoing chemotherapy. *Support Cancer Careupport Cancer Care*, *11*(11), 707–716. http://doi.org/10.1007/s00520-003-0504-2

Adamsen, L., Quist, M., Andersen, C., Moller, T., Herrstedt, J., Kronborg, D., … Rorth, M. (2009). Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. *Bmj*, *339*(oct131)b3410.http://doi.org/10.1136/bmj

Adamson, S., & Lorimer, R. (2014). 1380 letters to the editor july 2014–vol. 62, no. 7 jags. *JAGS*, *62*(7), 1380–1381

Ahmaidi, S., Masse-Biron, J., Adam, B., Choquet, D., Freville, M., Libert, J. P., & Prefaut, C. (1998). Effects of interval training at the ventilatory threshold on clinical and cardiorespiratory responses in elderly humans. *European Journal of Applied Physiology and Occupational Physiology*, *78*(2), 170–6. http://doi.org/10.1007/s004210050403

Ahn, K.-Y., Lee, M. K., Kim, D.-I., Park, J., Min, J., In Yang, H., Jeon, J. Y. (2016). Cardiopulmonary fitness, adiponectin, chemerin associated fasting insulin level in colorectal cancer patients. *Supportive Care in Cancer*. http://doi.org/10.1007/s00520-016-3095-4

Ainsworth, B. E., Haskell, W. L., Whitt, M. C., Irwin, M. L., Swartz, A. N. N. M., Strath, S. J., … Leon, A. S. (1995). Compendium of Physical Activities : an update of activity codes and MET intensities. *Medicine and Science in Sports and Exercise*, (12).

American College of Sports Medicine. (2009). American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Medicine and Science in Sports and Exercise*, *41*(3), 687–708. http://doi.org/10.1249/MSS.0b013e3181915670

Arthur (2000). effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. *Annals of Internal Medicine*, *133*(4), 253

Astorino, T., Allen, R., Roberson, D., & Jurancich, M. (2012). Effect of high intensity interval training on cardiovascular function, VO2 max and muscular force. *J Strength Cond Res*, *26*(1), 138–145.

Babraj, J. a, Vollaard, N. B. J., Keast, C., Guppy, F. M., Cottrell, G., & Timmons, J. a. (2009). Extremely short duration high intensity interval training substantially improves insulin action in young healthy males. *BMC Endocrine Disorders*, *9*, 3. http://doi.org/10.1186/1472-6823-9-3

Backman, M., Wengström, Y., Johansson, B., Sköldengen, I., Börjesson, S., Tärnbro, S., & Berglund, Å. (2014). A randomized pilot study with daily walking during adjuvant chemotherapy for patients with breast and colorectal cancer. *Acta Oncologica (Stockholm, Sweden)*, *53*(4), 510–20. http://doi.org/10.3109/0284186X.2013.873820

Bacon, A. P., Carter, R. E., Ogle, E. a, & Joyner, M. J. (2013). VO2max trainability and high intensity interval training in humans: a meta-analysis. *PloS One*, *8*(9), e73182. http://doi.org/10.1371/journal.pone.0073182

Bagley, L., Slevin, M., Bradburn, S., Liu, D., Murgatroyd, C., Morrissey, G., … Mcphee, J. S. (2016). Sex differences in the effects of 12 weeks sprint interval training on body fat mass and the rates of fatty acid oxidation and VO 2 max during exercise. http://doi.org/10.1136/bmjsem-2015-000056

Balady, G. J., Arena, R., Sietsema, K., Myers, J., Coke, L., Fletcher, G. F., … Milani, R. V. (2010). Clinician's Guide to

cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*, *122*(2), 191–225. http://doi.org/10.1161/CIR.0b013e3181e52e69

Bar-Or, O. (1987). The Wingate Anaerobic Test, An Update on Methodology, Reliability and Validity. *Sports Medicine*, *4*(6), 381–394.

Batacan, R. B., Duncan, M. J., Dalbo, V. J., Tucker, P. S., & Fenning, A. S. (2017). Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *British Journal of Sports Medicine*, *51*(6), 494–503. http://doi.org/10.1136/bjsports-2015-095841

Batacan, R., Duncan, M. J., Dalbo, V. J., Tucker, P. S., & Fenning, A. S. (2017). Effects of high-intensity interval training on cardiometabolic health : a systematic review and meta-analysis of intervention studies. *Br J Sports Med*, *51*, 494–503. http://doi.org/10.1136/bjsports-2015-095841

Beaver, W., Whipp, J., William, L., & Wasserman, K. (1986). A new method for detecting threshold by gas exchange anaerobic. *J Appl Physiol*, *60*, 2020–2027.

Benton, M. J., & Schlairet, M. C. (2012). Improvements in quality of life in women after resistance training are not

associated with age. *J Women Aging*, *24*(1), 59–69.

Berster, J. M., & Göke, B. (2008). Type 2 diabetes mellitus as risk factor for colorectal cancer. *Archives of Physiology and Biochemistry*, *114*(1), 84–98. http://doi.org/10.1080/13813450802008455

Bettelli, G. (2011). Preoperative evaluation in geriatric surgery: Comorbidity, functional status and pharmacological history. *Minerva Anestesiologica*, *77*(6), 637–646.

Bickel, H., Gradinger, R., Kochs, E., & Förstl, H. (2008). High Risk of Cognitive and Functional Decline after Postoperative Delirium. *Dementia and Geriatric Cognitive Disorders*, *26*(1), 26–31.

Biddle, S. J. H., & Batterham, A. M. (2015). High-intensity interval exercise training for public health: a big HIT or shall we HIT it on the head? *The International Journal of Behavioral Nutrition and Physical Activity*, *12*(1), 95. http://doi.org/10.1186/s12966-015-0254-9

Billat, L. V. (2001). Interval training for performance: a scientific and empirical practice. Special recommendations for middle- and long-distance running. Part I: aerobic interval training. *Sports Medicine (Auckland, N.Z.)*, *31*(1), 13–31.

Billeh, R., Hirsh, D., Barker, C., Jorgensen, B., Jeger, R.,

Ramanathan, K., … Jorde, U. P. (2006). Randomized, double-blind comparison of acute beta1-blockade with 50 mg metoprolol tartrate vs 25 mg carvedilol in normal subjects. *Congestive Heart Failure*, *12*(5), 254–257.

Binder, E. F., Schechtman, K. B., Ehsani, A. a, Steger-May, K., Brown, M., Sinacore, D. R., … Holloszy, J. O. (2002). Effects of exercise training on frailty in community-dwelling older adults: results of a randomized, controlled trial. *Journal of the American Geriatrics Society*, *50*(12), 1921–8.

Bobbio, A., Chetta, A., Ampollini, L., Primomo, G. L., Internullo, E., Carbognani, P., … Olivieri, D. (2008). Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery*, *33*(1), 95–8. http://doi.org/10.1016/j.ejcts.2007.10.003

Boereboom, C., Doleman, B., Lund, J., & Williams, J. (2016). Systematic review of pre-operative exercise in colorectal cancer patients. *Techniques in Coloproctology*, *20*(2), 81–89. http://doi.org/10.1007/s10151-015-1407-1

Boereboom, C. L., Phillips, B. E., Williams, J. P., & Lund, J. N. (2016). A 31-day time to surgery compliant exercise training programme improves aerobic health in the elderly.

Techniques in Coloproctology. http://doi.org/10.1007/s10151-016-1455-1

Boereboom, C. L., Williams, J. P., Leighton, P., & Lund, J. N. (2015). Forming a consensus opinion on exercise prehabilitation in elderly colorectal cancer patients: a Delphi study. *Techniques in Coloproctology*, *19*(6), 347–354. http://doi.org/10.1007/s10151-015-1317-2

Bouchard, C., An, P., Rice, T., Skinner, J. S., Wilmore, J. H., Leon, A. S., … Familial, D. C. R. (1999). Familial aggregation of VO2 max response to exercise training : results from the HERITAGE Family Study. *J Appl Physiol*, *87*(3), 1003–8.

Bouchard, C., Antunes-Correa, L. M., Ashley, E. A., Franklin, N., Hwang, P. M., Mattsson, C. M., … Wheeler, M. T. (2015). Personalized Preventive Medicine: Genetics and the Response to Regular Exercise in Preventive Interventions. *Progress in Cardiovascular Diseases*, *57*(4), 337–346. http://doi.org/http://dx.doi.org/10.1016/j.pcad.2014.08.005

Boule, N. G., Weisnagel, S. J., Lakka, T. A., Tremblay, A., Bergman, R. N., Rankinen, T., … Bouchard, C. (2005). Effects of exercise training on glucose homeostasis: the HERITAGE Family Study. *Diabetes Care*, *28*(1), 108–114.

http://doi.org/28/1/108 [pii]

Boulé NG, Haddad E, Kenny GP, Wells GA, S. R. (2001). Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: A meta-analysis of controlled clinical trials. *Jama*, *286*(10), 1218–1227. http://doi.org/10.1034/j.1600-0838.2002.120111_3.x

Bourke, L., Thompson, G., Gibson, D. J., Daley, A., Crank, H., Adam, I., … Saxton, J. (2011). Pragmatic lifestyle intervention in patients recovering from colon cancer: a randomized controlled pilot study. *Archives of Physical Medicine and Rehabilitation*, *92*(5), 749–55. http://doi.org/10.1016/j.apmr.2010.12.020

Broman, G., Quintana, M., Lindberg, T., Jansson, E., & Kaijser, L. (2006). High intensity deep water training can improve aerobic power in elderly women. *European Journal of Applied Physiology*, *98*(2), 117–23. http://doi.org/10.1007/s00421-006-0237-2

Brook, M. S., Wilkinson, D. J., Mitchell, W. K., Lund, J. N., Szewczyk, N. J., Greenhaff, P. L., … Atherton, P. J. (2016). Skeletal muscle hypertrophy adaptations predominate in the early stages of resistance exercise training , matching deuterium oxide-derived measures of muscle protein synthesis and mechanistic target of rapamycin complex 1

signaling. *FASEB Journal*, *29*(11), 4485–4496. http://doi.org/10.1096/fj.15-273755

Broskey, N. T., Boss, A., Fares, E., Greggio, C., Gremion, G., Hans, D., … Schl, L. (2015). Exercise efficiency relates with mitochondrial content and function in older adults, *3*, 1–9. http://doi.org/10.14814/phy2.12418

Bruns, E. R. J., van den Heuvel, B., Buskens, C., van Duijvendijk, P., Festen, S., Wassenaar, E. B., … van Munster, B. C. (2015). The effects of physical prehabilitation in older patients undergoing colorectal surgery: a systematic review. http://doi.org/10.1111/codi.13429

Bruseghini, P., Calabria, E., Tam, E., Milanese, C., Oliboni, E., Pezzato, A., … Capelli, C. (2015). Effects of eight weeks of aerobic interval training and of isoinertial resistance training on risk factors of cardiometabolic diseases and exercise capacity in healthy elderly subjects. *Oncotarget*, *6*(19).

Buffart, L. M., Kalter, J., Sweegers, M. G., Courneya, K. S., Newton, R. U., Aaronson, N. K., … Brug, J. (2017). Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. *Cancer Treatment Reviews*, *52*, 91–104. http://doi.org/10.1016/j.ctrv.2016.11.010

Burgomaster, K. a, Howarth, K. R., Phillips, S. M.,

Rakobowchuk, M., Macdonald, M. J., McGee, S. L., & Gibala, M. J. (2008). Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *The Journal of Physiology*, *586*(1), 151–60. http://doi.org/10.1113/jphysiol.2007.142109

Burgomaster, K. a, Hughes, S. C., Heigenhauser, G. J. F., Bradwell, S. N., & Gibala, M. J. (2005). Six sessions of sprint interval training increases muscle oxidative potential and cycle endurance capacity in humans. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *98*(6), 1985–90. http://doi.org/10.1152/japplphysiol.01095.2004

Burke, S. M., Brunet, J., Sabiston, C. M., Jack, S., Grocott, M. P. W., & West, M. a. (2013). Patients' perceptions of quality of life during active treatment for locally advanced rectal cancer: the importance of preoperative exercise. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer*, *21*(12), 3345–53. http://doi.org/10.1007/s00520-013-1908-2

Burke, S., West, M. A., Grocott, M., Brunet, J., & Jack, S. (2014). Exploring the experience of adhering to a prescribed pre-surgical exercise program for patients with advanced rectal cancer: A phenomenological study. *Psychology of Sport and Exercise*, *16*, 88–95.

Cancer Research UK. (2017). Bowel Cancer Mortality Statistics. Retrieved July 4, 2017, from http://www.cancerresearchuk.org/cancer-info/cancerstats/types/bowel/mortality/uk-bowel-cancer-mortality-statistics#trends

Carli, F., Charlebois, P., Stein, B., Feldman, L., Zavorsky, G., Kim, D. J., … Mayo, N. E. (2010). Randomized clinical trial of prehabilitation in colorectal surgery. *The British Journal of Surgery*, *97*(8), 1187–97. http://doi.org/10.1002/bjs.7102

Carli, F., Silver, J. K., Feldman, L. S., McKee, A., Gilman, S., Gillis, C., … Hirsch, B. (2017). Surgical Prehabilitation in Patients with Cancer. *Physical Medicine and Rehabilitation Clinics of North America*, *28*(1), 49–64. http://doi.org/10.1016/j.pmr.2016.09.002

Carter, N. D., Kannus, P., & Khan, K. M. (2001). Exercise in the Prevention of Falls in Older People and the Evidence. *Sports Medicine*, *31*(6), 427–438.

