Determining the need for, effectiveness and feasibility of bed-side measures to determine physical fitness in the older surgical patient.

By

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Thesis submitted for the degree of

PhD

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Acknowledgments.

I would like to take this opportunity to thank my supervisors, John Williams, Beth Phillips and Jon Lund for all of their support and patience throughout my time in research and their encouragement as I have written this thesis.

Amanda Gates has been of tremendous support and help, both practically in her role as research technician but also personally, I will always be indebted to her for this.

I would like to thank my husband, Mark Whitford, for his unswerving patience, support and for keeping me sane throughout. Also, thanks to my dogs for keeping my feet warm whilst I have written this thesis.

Finally, but not least of all, I would like to thank the many volunteers and patients who have taken part in my research, without their commitment this would not have been possible, they also brought a lot of joy to the studies.

Declaration of contributorship

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

Laura Carrick

Statistical support was provided formerly within the studies included in this thesis by Dr Brett Doleman, who in particular guided me through the required statistical requirements and analysis for my systematic review in Chapter 2 and the statistical modelling presented in Chapters 3.

Thesis Abstract.

Purpose.

The success of the NHS has resulted in a population which is aging(1), with those over 75 years of age undergoing surgery increasing(2). Frailty, a geriatric syndrome(3), is an independent risk factor for morbidity, mortality and increased LoS in hospital(4)(5). With physical function(6)(7)(8)(9)(10) and sarcopenia linked with frailty and adverse outcomes(7)(8), by addressing these modifiable factors through exercise interventions, there is the potential to improve older patient outcomes and QoL.

Methods.

A systematic review of the evidence for exercise-based therapies in the post-operative