Chan, K. E., Pathak, S., Smart, N. J., Batchelor, N., & Daniels, I. R. (2015). The impact of Cardiopulmonary Exercise Testing (CPET) on patients over 80 years undergoing elective colorectal cancer surgery. *Colorectal Disease*, n/a-n/a. http://doi.org/10.1111/codi.13139

Chandrabalan, V. V., McMillan, D. C., Carter, R., Kinsella, J.,

McKay, C. J., Carter, C. R., & Dickson, E. J. (2013). Pre-operative cardiopulmonary exercise testing predicts adverse post-operative events and non-progression to adjuvant therapy after major pancreatic surgery. *Hpb*, *15*(11), 899–907. http://doi.org/10.1111/hpb.12060

Cho, H., Yoshikawa, T., Oba, M. S., Hirabayashi, N., Shirai, J., Aoyama, T., … Tsuburaya, A. (2014). Matched pair analysis to examine the effects of a planned preoperative exercise program in early gastric cancer patients with metabolic syndrome to reduce operative risk: the Adjuvant Exercise for General Elective Surgery (AEGES) study group. *Annals of Surgical Oncology*, *21*(6), 2044–50. http://doi.org/10.1245/s10434-013-3394-7

Ciolac, E. G. (2012). Review Article High-intensity interval training and hypertension : maximizing the benefits of exercise ?, *2*(2), 102–110.

Collier, S. R., Kanaley, J. a, Carhart, R., Frechette, V., Tobin, M. M., Bennett, N., … Fernhall, B. (2009). Cardiac autonomic function and baroreflex changes following 4 weeks of resistance versus aerobic training in individuals with pre-hypertension. *Acta Physiologica (Oxford, England)*, *195*(3), 339–48. http://doi.org/10.1111/j.1748-1716.2008.01897.x

Collins, M. A., Hill, D. W., Cureton, K. J., & DeMello, J. J.

(1986). Plasma volume change during heavy-resistance weight lifting. *European Journal of Applied Physiology and Occupational Physiology*, *55*(1), 44–48. http://doi.org/10.1007/BF00422891

Cooper, C., & Storer, T. (2010). *Exercise testing and interpretation, A practical approach*. Cambridge.

Cornelissen, V. A., Verheyden, B., Aubert, A. E., & Fagard, R. H. (2009). Effects of aerobic training intensity on resting, exercise and post-exercise blood pressure, heart rate and heart-rate variability. *J Hum Hypertens*, *24*(3), 175–182.

Courneya, K. S., Booth, C. M., Gill, S., O'Brien, P., Vardy, J., Friedenreich, C. M., … Meyer, R. M. (2008). The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group. *Current Oncology (Toronto, Ont.)*, *15*(6), 279–85.

Courneya, K. S., Friedenreich, C. M., Quinney, H. a, Fields, a L. a, Jones, L. W., & Fairey, a S. (2003). A randomized trial of exercise and quality of life in colorectal cancer survivors. *European Journal of Cancer Care*, *12*(4), 347–57.

Craig CL, Marshall AL, S. M. (2003). International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*, *35*(8), 1381–1395.

Cramer, H., Lauche, R., Klose, P., Dobos, G., & Langhorst, J.

(2014). A systematic review and meta-analysis of exercise interventions for colorectal cancer patients. *European Journal of Cancer Care*, *23*(1), 3–14. http://doi.org/10.1111/ecc.12093

Cruz-Jentoft, A., Baeyens, J. P., & Zamboni, M. (2010). Sarcopenia : European consensus on definition and diagnosis Report of the European Working Group on Sarcopenia in Older People. *Age and Aging*, 1–12. http://doi.org/10.1093/ageing/afq034

Dasgupta, M., Rolfson, D. B., Stolee, P., Borrie, M. J., & Speechley, M. (2009). Frailty is associated with postoperative complications in older adults with medical problems. *Archives of Gerontology and Geriatrics*, *48*, 78–83. http://doi.org/10.1016/j.archger.2007.10.007

David, B. Y., & Cuthbertson, P. (1930). CXXXVIII . THE DISTURBANCE OF METABOLISM PRODUCED BY BONY AND NON-BONY INJURY , WITH NOTES ON CERTAIN ABNORMAL CONDITIONS OF BONE .

Day, J. R., Rossiter, H. B., Coats, E. M., Skasick, a, & Whipp, B. J. (2003). The maximally attainable VO2 during exercise in humans: the peak vs. maximum issue. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *95*(5), 1901–7. http://doi.org/10.1152/japplphysiol.00024.2003

De Brandt, J., Spruit, M. A., Derave, W., Hansen, D., Vanfleteren, L. E. G. W., & Burtin, C. (2016). Changes in structural and metabolic muscle characteristics following exercise-based interventions in patients with COPD: a systematic review. *Expert Review of Respiratory Medicine*, *10*(5), 521–545. http://doi.org/10.1586/17476348.2016.1157472

Deiner, S., & Silverstein, J. H. (2009). Postoperative delirium and cognitive dysfunction. *British Journal of Anaesthesia*, *103*, 41–46. http://doi.org/10.1093/bja/aep291

Denlinger, C. S., & Engstrom, P. F. (2011). Colorectal cancer survivorship: movement matters. *Cancer Prevention Research (Philadelphia, Pa.)*, *4*(4), 502–11. http://doi.org/10.1158/1940-6207.CAPR-11-0098

Desborough, J. ., & Hall, G. (1993). Endocrine response to surgery. *Anaesthesia Review*, *10*, 131–148.

Desborough, J. P. (2000). The stress response to trauma and surgery. *British Journal of Anaesthesia*, *85*(1), 109–117. http://doi.org/10.1093/bja/85.1.109

Devlin, N., Shah, K., & Feng, Y. (2016). Valuing Health-Related Quality of Life : An EQ-5D-5L Value Set for England, (January).

Dronkers, J. J., Lamberts, H., Reutelingsperger, I. M. M. D.,

Naber, R. H., Dronkers-Landman, C. M., Veldman, a, & van Meeteren, N. L. U. (2010). Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. *Clinical Rehabilitation*, *24*(7), 614–22. http://doi.org/10.1177/0269215509358941

Dronkers, J., Witteman, B., & van Meeteren, N. (2016). Surgery and functional mobility: doing the right thing at the right time. *Techniques in Coloproctology*, *20*(6), 339–341. http://doi.org/10.1007/s10151-016-1487-6

Dunne, D. F. J., Jack, S., Jones, R. P., Jones, L., Lythgoe, D. T., Malik, H. Z., … Fenwick, S. W. (2016). Randomized clinical trial of prehabilitation before planned liver resection. *British Journal of Surgery*, *103*(5), 504–512. http://doi.org/10.1002/bjs.10096

Dunne, D. F. J., Yip, V. S., Jones, R. P., McChesney, E. A., Lythgoe, D. T., Psarelli, E. E., … Fenwick, S. W. (2014). Enhanced recovery in the resection of colorectal liver metastases. *Journal of Surgical Oncology*, *110*(2), 197–202. http://doi.org/10.1002/jso.23616

Englesbe, M. J., Terjimanian, M. N., Lee, J. S., Sheetz, K. H., Harbaugh, C. M., Hussain, A., … Sonnenday, C. J. (2013). Morphometric age and surgical risk. *Journal of the American*

College of Surgeons, *216*(5), 976–985. http://doi.org/10.1016/j.jamcollsurg.2013.01.052

Etgen Jr., G. J., Brozinick Jr., J. T., Kang, H. Y., & Ivy, J. L. (1993). Effects of exercise training on skeletal muscle glucose uptake and transport. *Am J Physiol*, *264*(3 Pt 1), C727–33.

Etgen Jr., G. J., Jensen, J., Wilson, C. M., Hunt, D. G., Cushman, S. W., & Ivy, J. L. (1997). Exercise training reverses insulin resistance in muscle by enhanced recruitment of GLUT-4 to the cell surface. *The American Journal of Physiology*, *272*(5 Pt 1), E864-9.

Färkkilä, N., Sintonen, H., Saarto, T., Järvinen, H., Hänninen, J., Taari, K., & Roine, R. P. (2013). Health-related quality of life in colorectal cancer. *Colorectal Disease*, *15*, 215–222. http://doi.org/10.1111/codi.12143

Fleck, S., & Kraemer, W. (2014). *Designing resistance training programs*.

Folland, J. P., & Williams, A. G. (2007). The adaptations to strength training : morphological and neurological contributions to increased strength. *Sports Medicine (Auckland, N.Z.)*, *37*(2), 145–168.

Fontana, P., Betschon, K., Boutellier, U., & Toigo, M. (2011). Cardiac output but not stroke volume is similar in a Wingate

and VO_2 peak test in young men. *European Journal of Applied Physiology*, *111*(1), 155–158. http://doi.org/10.1007/s00421-010-1645-x

Franchi, M. V, Atherton, P. J., Reeves, N. D., Flück, M., Williams, J., Mitchell, W. K., … Narici, M. V. (2014). Architectural, functional and molecular responses to concentric and eccentric loading in human skeletal muscle. *Acta Physiologica (Oxford, England)*, *210*(3), 642–54. http://doi.org/10.1111/apha.12225

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., … Burke, G. (2001). Frailty in Older Adults : Evidence for a Phenotype. *Journal of Gerontology*, *56*(3), 146–157.

Frontera, W. R., Meredith, C. N., O'Reilly, K. P., & Evans, W. J. (1990). Strength training and determinants of VO2max in older men. *Journal of Applied Physiology (Bethesda, Md. : 1985)*, *68*(1), 329–33.

Fry, A. C. (2004). The Role of Resistance Exercise Intensity on Muscle Fibre Adaptations. *Sports Medicine*, *34*(10), 663–679.

Galvão, D. a, & Newton, R. U. (2005). Review of exercise intervention studies in cancer patients. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical*

Oncology,*23*(4),899909.http://doi.org/10.1200/JCO.2005.06.085

Gaskill, S. E., Ruby, B. C., Walker, A. V. A. J., Sanchez, O. A., Serfass, R. C., & Leon, A. S. (2001). Validity and reliability of combining three. *Medicine and Science in Sport and Exercise*, 1841–1848.

Geirsdottir, O. G., Arnarson, A., Briem, K., Ramel, A., Jonsson, P. V, & Thorsdottir, I. (2012). Effect of 12-week resistance exercise program on body composition, muscle strength, physical function, and glucose metabolism in healthy, insulin-resistant, and diabetic elderly Icelanders. *J Gerontol A Biol Sci Med Sci*, *67*(11), 1259–65. http://doi.org/10.1093/gerona/gls096

Gibala, M. (2009). Molecular responses to high-intensity interval exerciseThis paper is one of a selection of papers published in this Special Issue, entitled 14th International Biochemistry of Exercise Conference – Muscles as Molecular and Metabolic Machines, and has under. *Applied Physiology, Nutrition, and Metabolism*, *34*(3), 428–432. http://doi.org/10.1139/H09-046

Gibala, M. J., Little, J. P., Macdonald, M. J., & Hawley, J. a. (2012). Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal*

of Physiology, *590*(Pt 5), 1077–84. http://doi.org/10.1113/jphysiol.2011.224725

Gibala, M. J., Little, J. P., van Essen, M., Wilkin, G. P., Burgomaster, K. a, Safdar, A., … Tarnopolsky, M. a. (2006). Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *The Journal of Physiology*, *575*(Pt3),90111.http://doi.org/10.1113/jphysiol.2006.112094

Gibala, M., & McGee, S. L. (2008). Metabolic adaptations to short-term high-intensity interval training: a little pain for a lot of gain? *Exerc Sport Sci Rev*, *36*(2), 58–63.

Gielen, S. (2010). Cardiovascular effects of exercise training. *Circulation*, 122(12), 1221–1238.

Gillen, J. (2012). Acute high intensity interval exercise reduces the postprandial glucose response and prevalence of hyperglycaemia in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism*, *14*, 575–577.

Gillen, J. B., Percival, M. E., Ludzki, A., Tarnopolsky, M. a., & Gibala, M. J. (2013). Interval training in the fed or fasted state improves body composition and muscle oxidative capacity in overweight women. *Obesity*, *21*(11), 2249–2255. http://doi.org/10.1002/oby.20379

Gillis, C., Li, C., & Carli, F. (2014). Prehabilitation versus Rehabilitation: A Randomized Control Trial in Patients Undergoing Colorectal Resection for Cancer. *Anesthesiology*.

Gillis, C., Li, C., Lee, L., Awasthi, R., Augustin, B., Gamsa, A., … Carli, F. (2015). Prehabilitation versus Rehabilitation. *Anesthesiology*,*122*(6),1438.

Granata, C., Oliveira, R. S. F., Little, J. P., Renner, K., & Bishop, D. J. (2016). Training intensity modulates changes in PGC-1α and p53 protein content and mitochondrial respiration, but not markers of mitochondrial content in human skeletal muscle. *FASEB Journal*, *30*(2), 959–970. http://doi.org/10.1096/fj.15-276907

Greenlee, R. T., Hill-Harmon, M. B., Murray, T., & Thun, M. (2001). Cancer statistics, 2001. *CA: A Cancer Journal for Clinicians*,*51*(1),1536.http://doi.org/10.3322/canjclin.51.1.15

Griffiths, R., & Mehta, M. (2014). Frailty and anaesthesia: what we need to know. *Continuing Education in Anaesthesia, Critical Care & Pain*. http://doi.org/10.1093/bjaceaccp/mkt069

Guiraud, T., Juneau, M., Nigam, A., Gayda, M., Meyer, P., Mekary, S., … Bosquet, L. (2010). Optimization of high intensity interval exercise in coronary heart disease.

European Journal of Applied Physiology, *108*(4), 733–40. http://doi.org/10.1007/s00421-009-1287-z

Gunter, M. J., & Leitzmann, M. F. (2006). Obesity and colorectal cancer : epidemiology , mechanisms and candidate genes, *17*, 145–156. http://doi.org/10.1016/j.jnutbio.2005.06.011

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., … Wallace, R. B. (1994). A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *Journal of Gerontology*, *49*(2), M85-94.

Gurd, B., Giles, M., Bonafiglia, J., Raleigh, J., Boyd, J., Ma, J., … Scribbans, T. (2016). Incidence of nonresponse and individual patterns of response following sprint interval training. *Appl Physiol Nutr Metab*, *41*(3), 229–234.

Gustafsson, U. O., Scott, M. J., Schwenk, W., Demartines, N., Roulin, D., Francis, N., … Ljungqvist, O. (2012). Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clinical Nutrition (Edinburgh, Scotland)*, *31*(6), 783–800. http://doi.org/10.1016/j.clnu.2012.08.013

Harari, D. (2007). Proactive care of older people undergoing surgery ("POPS"): Designing , embedding , evaluating and

funding a comprehensive geriatric assessment service for older elective. *Age and Aging*, *36*, 190–196. http://doi.org/10.1093/ageing/afl163

Harris, R. A., Nishiyama, S. K., Wray, D. W., & Richardson, R. S. (2010). Ultrasound Assessment of Flow-Mediated Dilation. *Hypertension*, *55*, 1075–1085.

Harriss, D., Cable, N., George, K., Reilly, T., Renehan, A., & Haboubi, N. (2007). Physical activity before and after diagnosis of colorectal cancer: disease risk, clinical outcomes, response pathways and biomarkers. *Sports Med*, *37*(11), 947–960.

Haydon, a M. M., Macinnis, R. J., English, D. R., & Giles, G. G. (2006). Effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut*, *55*(1), 62–7. http://doi.org/10.1136/gut.2005.068189

Haywood, K. L., Garratt, a. M., & Fitzpatrick, R. (1994). Quality of life in older people: A structured review of generic self-assessed health instruments. *Quality of Life Research*, *14*(7), 1651–1668. http://doi.org/10.1007/s11136-005-1743-0

Hazell, T. J., Macpherson, R. E. K., Gravelle, B. M. R., & Lemon, P. W. R. (2010). 10 or 30-S Sprint Interval Training Bouts Enhance Both Aerobic and Anaerobic Performance.

European Journal of Applied Physiology, *110*(1), 153–60. http://doi.org/10.1007/s00421-010-1474-y

Heinonen, I., Helajärvi, H., Pahkala, K., Heinonen, O. J., Hirvensalo, M., Pälve, K., … Raitakari, O. T. (2013). Sedentary behaviours and obesity in adults : the Cardiovascular Risk in Young Finns Study. http://doi.org/10.1136/bmjopen-2013-002901

Helgerud, J. (2007). Aerobic high-intensity intervals improve VO2max more than moderate training. *Med Sci Sports Exerc.*, *39*(4), 665–71.

Helmy, S. A. K., & Wahby, M. A. M. (1999). The effect of anaesthesia and surgery on plasma cytokine production, 733–738.

Hennis, P. J., Meale, P. M., & Grocott, M. P. W. (2011). Cardiopulmonary exercise testing for the evaluation of perioperative risk in non-cardiopulmonary surgery. *Postgraduate Medical Journal* , *87*(1030), 550–557. http://doi.org/10.1136/pgmj.2010.107185

Henriksen, E. (2002). Exercise Effects of Muscle Insulin Signaling and Action; Effects of acute exercise and exercise training on insulin resistance. *Journal of Applied Physiology*, *93*(4), 788–796. http://doi.org/10.1152/japplphysiol.00017.2004

Hernon, J. (Norfolk and N. (2016). *PREPARE-ABC SupPoRtive Exercise Programmes for Accelerating REcovery after major ABdominal Cancer surgery (PREPARE-ABC) A multicentre , 3 arm , parallel randomised controlled trial of standard care alone versus standard care plus supervised hospital bas*.

Herrod, P. (2017). Non-pharmacological strategies to reduce blood pressure in older adults: a systematic review and meta-analysis. *Under Review*.

Heydari, M. (2013). High-intensity intermittent exercise and cardiovascular and autonomic function. *Clin Auton Res*, 57–65. http://doi.org/10.1007/s10286-012-0179-1

Higgins, J. P. T., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, a. D., … Sterne, J. a. C. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*, *343*, d5928–d5928. http://doi.org/10.1136/bmj.d5928

Hlatky, M., Bioneau, R., Higginbotham, M., Lee, K., D, M., Califf, R., … Pryor, D. (1989). A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). *The American Journal of Cardiology*, *64*(10), 651–654.

Holmes, M. D., Chen, W. Y., Feskanich, D., Kroenke, C. H., & Colditz, G. A. (2014). After Breast Cancer Diagnosis,

293(20), 2479–2486.

Hood, M., Little, J. P., Tarnopolsky, M. a., Myslik, F., & Gibala, M. J. (2011). Low-volume interval training improves muscle oxidative capacity in sedentary adults. Hood MS1, Little JP, Tarnopolsky MA, Myslik F, Gibala MJ. *Med Sci Sports Exerc.*, *43*(10), 1849–56.

Hopker, J. G., Jobson, S. a, & Pandit, J. J. (2011). Controversies in the physiological basis of the "anaerobic threshold" and their implications for clinical cardiopulmonary exercise testing. *Anaesthesia*, *66*(2), 111–23. http://doi.org/10.1111/j.1365-2044.2010.06604.x

Houborg, K., Jensen, M., & Rasmussen, P. (2006). Postoperative physical training following colorectal surgery: a randomised, placebo controlled study. *Scand J Surg*, *95*(1), 17–22.

Howley, E. T. (2001). Type of activity: resistance, aerobic and leisure versus occupational physical activity. *Medicine and Science in Sports and Exercise*, *33*(Supplement), S364–S369. http://doi.org/10.1097/00005768-200106001-00005

Huang, G., Gibson, C. A., & Zung, V. (2005). Controlled Endurance Exercise Training and V O 2max Changes in Older Adults : A Meta-Analysis, 217–225.

Huang, G. H., Ismail, H., Murnane, A., Kim, P., & Riedel, B. (2015). Structured exercise program prior to major cancer

surgery improves cardiopulmonary fitness: a retrospective cohort study. *Supportive Care in Cancer*, 1–9. http://doi.org/10.1007/s00520-015-3028-7

Hubbard, G., Adams, R., Campbell, A., Kidd, L., Leslie, S. J., Munro, J., & Watson, A. (2016). Is referral of postsurgical colorectal cancer survivors to cardiac rehabilitation feasible and acceptable? A pragmatic pilot randomised controlled trial with embedded qualitative study. *BMJ Open*, *6*(1), e009284. http://doi.org/10.1136/bmjopen-2015-009284

Huisman, M. G., Van Leeuwen, B. L., Ugolini, G., Montroni, I., Spiliotis, J., Stabilini, C., … Audisio, R. A. (2014). "Timed Up & Go": A screening tool for predicting 30-day morbidity in onco-geriatric surgical patients? A multicenter cohort study. *PLoSONE*,*9*(1)http://doi.org/10.1371/journal.pone.0086863

Hulzebos, E. (2006). Preoperative intensive inspiratory muscle trainging to prevent postoperative pulmonary complications in high risk patients ungoing CABG surgery: A randomized clinical trial. *JAMA*, *296*(15), 1851–1857.

Hurley, B. F., & Roth, S. M. (2000). Strength training in the elderly: effects on risk factors for age-related diseases. *Sports Medicine (Auckland, N.Z.)*, *30*(4), 249–68.

Idorn, M., & Hoiman, P. (2016). Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends Mol Med*.

http://doi.org/10.1016/j.molmed.2016.05.007

Iellamo, F., Caminiti, G., Sposato, B., Vitale, C., Massaro, M., Rosano, G., & Volterrani, M. (2014). Effect of High-Intensity interval training versus moderate continuous training on 24-h blood pressure profile and insulin resistance in patients with chronic heart failure. *Internal and Emergency Medicine*, *9*(5), 547–52. http://doi.org/10.1007/s11739-013-0980-4

Je, Y., Jeon, J. Y., Giovannucci, E. L., & Meyerhardt, J. A. (2013). Association between physical activity and mortality in colorectal cancer: A meta-Analysis of prospective cohort studies. *International Journal of Cancer*, *133*(8), 1905–1913. http://doi.org/10.1002/ijc.28208

Jelleyman, C., Yates, T., O'Donovan, G., Gray, L. J., King, J. A., Khunti, K., & Davies, M. J. (2015). The effects of high-intensity interval training on glucose regulation and insulin resistance: A meta-analysis. *Obesity Reviews*, *16*(11), 942–961. http://doi.org/10.1111/obr.12317

Jones, K., Claire, A. G., & Michael, C. (2017). Radiologically Determined Sarcopenia Predicts Morbidity and Mortality Following Abdominal Surgery : A Systematic Review and Meta-Analysis. *World Journal of Surgery*. http://doi.org/10.1007/s00268-017-3999-2

Jones, L. W., Peddle, C. J., Eves, N. D., Haykowsky, M. J.,

Courneya, K. S., Mackey, J. R., … Reiman, T. (2007). Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer*, *110*(3), 590–8. http://doi.org/10.1002/cncr.22830

Kaplan, N. (2014). Perioperative management of hypertension. *UpToDate*.

Kehlet, H. (2011). Fast-track surgery-an update on physiological care principles to enhance recovery. *Langenbeck's Archives of Surgery / Deutsche Gesellschaft Für Chirurgie*, *396*(5), 585–90. http://doi.org/10.1007/s00423-011-0790-y

Kessler, H. S., Sisson, S. B., & Short, K. R. (2012). The Potential for High-Intensity Interval Training to Reduce Cardiometabolic Disease Risk. *Sports Medicine*, *42*(6), 489–509.

Khan, M. R. (2011). Impact of age on outcome after colorectal cancer surgery in the elderly - a developing country perspective. *BMC Surgery*, *11*, 17. http://doi.org/10.1186/1471-2482-11-17

Kim, D. J., Mayo, N. E., Carli, F., Montgomery, D. L., & Zavorsky, G. S. (2009). Responsive measures to prehabilitation in patients undergoing bowel resection

surgery. *The Tohoku Journal of Experimental Medicine*, *217*(2), 109–15.

Kim, J., Chae, Y. K., & Chernoff, A. (2013). The Risk for Coronary Heart Disease According to Insulin Resistance with and without Type 2 Diabetes. *Endocrine Research*, *38*(4), 195–205. http://doi.org/10.3109/07435800.2013.766800

Kimmick, G. (2016). Clinical trial accrual in older cancer patients: The most important steps are the first ones. *Journal of Geriatric Oncology*, *7*(3), 158–161. http://doi.org/10.1016/j.jgo.2016.03.006

King, Abby, Taylor, C. (1989). Influence of regular aerobic exercise on psychological health: A randomized, controlled trial of healhty middle aged adults. *Health Psychology*, *8*(3), 305–324.

Knight, K. A., Moug, S. J., & West, M. A. (2017). Systematic review: the impact of exercise on mesenteric blood flow and its implication for preoperative rehabilitation. *Techniques in Coloproctology*. http://doi.org/10.1007/s10151-017-1589-9

Knowles, A. M., Herbert, P., Easton, C., Sculthorpe, N., & Grace, F. M. (2015). Impact of low-volume, high-intensity interval training on maximal aerobic capacity, health-related quality of life and motivation to exercise in ageing men. *Age*, *37*(2). http://doi.org/10.1007/s11357-015-9763-3

Kuan-Yin, L., Shiow-Ching, S., Yeur-Hur, L., Jin-Tung, L., & Jau-Yih, T. (2014). Comparison of the effects of a supervised exercise program and usual care in patients with colorectal cancer undergoing chemotherapy. *Cancer Nursing*, *37*(2), E21-29.

Kumar, V., Selby, A., Rankin, D., Patel, R., Atherton, P., Hildebrandt, W., … De, D. (2009). Age-related differences in the dose – response relationship of muscle protein synthesis to resistance exercise in young and old men. *J Physiol*, *1*, 211–217. http://doi.org/10.1113/jphysiol.2008.164483

Laughlin, M. H., & Roseguini, B. (2008). Mechanisms for exercise training-induced increases in skeletal muscle blood flow capacity: differences with interval sprint training versus aerobic endurance training. *Journal of Physiology and Pharmacology : An Official Journal of the Polish Physiological Society*, *59 Suppl 7*, 71–88.

Laursen, P. B. (2005). Influence of high-intensity interval training on adaptations in well-trained cyclists. *J Strength Cond Res*, *19*(3), 527–533.

Laursen, P. B. (2010). Training for intense exercise performance : high-intensity or high-volume training ? *Scandinavian Journal of Medicine and Science in Sports*, *20*, 1–10. http://doi.org/10.1111/j.1600-0838.2010.01184.x

Laursen, P. B., & Jenkins, D. G. (2002). The scientific basis for high-intensity interval training: optimising training programmes and maximising performance in highly trained endurance athletes. *Sports Medicine (Auckland, N.Z.)*, *32*(1), 53–73.

Lee, I.-M., & Paffenbarger, R. S. (2000). Associations of Light , Moderate , and Vigorous Intensity Physical Activity with Longevity: The Harvard Alumni Health Study. *American Journal of Epidemiology*, *151*(3), 293–299.

Leong, K. J., & Chapman, M. (2017). Current data about the benefit of prehabilitation for colorectal cancer patients undergoing surgery are not sufficient to alter the NHS cancer waiting targets. *Colorectal Disease*. http://doi.org/10.1111/ijlh.12426

Lepretre, P.-M., Vogel, T., Brechat, P.-H., Dufour, S., Richard, R., Kaltenbach, G., … Lonsdorfer, J. (2009). Impact of short-term aerobic interval training on maximal exercise in sedentary aged subjects. *International Journal of Clinical Practice*, *63*(10), 1472–8. http://doi.org/10.1111/j.1742-1241.2009.02120.x

Levett, D. Z. H., & Grocott, M. P. W. (2015). Cardiopulmonary Exercise Testing for Risk Prediction in Major Abdominal Surgery. *Anesthesiology Clinics*, *33*(1), 1–16.

http://doi.org/http://dx.doi.org/10.1016/j.anclin.2014.11.001

Levinger, I., Shaw, C. S., Stepto, N. K., Cassar, S., McAinch, A. J., Cheetham, C., & Maiorana, A. J. (2015). What doesn't kill you makes you fitter: A systematic review of high-intensity interval exercise for patients with cardiovascular and metabolic diseases. *Clinical Medicine Insights: Cardiology*, *9*, 53–63. http://doi.org/10.4137/CMC.S26230

Li, C., Carli, F., Lee, L., Charlebois, P., Stein, B., Liberman, A. S., … Feldman, L. S. (2013). Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surgical Endoscopy*, *27*(4), 1072–82. http://doi.org/10.1007/s00464-012-2560-5

Lieffers, J. R., Bathe, O. F., Fassbender, K., Winget, M., & Baracos, V. E. (2012). Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *British Journal of Cancer*, *107*(6), 931–936. http://doi.org/10.1038/bjc.2012.350

Liou, K., Ho, S., Fildes, J., & Ooi, S.-Y. (2016). High Intensity Interval versus Moderate Intensity Continuous Training in Patients with Coronary Artery Disease: A Meta-analysis of Physiological and Clinical Parameters. *Heart, Lung and*

Circulation, *25*(2), 166–174. http://doi.org/10.1016/j.hlc.2015.06.828

Litt, M., Kleppinger, A., & Judge, J. (2002). Initiation and maintenence of exercise behaviour in older women: predictors from social learning model. *J Behav Med*, *25*, 83–97.

Little, J. P., Safdar, A., Wilkin, G. P., Tarnopolsky, M. a, & Gibala, M. J. (2010). A practical model of low-volume high-intensity interval training induces mitochondrial biogenesis in human skeletal muscle: potential mechanisms. *The Journal of Physiology*, *588*(Pt 6), 1011–22. http://doi.org/10.1113/jphysiol.2009.181743

Lunt, H., Draper, N., Marshall, H. C., Logan, F. J., Hamlin, M. J., Shearman, J. P., … Frampton, C. M. A. (2014). High intensity interval training in a real world setting: A randomized controlled feasibility study in overweight inactive adults, measuring change in maximal oxygen uptake. *PLoS ONE*, *9*(1), 1–11. http://doi.org/10.1371/journal.pone.0083256

Lynch, J., SP, H., TA, L., & al, et. (1996). MOderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Archives of Internal Medicine*, *156*(12),

1307–1314.

Macdougall, J. D., Hicks, A. L., Macdonald, J. R., Mckelvie, R. S., Green, H. J., Smith, K. M., … Flack, J. R. (1998). Muscle performance and enzymatic adaptations to sprint interval training females during sprint interval training kinetics in humans Mus c le per fo rman c e and enzymati c adaptati o ns t o sprint interval training. *Physiol, J Appl*, *84*, 2138–2142.

Maheswaran, H., Weich, S., Powell, J., & Stewart-Brown, S. (2012). Evaluating the responsiveness of the Warwick Edinburgh Mental Well-Being Scale (WEMWBS): group and individual level analysis. *Health and Quality of Life Outcomes*, *10*(1), 156. http://doi.org/10.1186/1477-7525-10-156

Malietzis, G., Currie, A. C., Athanasiou, T., Johns, N., Anyamene, N., Glynne-Jones, R., … Jenkins, J. T. (2016). Influence of body composition profile on outcomes following colorectal cancer surgery. *British Journal of Surgery*, *103*(5), 572–580. http://doi.org/10.1002/bjs.10075

Manini, T. M., Everhart, J. E., Schoeller, D. A., Colbert, L. H., Tylavsky, F., Bauer, D. C., … Harris, T. B. (2006). Daily Activity Energy Expenditure and Mortality Among Older Adults. *JAMA*, *296*(2), 171–179.

Mayo, N. E., Feldman, L., Scott, S., Zavorsky, G., Kim, D. J., Charlebois, P., … Carli, F. (2011). Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. *Surgery*, *150*(3), 505–14. http://doi.org/10.1016/j.surg.2011.07.045

McArdle, W. D., Katch, F., & Katch, V. (1996). *Exercise physiology* (Fifth Edit). Lippincott, Williams and Wilkins.

McCartney, N., Spriet, L. L., Heigenhauser, G. J., Kowalchuk, J. M., Sutton, J. R., & Jones, N. L. (1986). Muscle power and metabolism in maximal intermittent exercise. *Journal of Applied Physiology (Bethesda, Md. : 1985)*, *60*(4), 1164–9.

McGarrah, R. W., Slentz, C. A., & Kraus, W. E. (2016). The Effect of Vigorous- Versus Moderate-Intensity Aerobic Exercise on Insulin Action. *Current Cardiology Reports*, *18*(12), 117. http://doi.org/10.1007/s11886-016-0797-7

Mckenzie, D. C. (2012). Respiratory physiology : adaptations to high-level exercise, 381–384. http://doi.org/10.1136/bjsports-2011-090824

Meredith, C. N., Frontera, W. R., Fisher, E. C., Hughes, V. a, Herland, J. C., Edwards, J., & Evans, W. J. (1989). Peripheral effects of endurance training in young and old subjects. *Journal of Applied Physiology (Bethesda, Md. :*

1985), *66*(6), 2844–9.

Metcalfe, R. S., Koumanov, F., Ruffino, J. S., Stokes, K. A., Holman, G. D., Thompson, D., & Vollaard, N. B. J. (2015). Physiological and molecular responses to an acute bout of reduced-exertion high-intensity interval training (REHIT). *European Journal of Applied Physiology*, *115*(11), 2321–2334. http://doi.org/10.1007/s00421-015-3217-6

Metcalfe, R. S., Tardif, N., Thompson, D., & Vollaard, N. B. J. (2016). Changes in aerobic capacity and glycaemic control in response to reduced-exertion high-intensity interval training (REHIT) are not different between sedentary men and women. *Applied Physiology, Nutrition, and Metabolism*, *41*(11), 1117–1123. http://doi.org/10.1139/apnm-2016-0253

Meyer, P., Normandin, E., Gayda, M., Billon, G., Guiraud, T., Bosquet, L., … Nigam, A. (2012). High-intensity interval exercise in chronic heart failure: protocol optimization. *Journal of Cardiac Failure*, *18*(2), 126–33. http://doi.org/10.1016/j.cardfail.2011.10.010

Meyerhardt, J. a, Heseltine, D., Niedzwiecki, D., Hollis, D., Saltz, L. B., Mayer, R. J., … Fuchs, C. S. (2006). Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB

89803. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *24*(22), 3535–41. http://doi.org/10.1200/JCO.2006.06.0863

Milanović, Z., Sporiš, G., & Weston, M. (2015). Effectiveness of High-Intensity Interval Training (HIT) and Continuous Endurance Training for VO2max Improvements: A Systematic Review and Meta-Analysis of Controlled Trials. *Sports Medicine*, *45*, 1469–1481. http://doi.org/10.1007/s40279-015-0365-0

Minnella, E., Bousquet-Dion, G., Awasthi, R., Scheede-Bergdahl, C., & Carli, F. (2017). Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. *Acta Oncol*, *12*, 1–6.

Mishra, S., Rw, S., C, S., PM, G., DR, B., & O, T. (2012). Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev*, *15*(8), CD008465. http://doi.org/10.1002/14651858

Mitchell, W. K., Williams, J., Atherton, P., Larvin, M., Lund, J., & Narici, M. (2012). Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. *Frontiers in Physiology*, *3 JUL*(July),

1–18. http://doi.org/10.3389/fphys.2012.00260

Moghadamyeghaneh, Z., Mills, S. D., Carmichael, J. C., Pigazzi, A., & Stamos, M. J. (2015). Risk factors of postoperative myocardial infarction after colorectal surgeries. *The American Surgeon*, *81*(4), 358–364.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Academia and Clinic Annals of Internal Medicine Preferred Reporting Items for Systematic Reviews and Meta-Analyses : *Annulas of Internal Medicine*, *151*(4), 264–269.

Moholdt, T. T., Amundsen, B. H., Rustad, L. A., Wahba, A., Løvø, K. T., Gullikstad, L. R., … Slørdahl, S. a. (2009). Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *American Heart Journal*, *158*(6), 1031–7. http://doi.org/10.1016/j.ahj.2009.10.003

Molmen-Hansen, H. E., Stolen, T., Tjonna, A. E., Aamot, I. L., Ekeberg, I. S., Tyldum, G. A., … Stoylen, A. (2012). Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *European Journal of Preventive Cardiology*, *19*(2), 151–60. http://doi.org/10.1177/1741826711400512

Moran, J., Guinan, E., McCormick, P., Larkin, J., Mockler, D.,

Hussey, J., … Wilson, F. (2016). The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: A systematic review and meta-analysis. *Surgery (United States)*, *160*(5), 1189–1201. http://doi.org/10.1016/j.surg.2016.05.014

Morielli, A., Usmani, N., Boulé, N., Tankel, K., Severin, D., Nijjar, T., … Courneya, K. (2016). A Phase I Study Examining the Feasibility and Safety of an Aerobic Exercise Intervention in Patients With Rectal Cancer During and After Neoadjuvant Chemoradiotherapy. *Oncology Nursing Forum*, *43*(3), 352–362. http://doi.org/10.1188/16.ONF.352-362

Moriello, C., Mayo, N., Feldman, L., & Carli, F. (2008). Validating the Six-Minute Walk Test as a Measure of recvoery after elective colorectal resection. *Arch Phys Med Rehab*, *89*, 1083–1089. http://doi.org/10.1016/j.apmr.2007.11.031

Morra, E. A., Zaniqueli, D., Rodrigues, S. L., El-Aouar, L. M., Lunz, W., Mill, J. G., & Carletti, L. (2014). Long-term intense resistance training in men is associated with preserved cardiac structure/function, decreased aortic stiffness, and lower central augmentation pressure. *Journal of Hypertension*, *32*(2), 286–293. http://doi.org/10.1097/HJH.0000000000000035

Morris, E., Taylor, E. F., Thomas, J. D., Quirke, P., Finan, P. J., Coleman, M. P., … Forman, D. (2011). Thirty-day postoperative mortality after colorectal cancer surgery in England. *Gut*, *60*(6), 806–13. http://doi.org/10.1136/gut.2010.232181

Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G., & Parks, J. W. (1953). CORONARY HEART-DISEASE AND PHYSICAL ACTIVITY OF WORK. *The Lancet*, *262*(6795), 1053–1057. http://doi.org/10.1016/S0140-6736(53)90665-5

Murphy, M., Black, N., Lamping, D., McKee, C., Sanderson, C., Askham, J., & Marteau, T. (1998). *Consensus development methods, and their use in clinical guideline development*.

Myers, J., Kaykha, A., George, S., Abella, J., Zaheer, N., Lear, S., … Froelicher, V. (2014). Fitness versus physical activity patterns in predicting mortality in men. *The American Journal of Medicine*, *117*(12), 912–918. http://doi.org/10.1016/j.amjmed.2004.06.047

Myers, J., Voodi, L., Umann, T., & Froelicher, V. F. (2000). A survey of exercise testing: methods, utilization, interpretation, and safety in the VAHCS. *Journal of Cardiopulmonary Rehabilitation*, *20*(4), 251–258.

National Cancer Action Team, & National Cancer Intelligence

Network. (2007). *CANCER WAITING TIMES: A Guide (Version 7)*.

National Center for Chronic Disease Prevention and Health Promotion CDC. (1999). CHAPTER 3: Physiologic Responses and Long-Term Adaptations to Exercise. *Physical Activity and Health: A Report of the Surgeon General*, 61–77.

Newton, R. (2011). Exercise is medicine for chronic disease managment. *Journal of Science and Medicine in Sport*, *14*(1), e15. http://doi.org/10.1016/j.jsams.2011.11.032

NHS England. (2015). *Cancer Waiting Times, January to March 2015 - Commissioner Data The latest quarterly statistics on waiting times for suspected and diagnosed cancer patients accessing services within the NHS were released by NHS England on 20*.

Nytrøen, K., Rustad, L. a, Aukrust, P., Ueland, T., Hallén, J., Holm, I., … Gullestad, L. (2012). High-intensity interval training improves peak oxygen uptake and muscular exercise capacity in heart transplant recipients. *American Journal of Transplantation : Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, *12*(11), 3134–42. http://doi.org/10.1111/j.1600-6143.2012.04221.x

Nytrøen, K., Yardley, M., Rolid, K., Bjørkelund, E., Karason, K.,

Wigh, J. P., … Gullestad, L. (2016). Design and rationale of the HITTS randomized controlled trial: Effect of High-intensity Interval Training in de novo Heart Transplant Recipients in Scandinavia. *American Heart Journal*, *172*, 96–105. http://doi.org/10.1016/j.ahj.2015.10.011

O'Doherty, a F., West, M., Jack, S., & Grocott, M. P. W. (2013). Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. *British Journal of Anaesthesia*, *110*(5), 679–89. http://doi.org/10.1093/bja/aes514

Oettle. (1991). Effect of moderate exercise on bowel habit. *Gut*, *32*, 941–944.

Olsen, C., Wilson, L. F., Kendall, B. J., Bain, C. J., Whiteman, D. C., & Neale, R. E. (2015). Cancers in Australia in 2010 attributable to infectious agents. *Australian and New Zealand Journal of Public Health*, *39*(5), 446–451. http://doi.org/10.1111/1753-6405.12445

Ortega, F., Toral, J., Cejudo, P., Villagomez, R., Sánchez, H., Castillo, J., & Montemayor, T. (2002). Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *166*(5), 669–74. http://doi.org/10.1164/rccm.2107081

Osawa, Y. (2014). Effects of 16-week high-intensity interval

training using upper and lower body ergometers on aerobic fitness and morphological changes in healthy men : a preliminary study. *Open Access Journal of Sports Medicine*, *5*, 257–265.

Palange, P., Ward, S. a, Carlsen, K.-H., Casaburi, R., Gallagher, C. G., Gosselink, R., … Whipp, B. J. (2007). Recommendations on the use of exercise testing in clinical practice. *The European Respiratory Journal*, *29*(1), 185–209. http://doi.org/10.1183/09031936.00046906

Partridge, J. S. L., Harari, D., & Dhesi, J. K. (2012). Frailty in the older surgical patient: a review. *Age and Ageing*, *41*(2), 142–7. http://doi.org/10.1093/ageing/afr182

Paterson, D. H., & Warburton, D. E. R. (2010). Physical activity and functional limitations in older adults : a systematic review related to Canada ' s Physical Activity Guidelines. *International Journal of Behavioural Nutrition and Physical Activity*, *7*(38).

Petersen, a. M. W., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *J Appl Physiol*, *98*, 1154–1162. http://doi.org/10.1152/japplphysiol.00164.2004.

Phillips, B. E., Smith, K., Liptrot, S., Atherton, P. J., Varadhan, K., Rennie, M. J., … Williams, J. P. (2013). Effect of colon cancer and surgical resection on skeletal muscle

mitochondrial enzyme activity in colon cancer patients: a pilot study. *Journal of Cachexia, Sarcopenia and Muscle*, *4*(1), 71–7. http://doi.org/10.1007/s13539-012-0073-7

Phillips, B. E., Williams, J. P., Gustafsson, T., Bouchard, C., Rankinen, T., Knudsen, S., … Atherton, P. J. (2013). Molecular Networks of Human Muscle Adaptation to Exercise and Age. *PLoS Genetics*, *9*(3). http://doi.org/10.1371/journal.pgen.1003389

Phillips, B., Kelly, B., Lilja, M., Gustavo Ponce-González, J., Brogan, R., Morris, D., … Timmons, J. A. (2017). A practical and time-efficient high-intensity interval training programme modifies cardio-metabolic risk-factors in adults at risk for developing Type II diabetes.

Pichot, V., Roche, F., Denis, C., Garet, M., Duverney, D., Costes, F., & Barthélémy, J.-C. (2005). Interval training in elderly men increases both heart rate variability and baroreflex activity. *Clinical Autonomic Research : Official Journal of the Clinical Autonomic Research Society*, *15*(2), 107–15. http://doi.org/10.1007/s10286-005-0251-1

Pinto, B. M., Papandonatos, G. D., Goldstein, M. G., Marcus, B. H., & Farrell, N. (2013). Home-based physical activity intervention for colorectal cancer survivors. *Psycho-Oncology*, *22*(1), 54–64. http://doi.org/10.1002/pon.2047

Pluim, B. M., Zwinderman, A. H., van der Laarse, A., & van der Wall, E. E. (2000). The Athlete's Heart. *Circulation*, *101*(3), 336 LP-344.

Raitakari, O. T., & Celermajer, D. S. (2000). Flow-mediated dilatation. *British Journal of Clinical Pharmacology*, 397–404.

Rakobowchuk, M., Tanguay, S., Burgomaster, K. A., Howarth, K. R., Gibala, M. J., & Macdonald, M. J. (2008). Sprint interval and traditional endurance training induce similar improvements in peripheral arterial stiffness and flow-mediated dilation in healthy humans, *1*, 236–242. http://doi.org/10.1152/ajpregu.00069.2008.

Raleigh, J., Giles, M., Scribbans, T., Edgett, B., Sawula, L., Bonafiglia, J., … Gurd, B. (2016). The impact of work-matched interval training on V̇O2peak and V̇O2 kinetics: diminishing returns with increasing intensity. *Appl Physiol Nutr Metab*, *41*(7), 706–713.

Ramonell, K. M., Fang, S., Perez, S. D., Srinivasan, J. K., Sullivan, P. S., Galloway, J. R., … Shaffer, V. O. (2016). Development and Validation of a Risk Calculator for Renal Complications after Colorectal Surgery Using the National Surgical Quality Improvement Program Participant Use Files. *The American Surgeon*, *82*(12), 1244–1249.

Ramos, J. S., Dalleck, L. C., Tjonna, A. E., Beetham, K. S., & Coombes, J. S. (2015). The Impact of High-Intensity Interval Training Versus Moderate-Intensity Continuous Training on Vascular Function: a Systematic Review and Meta-Analysis. *Sports Medicine*, *45*(5), 679–692. http://doi.org/10.1007/s40279-015-0321-z

Ready, A. E., Eynon, R. B., & Cunningham, D. A. (1981). Effect of interval training and detraining on anaerobic fitness in women. *Canadian Journal of Applied Sport Sciences. Journal Canadien Des Sciences Appliquees Au Sport*, *6*(3), 114–118.

Reeves, N. D., Maganaris, C. N., & Narici, M. V. (2004). Ultrasonographic assessment of human skeletal muscle size. *European Journal of Applied Physiology*, *91*(1), 116–8. http://doi.org/10.1007/s00421-003-0961-9

Rikli, R., & Jones, C. J. (1999). Development and validity of a functional fitness test for community-residing older adults. *Journal of Aging and Physical Activity*, *7*, 129–161.

Robinson, E. H., Stout, J. R., Miramonti, A. a, Fukuda, D. H., Wang, R., Townsend, J. R., … Hoffman, J. R. (2014). High-intensity interval training and β-hydroxy-β-methylbutyric free acid improves aerobic power and metabolic thresholds. *Journal of the International Society of Sports Nutrition*, *11*, 16. http://doi.org/10.1186/1550-2783-11-16

Roca, J., Lacy, Ã. A. M., Barberan-garcia, A., & Ubre, Ã. M. (2017). Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery A Randomized Blinded Controlled Trial. *Annals of Surgery*. http://doi.org/10.1097/SLA.0000000000002293

Rolfson, Majumdar, Tsuyuki, & Rockwood. (2006). Validity and reliability of the Edmonton Frail Scale. *Age and Ageing*, *35*(5), 523–526. http://doi.org/10.1093/ageing/afl023

Ross, R., Blair, S. N., Arena, R., Church, T. S., Despr??s, J. P., Franklin, B. A., … Wisl??ff, U. (2016). Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation*, *134*, 1–48. http://doi.org/10.1161/CIR.0000000000000461

Rowell, A. (1993). *Human cardiovascular control.* Oxford university press.

Ruas, J. L., White, J. P., Rao, R. R., Kleiner, S., Brannan, K. T., Harrison, B. C., … Spiegelman, B. M. (2012). A PGC-1α isoform induced by resistance training regulates skeletal muscle hypertrophy. *Cell*, *151*(6), 1319–31. http://doi.org/10.1016/j.cell.2012.10.050

Russo, C. R. (2009). The effects of exercise on bone . Basic

concepts and implications for the prevention of fractures. *Clinical Cases in Mineral and Bone Metabolism*, *6*(3), 223–228.

Saadatnia, A., Ebrahim, K., & Rashidlamir, A. (2016). Echocardiographic Evaluation of the Effects of High-Intensity Interval Training on Cardiac Morphology and Function. *Arch Cardiovascular Imaging*, *e36007*. http://doi.org/10.5812/acvi.36007.Brief

Santa Mina, D., Clarke, H., Ritvo, P., Leung, Y. W., Matthew, a G., Katz, J., … Alibhai, S. M. H. (2013). Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. *Physiotherapy*. http://doi.org/10.1016/j.physio.2013.08.008

Santos, D. A., Silva, A. M., Baptista, F., Santos, R., Vale, S., Mota, J., & Sardinha, L. B. (2012). Sedentary behavior and physical activity are independently related to functional fi tness in older adults. *EXG*, *47*(12), 908–912. http://doi.org/10.1016/j.exger.2012.07.011

Schutzer, K., & Graves, S. (2004). Barriers and motivations to exercise in older adults. *Preventative Medicine*, *39*, 1056–1061.

Sebio Garcia, R., Yáñez Brage, M. I., Giménez Moolhuyzen, E., Granger, C. L., & Denehy, L. (2016). Functional and

postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. *Interactive CardioVascular and Thoracic Surgery*, ivw152. http://doi.org/10.1093/icvts/ivw152

Segal, R., Zwaal, C., Green, E., Tomasone, J., Loblaw, A., & Petrella, T. (2017). Exercise for People with Cancer. *Curr Oncol*, *24*(1), 40–46.

Selva, I., Bird, S., & Shield, A. (2017). ARE ASSOCIATED WITH STRENGTH AND FUNCTIONAL CAPACITY IN OLDER ADULTS. *Ultrasound in Med and Biol*, *43*(3), 586–594. http://doi.org/10.1016/j.ultrasmedbio.2016.11.013

Sheeran, P., & Hall, G. (1997). Cytokines in anaesthesia. *BJA*, 201–219.

Singh, F., Newton, R. U., Baker, M. K., Spry, N. A., Taaffe, D. R., & Galvão, D. A. (2017). Feasibility and Ef fi cacy of Presurgical Exercise in Survivors of Rectal Cancer Scheduled to Receive Curative Resection. *Clinical Colorectal Cancer*, 1–8. http://doi.org/10.1016/j.clcc.2017.03.010

Singh, F., Newton, R. U., Galvão, D. a, Spry, N., & Baker, M. K. (2013). A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surgical Oncology*, *22*(2), 92–104. http://doi.org/10.1016/j.suronc.2013.01.004

Skutnik, B. C., Smith, J. R., Johnson, A. M., Kurti, S. P., & Harms, C. A. (2016). The Effect of Low Volume Interval Training on Resting Blood Pressure in Pre-hypertensive Subjects: A Preliminary Study. *The Physician and Sportsmedicine*, *44*(2), 177–183. http://doi.org/10.1080/00913847.2016.1159501

Slattery, M. (2004). Physical activity and colorectal cancer. *Sports Med*, *34*(4), 239–252.

Slattery, M. L., & Potter, J. D. (2002). Physical activity and colon cancer: confounding or interaction? *Medicine and Science in Sports and Exercise*, *34*(6), 913–919.

Songsorn, P., Lambeth-Mansell, A., Mair, J. L., Haggett, M., Fitzpatrick, B. L., Ruffino, J., … Vollaard, N. B. J. (2016). Exercise training comprising of single 20-s cycle sprints does not provide a sufficient stimulus for improving maximal aerobic capacity in sedentary individuals. *European Journal of Applied Physiology*, *116*(8), 1511–1517. http://doi.org/10.1007/s00421-016-3409-8

Sothisrihari, S., Wright, C., Hammond, T., Hospital, B., Essex, C. R., Hospital, B., … Kingdom, U. (2016). Should Pre-operative Optimisation of Colorectal Cancer Patients Supersede the Demands of the 62 Day Pathway? *Colorectal Disease*. http://doi.org/10.1111/ijlh.12426

Spanjer, J., Krol, B., Brouwer, S., Popping, R., Groothoff, J. W., & van der Klink, J. J. L. (2010). Reliability and validity of the Disability Assessment Structured Interview (DASI): a tool for assessing functional limitations in claimants. *Journal of Occupational Rehabilitation*, *20*(1), 33–40. http://doi.org/10.1007/s10926-009-9203-2

Speck, R. M., Courneya, K. S., Mâsse, L. C., Duval, S., & Schmitz, K. H. (2010). An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Journal of Cancer Survivorship : Research and Practice*, *4*(2), 87–100. http://doi.org/10.1007/s11764-009-0110-5

Spencer, N. (2015). *Easier said than done, why we struggle with healthy behaviours and what to do about it*. *RSA*.

Sprangers, M. A. G., Te Velde, A., & Aaronson, N. K. (1999). The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). *European Journal of Cancer*, *35*(2), 238–247. http://doi.org/10.1016/S0959-8049(98)00357-8

Spriet, L. (1995). *Anaerobic metabolism during high-intensity exercise. Exercise metabolism.* (M. Hargreaves, Ed.). Human kinetics.

Stohr, E. J., Stembridge, M., Shave, R., Samuel, T. J., Stone,

K., & Esformes, J. I. (2017). Systolic and Diastolic LV Mechanics during and following Resistance Exercise. *Medicine and Science in Sports and Exercise*. http://doi.org/10.1249/MSS.0000000000001326

Strunden, M. S. (2011). Perioperative fluid and volume management : physiological basis , tools and strategies. *Annals of Intensive Care*, *1*(1), 2. http://doi.org/10.1186/2110-5820-1-2

Talanian, J. L., Galloway, S. D. R., Heigenhauser, G. J. F., Bonen, A., & Spriet, L. L. (2007). Two weeks of high-intensity aerobic interval training increases the capacity for fat oxidation during exercise in women, *1*, 1439–1447. http://doi.org/10.1152/japplphysiol.01098.2006.

Tennant, R., Hiller, L., Fishwick, R., Platt, S., Joseph, S., Weich, S., … Stewart-Brown, S. (2007). The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. *Health and Quality of Life Outcomes*, *5*, 63. http://doi.org/10.1186/1477-7525-5-63

Tew, G. a, Weston, M., Kothmann, E., Batterham, A. M., Gray, J., Kerr, K., … Danjoux, G. (2014). High-intensity interval exercise training before abdominal aortic aneurysm repair (HIT-AAA): protocol for a randomised controlled feasibility trial. *BMJ Open*, *4*(1), e004094.

http://doi.org/10.1136/bmjopen-2013-004094

Thomas, R. J., Ken, S. A., & Jimenez, A. (2016). Exercise-induced biochemical changes and their potential influence on cancer : a scientific review. *BJSM*, *0*, 1–8. http://doi.org/10.1136/bjsports-2016-096343

Timmerman, H., de Groot, J. F., Hulzebos, H. J., de Knikker, R., Kerkkamp, H. E. M., & Meeteren, V. (2011). Feasibility and prelimianary effectiveness of preoperative therapeutic exercise in patients with cancer: A pragmatic study. *Physiotherapy Theory and Practice*, *27*(2), 117–124.

Timmons, J. a, Knudsen, S., Rankinen, T., Koch, L. G., Jensen, T., Keller, P., … Pahor, M. (2010). Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans The effect of increased physical activity on pulmonary diffusing capacity in unfit women. *Journal of Applied Physiology*, *108*, 1487–1496. http://doi.org/10.1152/japplphysiol.01295.2009

Tresierras, M. A., & Balady, G. J. (2009). Resistance training in the treatment of diabetes and obesity: mechanisms and outcomes. *Journal of Cardiopulmonary Rehabilitation and Prevention*, *29*(2), 67–75. http://doi.org/10.1097/HCR.0b013e318199ff69

Treuth, M. S., & Ryan, A. S. (1994). Effects of strength training composition in older men on total and regional body. *American Physiological Society*.

UK Department of Health. (2015). *Quality of Life of Colorectal Cancer Survivors in England*.

Umpierre, D., Kramer, C. K., Leita, C. B., Gross, J. L., Ribeiro, J. P., & Schaan, B. D. (2011). Physical Activity Advice Only or Structured exercise training and association With HbA 1c Levels in Type 2 Diabetes. *JAMA: The Journal of the American Medical Association*, *305*, 1790–1799. http://doi.org/10.1001/jama.2011.576

Valkenet, K., Trappenburg, J. C. A., Schippers, C. C., Wanders, L., Lemmens, L., Backx, F. J. G., & van Hillegersberg, R. (2016). Feasibility of Exercise Training in Cancer Patients Scheduled for Elective Gastrointestinal Surgery. *Digestive Surgery*,*33*(5),439–447. http://doi.org/10.1159/000445958

Vella, C. A., & Robergs, R. A. (2005). REVIEW A review of the stroke volume response to upright exercise in healthy subjects,(August2004).http://doi.org/10.1136/bjsm.2004.013037

Vogiatzis, I., Nanas, S., & Roussos, C. (2002). Interval training as an alternative modality to continuous exercise in patients with COPD. *European Respiratory Journal*, *20*(1), 12–19.

http://doi.org/10.1183/09031936.02.01152001

Walsh, N. P., Gleeson, M., Shephard, R. J., Jeffrey, M. G., Woods, A., Bishop, N. C., … Rogers, C. J. (2011). Part one : Immune function and exercise, 6–63.

Walter, C. J. (2009). Enhanced recovery in colorectal resections: A systematic review and meta-analysis. *Colorectal Disease*, *11*(4), 344–353. http://doi.org/10.1111/j.1463-1318.2009.01789.x

Warburton, D. E. R., McKenzie, D. C., Haykowsky, M. J., Taylor, A., Shoemaker, P., Ignaszewski, A. P., & Chan, S. Y. (2005). Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *The American Journal of Cardiology*, *95*(9), 1080–4. http://doi.org/10.1016/j.amjcard.2004.12.063

Wasserman, K. (1978). Breathing during Exercise. *New England Journal of Medicine*, *298*(14), 780–785. http://doi.org/10.1056/NEJM197804062981408

Wasserman, K. (1986a). The anaerobic threshold: definition, physiological significance and identification. *Advances in Cardiology*, *35*(1–23).

Wasserman, K. (1986b). The anaerobic threshold: definition, physiological significance and identification. *Adv Cardiol*, *35*, 1–23.

Weisman, I. M., Marciniuk, D., Martinez, F. J., Sciurba, F., Sue, D., Myers, J., … Sietsema, K. (2003). ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine*, *167*(2), 211–77. http://doi.org/10.1164/rccm.167.2.211

Wells, G. a, Shea, B., Connell, D. O., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta- analyses.

Wesley, V. (2009). The Delphi Technique: A review. *International Journal of Therapy and Rehabilitation*, *16*(2), 69–76.

West, M. A., Asher, R., Browning, M., Minto, G., Swart, M., Richardson, K., … Grocott, M. P. W. (2016). Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. *British Journal of Surgery*. http://doi.org/10.1002/bjs.10112

West, M. A., Jack, S., & Grocott, M. P. W. (2011). Perioperative cardiopulmonary exercise testing in the elderly. *Best Practice & Research. Clinical Anaesthesiology*, *25*(3), 427–37. http://doi.org/10.1016/j.bpa.2011.07.004

West, M. A., Loughney, L., Barben, C. P., Sripadam, R., Kemp,

G. J., Grocott, M. P. W., & Jack, S. (2014). The effects of neoadjuvant chemoradiotherapy on physical fitness and morbidity in rectal cancer surgery patients. *European Journal of Surgical Oncology*, *40*(11), 1421–1428. http://doi.org/10.1016/j.ejso.2014.03.021

West, M. A., Loughney, L., Lythgoe, D., Barben, C. P., Sripadam, R., Kemp, G. J., … Jack, S. (2014). Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *British Journal of Anaesthesia*, 1–8. http://doi.org/10.1093/bja/aeu318

West, M. A., Lythgoe, D., Barben, C. P., Noble, L., Kemp, G. J., Jack, S., & Grocott, M. P. W. (2014). Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. *British Journal of Anaesthesia*, *112*(4), 665–71. http://doi.org/10.1093/bja/aet408

West, M. A., Parry, M. G., Lythgoe, D., Barben, C. P., Kemp, G. J., Grocott, M. P. W., & Jack, S. (2014). Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery. *The British Journal of Surgery*, *101*(9), 1166–72. http://doi.org/10.1002/bjs.9551

Weston, A. (1997). Skeletal muscle buffering capacity and

endurance performance after high-intensity interval training by well-trained cyclists. *Eur J Appl Physiol Occup Physiol*, *75*(1), 7–13.

Weston, M., Taylor, K. L., Batterham, A. M., & Hopkins, W. G. (2014). Effects of Low-Volume High-Intensity Interval Training (HIT) on Fitness in Adults: A Meta-Analysis of Controlled and Non-Controlled Trials. *Sports Medicine (Auckland, N.Z.)*, *44*(7), 1005–17. http://doi.org/10.1007/s40279-014-0180-z

Weston, M., Weston, K. L., Prentis, J. M., & Snowden, C. P. (2016). High-intensity interval training (HIT) for effective and time-efficient pre-surgical exercise interventions. *Perioperative Medicine (London, England)*, *5*(January), 2. http://doi.org/10.1186/s13741-015-0026-8

White, J. P., Baltgalvis, K. A., Puppa, M. J., Sato, S., Baynes, J. W., Carson, J. A., & Carolina, S. (2011). Muscle oxidative capacity during IL-6-dependent cancer cachexia, (5), 201–211. http://doi.org/10.1152/ajpregu.00300.2010.

Williams, J. P., Nyasavajjala, S. M., Phillips, B. E., Chakrabarty, M., & Lund, J. N. (2014). Surgical resection of primary tumour improves aerobic performance in colorectal cancer. *European Journal of Surgical Oncology : The Journal of the European Society of Surgical Oncology and the British*

Association of Surgical Oncology, *40*(2), 220–6. http://doi.org/10.1016/j.ejso.2013.11.009

Williams, J. P., Phillips, B. E., Smith, K., Atherton, P. J., Rankin, D., Selby, A. L., … Rennie, M. J. (2012). Effect of tumor burden and subsequent surgical resection on skeletal muscle mass and protein turnover in colorectal cancer patients. *AM J Clin Nutr*, *96*(5), 1064–1071. http://doi.org/10.3945/ajcn.112.045708.1064

Wilmore, D. W. (2002). From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. *Annals of Surgery*, *236*(5), 643–8. http://doi.org/10.1097/01.SLA.0000032942.79841.ED

Wilson, R. J. T., Davies, S., Yates, D., Redman, J., & Stone, M. (2010). Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *British Journal of Anaesthesia*, *105*(3), 297–303. http://doi.org/10.1093/bja/aeq128

Wisløff, U. (2007). Superior cardiovascular effect of aerobic interval training vs moderate continuous training in heart failure patients. *Circulation*, *115*, 3086–3094.

World Health Organisation. (2010a). *Global recommendations on physical activity for health*. *World Health Organisation*.

World Health Organisation. (2010b). Global recommendations

on physical activity for health.

Wydra, J., Kruszewski, W., Jasiński, W., Szajewski, M., Ciesielski, M., Szefel, J., & Walczak, J. (2013). Is age a risk factor of postoperative complications in colorectal cancer? *Polski Przeglad Chirurgiczny*, *85*(9), 491–5. http://doi.org/10.2478/pjs-2013-0076

Xie, B., Yan, X., Cai, X., & Li, J. (2017). Effects of High-Intensity Interval Training on Aerobic Capacity in Cardiac Patients: A Systematic Review with Meta-Analysis. *BioMed Research International*, *2017*. http://doi.org/10.1155/2017/5420840

8 Appendices

8.1 Ethics approvals

8.1.1 University of Nottingham Medical School ethics committee approval for HIT study

Ethics Reference No: J14112013 SoM MS GEM
Study Title : Determining the effectiveness of a high intensity interval training exercise programme in the healthy, elderly population.
Chief Investigator: Dr John Williams, Clinical Associate Professor/Consultant Anaesthetist, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, Royal Derby Hospital.
Co Investigators : Miss Catherine Boereboom, Clinical Research Fellow, Mr Jon Lund, Clinical Associate Professor/Consultant Colorectal Surgeon, Dr Bethan Phillips, Research Fellow, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, Royal Derby Hospital.

Duration of Study: 01.01.2014-31.12.2015 2yrs No of Subjects 25 (60-75yrs)

Thank you for your letter dated 17th January 2014 responding to the issues raised by the Committee at its meeting on 14th November 2013 and the following revised documents were received as requested:
1. UoN FMHS Med Sch Research Ethics Application form v 5 dated 17.01.2014.
2. Appendix 1 Project Proposal, version 5.0, 17.01.2014.
3. Appendix 2 Participant Information Sheet version 5.0, 17 January 2014.
4. Appendix 3 Consent form, Final Version 5.0: 17 January 2014
5. Appendix 4 Poster version 5.0, 17 January 2014
6. Appendix 5 Medical Screening Questionnaire version 5.0, 17 January 2014.
7. Appendix 6 Letter to participant GP version 5.0, 17 January 2014

8. Appendix 7 Recruitment Letter version 5.0, 17 January 2014.
9. Appendix 9 DEXA Scan Information Leaflet version 1.0 October 2013
10. Appendix 10 Invitation letter for mailshot version 5.0 17 January 2014

These have been reviewed and are satisfactory and the study is approved. Approval is given on the understanding that the Conditions of Approval set out below are followed.

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).
2. You must notify the Chair of any serious or unexpected event.
3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.
4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely
Dr Clodagh Dugdale
Chair, Nottingham University Medical School Research Ethics Committee
FMHS Medical School Research Ethics Committee
Membership 2013/2014

8.1.2 East Midlands (Derby) research ethics committee approval for HITCa study (covering letter)

NHS
Health Research Authority
NRES Committee East Midlands - Derby
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 883 9525

12 September 2014

Dr John Williams
Consultant anaesthetist and clinical associate professor
University of Nottingham
Division of Medical Sciences and Graduate Entry Medicine, School of Medicine
Royal Derby Hospital
Uttoxeter Road, Derby
DE22 3DT

Dear Dr Williams

Study title:	**Effectiveness of short term, high intensity, interval exercise training in older colorectal cancer patients in improving preoperative fitness**
REC reference:	**14/EM/1131**
Protocol number:	**14064**
IRAS project ID:	**144242**

Thank you for your letter of 12 September 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Tracy Leavesley, NRESCommittee.EastMidlands-Derby@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the

8.2 Participant information sheets

8.2.1 HIT study participant information sheet

Participant Information Sheet (Version 5.0, January 2014)

Determining the effectiveness of a high intensity interval training exercise programme in the healthy, elderly population

Miss Catherine Boereboom MBChB (Hons), MRCS, Clinical Research Fellow, Division of Graduate Entry Medicine and Health, School of Medicine, University of Nottingham, and Surgical Registrar, Royal Derby Hospital.

Dr John Williams, BSc (Hons), MBChB, FRCA, PhD, FFPMRCA, Clinical Associate Professor, Division of Graduate Entry Medicine and Health, School of Medicine, University of Nottingham, and Honorary Consultant Anaesthetist, Royal Derby Hospital.

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

Dr Bethan Phillips, BSc (Hons), PhD, Research Fellow, Division of Graduate Entry Medicine and Health, School of Medicine, University of Nottingham.

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

What is the purpose of the study?

Previous research has shown that healthy people, and those with heart disease or diabetes, who undergo low intensity exercise programmes get fitter. Fitter people tend to recover better from major surgery than those who are less fit. The problem with these traditional exercise programmes is that they last many weeks and so are not suitable for people awaiting urgent surgery. Also, not all people respond to exercise in the same way and some people show a greater improvement in fitness with short, high intensity bursts than low intensity, endurance programmes.

High intensity interval training can be done in a much shorter time than traditional endurance training.

We know that you are not awaiting urgent surgery. However, we want to see how much we can improve the fitness levels of a group of healthy people aged between 60 and 75 years in a short time period of 4 weeks using a high intensity interval training exercise

programme. This information will help to develop further studies in patients awaiting cancer surgery.

Why have I been invited?

You are being invited to take part because you are between 60 and 75 years old and healthy. We are inviting 24 participants like you to take part.

You will not be able to take part in the study if you have:

- Uncontrolled hypertension (Blood Pressure > 140/100)
- Angina
- Previous stroke/TIA (mini stroke)
- Significant heart, blood vessel or lung disease
- If you have been a subject in any other research study in the last three months which involved: taking a drug; being paid a disturbance allowance; having an invasive procedure (e.g. blood sample >50ml) or exposure to ionising radiation.

Do I have to take part?

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

What will happen to me if I take part?

As a research participant you will be asked to take part in 3 high intensity exercise sessions each week, lasting 16.5 minutes each, for 4 weeks (total 12 sessions). The high intensity exercise will be performed on a stationary exercise bicycle. You will be accompanied at all times by member of medically trained research staff. We will use information gained during your baseline "testing" session to see how difficult to make the cycling to improve your fitness. After a warm up you will cycle for 60 seconds against a high resistance then 90 seconds with no resistance, this will be repeated 5 times and then there will be a cool down period.

An assessment session when your consent and pre study blood tests will be taken will last 1 hour. The baseline session (prior to the training sessions) and the reassessment session (after the last training session) will last for approximately 1 hour. There will be 15 trips to the research unit in total

In the longer baseline and reassessment sessions you will –

- Have a whole-body scan to measure your fat, muscle and bone composition. These Dual Energy X-Ray Absorptiometry (DXA) body scans will expose you to a low dose of radiation; 1 DXA scan is the equivalent to 3 days natural background radiation. Please see attached DXA information sheet.

- Have an ultrasound (jelly) scan of your thigh muscles.
- Undergo some simple exercise tests (balance, walking and standing from a chair)
- Answer some questionnaires about your health and quality of life.
- Cycle wearing a facemask to measure your breathing and a heart monitor to measure your heart rate. The resistance that you cycle against on the exercise bike will slowly increase over the baseline "testing" session until you have to stop because you can no longer continue cycling. We will use this level to work out how difficult to make your training sessions.

All sessions will take place at the University of Nottingham Medical School at the Royal Derby Hospital.

What are the possible disadvantages and risks of taking part?

All exercise sessions will be supervised by a member of research staff trained in hospital life support and a medical doctor will be available at all times. Exercise will be stopped immediately at any complaint of chest tightness or pain, light headedness, palpitations or other feelings of discomfort from the participants. You heart tracing and blood pressure will also be monitored every time you use the exercise bike and your session will be stopped if the medical team have any concerns with these.

Minor bruising may occur with the blood tests taken twice during the study.

What are the possible benefits of taking part?

The information we get from this study will help assess whether we can make a difference to healthy, older peoples fitness in a short time period. We can then go on to see whether the fitness of people with cancer can be improved and then whether their recovery after cancer surgery can be made easier.

What happens when the research study stops?

Your information will be used in an anonymised fashion to compare the measurements we make before and after the training program. The data will be stored, analysed and published in a way that it will not be possible to identify individual participants.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you should then contact the Ethics Committee Secretary;

Louise Sabir

UoN Faculty of Medicine & Health Sciences Research Ethics Committee

c/o School of Medicine Education Centre (Medical Courses Office),

B Floor, Medical School

QMC Campus

Nottingham University Hospitals
NG7 2UH
e-mail: louise.sabir@nottingham.ac.uk

Will my taking part in the study be kept confidential?

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

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

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. The lead research fellow and principle investigator (who oversees the study) will have access to your information. Any information about you which leaves the institution will have your personal details removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept at the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

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

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will be sent a letter with the contact details of the researchers. It will explain the study and what we are asking the participants to do. Any queries will be answered by the research team.

What will happen to any samples I give?

After analysis, all samples will be disposed of in accordance with the Human Tissue Authorities 2006 codes of practice.

What will happen to the results of the research study

This research is likely to be published in a scientific journal and presented at scientific meetings. If you wish, you will be sent an abbreviated version of the written report. No

participants will be identified in the report. This work will also form part of a larger project and go towards the thesis for a research PhD.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and is being funded by the University.

Who has reviewed the study?

All research in the University of Nottingham is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by The University of Nottingham Medical School Ethics Committee.

Further information and contact details

Miss Catherine Boereboom (MBChB MRCS), Surgical Registrar and PhD student
Departments of General Surgery and Molecular, Metabolic and Clinical Physiology,
Royal Derby Hospital
Email: catboereboom@doctors.org.uk
Phone: 01332 724 731/Study mobile phone number 07557 566 018

8.2.2 HITCa study patient information sheet

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Participant Information Sheet
Final version 3.0 18.03.16

Determining the effectiveness of a high intensity interval training exercise programme in colorectal cancer patients.

Dr John Williams, Miss Catherine Boereboom, Mr Jon Lund, Dr Beth Phillips

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

What is the purpose of the study?
It is well known that exercise makes people more fit.
Fitter people tend to recover better from cancer treatment (surgery or chemotherapy and radiotherapy) than those who are less fit. The problem with traditional exercise programmes is that they take many weeks to have an effect and so are not suitable for people awaiting urgent treatment.
Also, not all people respond to exercise in the same way and some people show a greater improvement in fitness with short, high intensity bursts than low intensity, endurance programmes.
High intensity interval training can be done in a much shorter time than traditional endurance training.
We want to see how much we can improve the fitness in a group of people with bowel cancer in the time before their treatment starts using a high intensity interval training exercise programme.
This work is part of an educational PhD project and will go on to inform larger studies in colorectal cancer care.
Why have I been invited?
You are being invited to take part because you are due to have treatment for bowel cancer. We are inviting 24 participants like you to take part.
You will not be able to take part in the study if you:

- Have uncontrolled high blood pressure (over 160/100mmHg)
- Have angina
- Have had a previous stroke/TIA (mini stroke)
- Have significant heart, blood vessel or lung disease

- Have blood clotting or scarring disorders
- Are currently having chemotherapy or radiotherapy
- Provide a positive pregnancy test
- Are younger than 18 years old or older than 98 years old
- If you have been a subject in any other research study in the last three months which involved: taking a drug; being paid a disturbance allowance; having an invasive procedure (e.g. blood sample >50ml) or exposure to ionising radiation.
- **Do I have to take part?**

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

What will happen to me if I take part?

The study will start with an assessment session when your consent, pre study blood tests, heart tracing, height and weight and blood pressure will be taken. You will be asked to fill out a medical questionnaire and your heart and lungs will be examined by a doctor listening to your chest. As well as routine bloods for health screening such as liver and kidney function tests we will collect blood to be stored. The reason for this is that there is some emerging evidence that some people, with specific genes do not respond to exercise. In the near future when further work has been done on this we would like to look back and test the genes of volunteers who have responded differently to others to see if they also have these certain genes. This session will last less than 1 hour.

You will also be given a drink of water to take home. This water is labelled with a molecule (deuterium oxide - D_2O) that allows it to be traced in the body. This is harmless and tastes very much like ordinary tap water. You will be called at home and asked to drink the water at certain times depending on when your baseline visit is scheduled. You will be asked to collect a saliva sample in a tube before and after drinking the water.

The baseline session (prior to the training sessions) and the reassessment session (after the last training session) will last for approximately 1.5 hours.

At these sessions you will –

- Have a whole-body scan to measure your fat, muscle and bone composition. These Dual Energy X-Ray Absorptiometry (DXA) body scans will expose you to a low dose of radiation; 1 DXA scan is the equivalent to 3 days natural background radiation.
- Have an ultrasound (jelly) scan of your thigh muscles.
- Have an ultrasound (jelly) scan of your heart (an echocardiogram)
- Undergo some simple exercise tests (balance, walking and standing from a chair)
- Answer some questionnaires about your health and quality of life.
- Cycle wearing a facemask to measure your breathing and a heart monitor. The resistance that you cycle against on the exercise bike will slowly increase over the cycling test until you feel that you have to stop because you can no longer continue cycling. We will use this level to work out how difficult to make your training sessions.
- Have a biopsy (small sample) of your thigh muscle taken. This will be performed

by a doctor trained in the procedure. It will be done under sterile conditions and with local anaesthetic to numb the area. A small cut (~1cm) will be made halfway down the outside of your thigh, a small amount (roughly pea sized) of muscle will be taken and a stitch placed to close the cut. A dressing will be placed over it. Many research volunteers have muscle biopsies under local anaesthetic and cope very well with the procedure, they do not find it particularly painful.

For the remainder of the study you will be asked to take part in 3-4 high intensity exercise sessions each week, lasting 16.5 minutes each, until your operation or the start of your chemotherapy (total of approximately 12 sessions). The high intensity exercise will be performed on a stationary exercise bicycle. You will be accompanied at all times by member of medically trained research staff. We will use information gained during your baseline "testing" session to see how difficult to make the cycling to improve your fitness. After a warm up you will cycle for 60 seconds against a very high resistance then 90 seconds with no resistance, this will be repeated 5 times and then there will be a cool down period. During the exercise period you will also be asked to take "top up" drinks of the D_2O water with saliva samples before and after the drinks.

At your reassessment visit you will repeat all the tests done at the baseline visit. If you are due to start chemotherapy you will have a biopsy at reassessment. If you are due to have an operation you can choose whether to have your second biopsy at the reassessment visit or whether you would prefer to have it taken whilst you are under general anaesthetic for your cancer operation.

The screening visit, baseline visit, all HIT exercise sessions and the reassessment visit will take place at the University of Nottingham Medical School building behind the Royal Derby Hospital. There will be approximately 16 visits to the Medical School in total depending on the amount of time before your cancer treatment starts. If your cancer treatment is delayed for any reason training will continue until close to the start of your treatment. The reassessment session will be no later than 2 days before your cancer treatment.

Expenses and payments Participants will not be paid an inconvenience allowance or travel costs to participate in the study. There are parking spaces available at the medical school so that hospital parking charges may be avoided. Any additional parking fees will be reimbursed by the university.

What are the possible disadvantages and risks of taking part?

Exercise Those unaccustomed to exercise may feel some muscle tiredness after each HIT training session. This will be self-limiting. You will be monitored during your training sessions and medically trained staff will be present. Exercise will be stopped immediately if you feel unwell or experience any chest tightness or pain, light headedness, palpitations or other feelings of discomfort. Your heart tracing and blood pressure will also be monitored every time you use the exercise bike and your session will be stopped if the medical team have any concerns with these. These sessions will be take place in the University of Nottingham Medical School building (attached to but not technically part of the Royal Derby Hospital) if the medics supervising your sessions thought it necessary or in an emergency you would be accompanied to the hospital for further investigations or an ambulance would be called.

Muscle biopsies. Biopsies will be performed twice during the study. These will be taken from the thigh either under local anaesthetic or whilst you are under general anaesthetic for your cancer operation. The skin will be prepared with surgical cleansing solution and local anaesthetic will be injected. The procedure will be performed by a doctor trained in the procedure.

The risks of muscle biopsy include:

a) Bleeding: You will be screened for blood clotting disorders and excluded where appropriate. It is normal for some bleeding to occur following a muscle biopsy, however

bruising will be minimized by pressing on the wound, a single stitch is applied then a compression bandage will be applied for at least 4 hours following biopsy. In rare occasions, there may still be some bleeding, leading to a bruise which may uncomfortable.

b) Infection: Since the skin will be cut, there is a possibility of an infection. However, a surgical scrub is used to clean the region and the procedure will be carried out under sterile conditions. In unlikely event of infection you will be briefed to recognize the symptoms (reddening, swelling, pain) and instructed to contact either the medical supervisor for this study or your GP immediately.

c) *Nerve Damage:* There is a theoretical possibility of nerve damage; however, there are no large nerve branches in the region of the thigh where the muscle sample will be taken. In rare instances, small branches may be damaged and caused reduced sensation in the area. However, this resolves within 6 to 12 months.

d) *Scar*: There will be a small scar (less than 1cm) at the site of the biopsy, it will virtually disappear over the course of a couple of years.

Auditing of our studies involving muscle biopsies, have found the procedure to be well tolerated by subjects with no significant complications reported.

Please speak to the research team if you do not want to have biopsies but would like to take part in the exercise section of the study, you may still be able to take part.

Blood tests. Blood will be taken 2 times during the study period. This will be done by a person experienced in this technique. Bruising can be a minor complication of taking blood and is self-limiting.

D_2O. Prior to your biopsies you will be given a drink of water, the molecules of this water are tagged with a tracer to allow us to measure the amounts of different molecules in the muscle. This will help us tell whether the exercise has changed the way and amount of muscle that is made. It is a harmless tracer and is not radioactive. The only known side effect is occasional dizziness and nausea when used in high doses, for this reason we advise you not to drive for 2-3 hours after the drink. This study will use a low dose of D_2O and will be given in small amounts over a few hours whilst at home, to minimize the risk of dizziness. You will be asked to give a saliva sample before and after taking the D_2O (this can be collected at home and brought in the next day).

DXA scan. The DXA scan involves you receiving a low dose X-ray, which is a form of radiation.

We're constantly being exposed to natural radiation from the environment around us - from the earth, through rays from outer space, even from the food we eat. The radiation dose that you receive is less than 1µSv per scan. This is equivalent to the amount of radiation that you would be exposed to if you spent 15min on a transatlantic flight or the amount of radiation contained in 10 brazil nuts.

Although the dose of radiation you would be exposed to during the DXA scan is minimal, there is a risk that even small doses of radiation can cause cancer.

The Health Protection Agency estimate that the risk of developing cancer following a dose **10 times** that of a DXA scan is approximately 1 in 20,000. This is the same as the chance of becoming a professional athlete.

Any complication that may occur will be dealt with in accordance with standard NHS practice.

What are the possible benefits of taking part?

The information we get from this study will help assess whether we can make a difference to the fitness of bowel cancer patients in the short time period before their cancer treatment. It is known that people who are fitter are able to recover from surgery/chemotherapy and radiotherapy more quickly and with fewer complications. However, this study is not designed to show an improvement in recovery but to show

whether or not it is possible to improve fitness in the first place. Information from this study will be used to inform future work on exercise and recovery after cancer treatment.

What happens when the research study stops?

Your information will be used in an anonymised fashion to compare the measurements we make before and after the training program. The data will be stored, analysed and published in a way that it will not be possible to identify individual participants.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you should then contact the Patient Advice and Liaison Service at the Royal Derby Hospital.

Free phone: 0800 783 7691
Office: 01332 785156
Email: dhft.contactpals@nhs.net
Text: 07799 337500

Will my taking part in the study be kept confidential?

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

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

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. The lead research fellow and principle investigator (who oversees the study) will have access to your information. Any information about you which leaves the institution will have your personal details removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept at the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

With your permission, photos maybe taken of you in the exercise lab, no photos of surgical procedures will be taken. These will be edited so that you cannot be identified. They will be used for educational presentations only and will be entirely voluntary.

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

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights or medical care being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will be sent a letter explain that you have consented to take part in the study and explaining what the study involves. Any unexpected blood/exercise test results or clinical examination findings will be passed on to your GP for further follow up. Any queries will be answered by the research team.

What will happen to any samples I give?

We would also like to seek your consent so that any remaining samples may be stored and used in possible future research – this is optional (please indicate you agree to this on the consent form). The samples will be stored with a code unique to you and securely at the University of Nottingham under the University's Human Tissue Research Licence (no 12265).

Some of these future studies may be carried out by researchers other than current team of researchers in the Clinical Physiology Unit who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and you will not be identified in anyway.

If you do not agree to the use of your samples in the future, after analysis for this study, any remaining samples will be disposed of in accordance with the Human Tissue Authority's 2006 codes of practice.

Will any genetic tests be done?

Blood samples will be stored so that in the future, when further work on which genes affect response to exercise are found, they can be checked against the results from this study.

Please see above section – What will happen to me if I take part?

What will happen to the results of the research study?

This research is likely to be published in a scientific journal and presented at scientific meetings. If you wish, you will be sent an abbreviated version of the written report. No participants will be identified in the report. This work will form part of a larger project and go towards the thesis for a research PhD. Photos may be taken during the study for illustration during presentation to scientific meetings. You will always be asked whether this is acceptable to you prior to recording.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and is being funded by the University.

Who has reviewed the study?

All research in the University of Nottingham is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the NHS Research Ethics Committee.

Further information and contact details

Miss Catherine Boereboom
Surgical Research Fellow, University of Nottingham, Royal Derby Hospital
Email: catboereboom@doctors.org.uk
Phone: 01332 724 731
Dr John Williams, Chief Investigator,
Department of Clinical Physiology, University of Nottingham, Royal Derby Hospital
Email: john.williams7@nottingham.ac.uk
Phone: 01332 724641

Thank you for your interest in this study.

8.3 Consent forms

8.3.1 HIT consent form

CONSENT FORM
(Final version 5.0: Jan 2014)

Title of Study: **Determining the effectiveness of a high intensity interval training exercise programme in the healthy, elderly population**

REC ref: J14112013 SoM MS GEM

Name of Researcher……

Name of Participant…… **Please initial box**

1. I confirm that I have read and understand the information sheet version number 5.0, dated January 2014, for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of data collected in the study may be looked at by authorise individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
4. I understand that some of these studies may be carried out by researchers other than current team of clinical researchers based at University of Nottingham Medical School at the Royal Derby Hospital, who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and I will not be identified in anyway. ☐
5. I understand that my GP will be informed that I am taking part in this study and will be told if any of my blood tests, clinical measurements or DXA scans show any significant abnormality. ☐
6. I have not been a subject in any other research study in the last three months which involved: taking a drug; being paid a disturbance allowance; having an invasive procedure (eg blood sample >50ml) or exposure to more than 6mSv of ionising radiation in the last 12 months. ☐
7. I voluntarily agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent (if different from Principal Investigator)	Date	Signature
Name of Principal Investigator	Date	Signature

8.3.2 HITCa consent form

CONSENT FORM
(Final version 3.0, 18.03.16)

Title of Study: Determining the effectiveness of a high intensity interval training exercise programme in the colorectal cancer population

REC ref: 14/EM/1131
Name of Researcher:

Name of Participant: **Please initial box**
(NB. Sections 4, 5 and 6 are optional)

1. I confirm that I have read and understand the information sheet version number Final v3.0 dated 18.03.16 for the above study and have had the opportunity to ask questions. ☐

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

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

4. **Optional section**
I consent to being the subject of photographs to be used to illustrated the study in academic presentations, I understand that I will not be identifiable from these images ☐

5. I understand and agree that blood samples will be taken for analysis of screening health tests, baseline D_2O levels and genetic analysis ☐

6. **Optional section**
Saliva samples will be taken for D_2O levels and muscle samples (biopsies) will be taken to look at muscle protein synthesis. ☐

Optional section

7. Consent for storage and use in possible future research
I agree that the samples I have given and the information gathered about me can be stored by the Department of Clinical Physiology at the University of Nottingham Medical School at the Royal Derby Hospital, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than current team in the Clinical Physiology Department, who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and I will not be identified in anyway. ☐

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

9. I agree to take part in the above study. ☐

8.4 Quality of life Questionnaires

8.4.1 EuroQoL 5 dimension

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

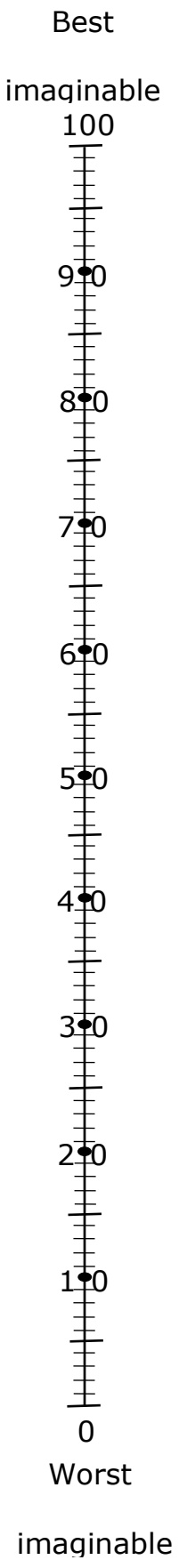
I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



8.4.2 International physical activity questionnaire, example

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (October 2002)[i]

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

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

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

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

Translation from English and Cultural Adaptation
Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

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

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

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

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

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

   ☐ Yes

   ☐ No → ***Skip to PART 2: TRANSPORTATIO***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

   _____ **days per week**

   ☐ No vigorous job-related physical activity → ***Skip to questio***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

   _____ **hours per day**
   _____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

   _____ **days per week**

   ☐ No moderate job-related physical activity → ***Skip to questio***

8.4.3 Dukes activity status index

PROVIDENCE Heart and Vascular Institute

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

[1]**Duke Activity Status Index**

The Duke Activity Status Index is a self-administered questionnaire that measures a patient's functional capacity. It can be used to get a rough estimate of a patient's peak oxygen uptake.

		Yes	No
1	Can you take care of yourself (eating, dressing, bathing or using the toilet)?	2.75	0
2	Can you walk indoors, such as around your house?	1.75	0
3	Can you walk a block or two on level ground?	2.75	0
4	Can you climb a flight of stairs or walk up a hill?	5.50	0
5	Can you run a short distance?	8.00	0
6	Can you do light work around the house, such as dusting or washing dishes?	2.70	0
7	Can you do moderate work around the house, such as vacuuming, sweeping floors or carrying in groceries?	3.50	0
8	Can you do heavy work around the house, such as scrubbing floors or lifting and moving heavy furniture?	8.00	0
9	Can you do yard work, such as raking leaves, weeding or pushing a power mower?	4.50	0
10	Can you have sexual relations?	5.25	0
11	Can you participate in moderate recreational activities, such as golf, bowling, dancing, doubles tennis or throwing a baseball or football?	6.00	0
12	Can you participate in strenuous sports, such as swimming, singles tennis, football, basketball or skiing?	7.50	0

Duke Activity Status Index (DASI) = sum of "Yes" replies _____

VO2peak = (0.43 x DASI) + 9.6

VO2peak = _____ ml/kg/min ÷ 3.5 ml/kg/min = _____ METS

[1]

8.4.4 Warwick Edinburgh mental wellbeing scale

The Warwick-Edinburgh Mental Well-being Scale (WEMWBS)

Below are some statements about feelings and thoughts.

Please tick the box that best describes your experience of each over the last 2 weeks

STATEMENTS	None of the time	Rarely	Some of the time	Often	All of the time
I've been feeling optimistic about the future	1	2	3	4	5
I've been feeling useful	1	2	3	4	5
I've been feeling relaxed	1	2	3	4	5
I've been feeling interested in other people	1	2	3	4	5
I've had energy to spare	1	2	3	4	5
I've been dealing with problems well	1	2	3	4	5
I've been thinking clearly	1	2	3	4	5
I've been feeling good about myself	1	2	3	4	5
I've been feeling close to other people	1	2	3	4	5
I've been feeling confident	1	2	3	4	5
I've been able to make up my own mind about things	1	2	3	4	5
I've been feeling loved	1	2	3	4	5
I've been interested in new things	1	2	3	4	5
I've been feeling cheerful	1	2	3	4	5

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8.4.5 European organisation for research and treatment of cancer quality of life questionnaire

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

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

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

Please go on to the next page

EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

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

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

Please go on to the next page

8.4.6 HIT acceptability questionnaire (designed in house)

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

HIT Acceptability Questionnaire

Please rate how strongly you agree with the following statements regarding HIT exercise training.

1 – Strongly disagree
2 – Disagree
3 – Neither
4 - Agree
5 – Strongly agree

	Disagree				Agree
The HIT study was adequately explained	1	2	3	4	5
HIT has been an enjoyable experience	1	2	3	4	5
HIT has been a significant time burden	1	2	3	4	5
I would recommend HIT to friends	1	2	3	4	5
HIT has been physically more demanding than I expected	1	2	3	4	5
I would perform the same HIT regime again	1	2	3	4	5
This study has interfered with other aspects of my life due to					
a) the time commitment	1	2	3	4	5
b) the travelling involved	1	2	3	4	5
c) the physical strain	1	2	3	4	5
I believe HIT has improved my fitness	1	2	3	4	5
I have am pleased to have done something to improve my fitness	1	2	3	4	5
I would have preferred to exercise in a group setting	1	2	3	4	5
I would have preferred to exercise at home	1	2	3	4	5

What has been the most challenging part of the HIT training?

What has been the best part of the HIT training?

8.5 Experimental data

8.5.1 CPET data from HIT study

	Before HIT	After HIT	
VCO_2 (l/min)	1.92 ±0.58	2.10 ±0.64	**p<0.05**
VO_2 (l/min)	1.78 ±0.50	1.93 ±0.54	**p<0.01**
VO_2/kg (ml/kg/min)	23.90 ±4.68	26.2 ±5.44	**p<0.01**
VO_2 AT (ml/kg/min)	17.86 ±4.45	20.21 ±4.11	**p<0.01**
VO_2 AT/VO_2 (%)	85.8 ±10.38	91.14 ±12.74	p>0.05
RCP/ VO_2 (%)	78.86 ±13.38	84.00 ±13.55	p>0.05
RER	1.08 ±0.071	1.08 ±0.06	p>0.05
O_2pulse(100ml/beat/kg)	17.06 ±3.65	18.52 ±3.65	**p<0.0001**
VE (l/min)	55.24 ±17.58	63.76 ±19.27	**p<0.01**
Vt (l)	2.07 ±0.69	2.11 ±0.72	P>0.05
Bf (/min)	27.38 ±4.63	31.24 ±6.06	**p<0.001**
BR (l/min)	50.43 ±17.85	41.86 ±15.41	**p<0.01**
VE/VO_2	29.59 ±4.17	31.20 ±3.85	p<0.05
VE/VCO_2	27.45 ±3.15	28.89 ±3.17	**p<0.01**
$PETO_2$ (mmHg)	113.1 ±5.20	117.6 ±4.34	**p<0.0001**
$PETCO_2$ (mmHg)	37.95 ±4.49	35.90 ±4.06	**p<0.01**

8.5.2 CPET data from HITCa study

	Before HIT	After HIT	
VCO_2 (l/min)	2.12 ±0.63	2.15 ±0.66	p>0.05
VO_2 (l/min)	2.05 ±0.59	2.05 ±0.60	p>0.05
VO_2/kg (ml/kg/min)	23.8 ±7.2	24.3 ±8.0	p>0.05
VO_2 AT (ml/kg/min)	13.99 ±3.4	14.47 ±4.5	p>0.05
VO_2 AT (l/min)	1.2 ±0.29	1.2 ±0.31	p>0.05
VO_2 AT/VO_2 (%)	91.3 ±11	78.1 ±15	**p<0.01**
RCP/ VO_2 (%)	83.2 ±9.7	83.6 ±6.6	p>0.05
RER	1.04 ±0.07	1.05 ±0.13	p>0.05
O_2pulse(100ml/beat/kg)	17.68 ±4.64	17.95 ±4.5	p>0.05
VE (l/min)	63.7 ±16.9	66.9 ±20	p>0.05
Vt (l)	2.2 ±0.65	2.2 ±0.79	p>0.05
Bf (/min)	30 ±7	32 ±8	**p<0.05**
BR (l/min)	57.5 ±22	53.0 ±24.6	p>0.05
VE/VO_2	29.9 ±3.8	31.1 ±4.5	**p<0.05**
VE/VCO_2	28.8 ±3.2	30.0 ±5.9	p>0.05
$PETO_2$ (mmHg)	112.9 ±4.4	113.9 ±5.2	p>0.05
$PETCO_2$ (mmHg)	36.3 ±3.6	36.2 ±5	p>0.05

8.5.3 DEXA data from HIT study

	Before HIT	**After HIT**	
A/G Ratio	1.07 ±0.22	1.03 ±0.23	p>0.05
Total body tissue (kg)	68.49 ±10.5	68.19 ±10.4	p>0.05
Total body fat mass (g)	23336 ±7026	22904 ±6693	p>0.05
% fat mass to total mass	34.4 ±10	34.0 ±9.8	p>0.05
Total body lean mass (g)	45154 ±11142	45282 ±11068	p>0.05
% lean mass to total mass	65.6 ±10	66.0 ±9.8	p>0.05
Abdominal fat mass (g)	2783 ±938	2690 ±913	**p<0.05**
Leg lean mass (g)	4133 ±1271	4220 ±1236	**p<0.05**
Bone mineral density (g/cm^2)	1.18 ±0.11	1.19 ±0.12	p>0.05

8.5.4 DEXA data from HITCa study

	Before HIT	**After HIT**	
A/G Ratio	1.32	1.31	p>0.05
Total body tissue (kg)	83.5 IQR 12.8	83.8 IQR 11.75	p>0.05
Total body fat mass (g)	31595 IQR 10557	31643 IQR 9251	p>0.05
% fat mass to total mass	37.6 ±7.7	37.0 ±7.5	p>0.05
Total body lean mass (g)	51762 ±9239	52469 ±9488	p>0.05
% lean mass to total mass	61.4 ±8.2	60.9 ±9.8	p>0.05
Abdominal fat mass (g)	11531 ±1644	11662 ±1398	p>0.05
Leg lean mass (g)	17333 ±3407	17467 ±3705	p>0.05
Bone mineral density (g/cm^2)	1.26 ±0.18	1.24 ±0.16	**p<0.05**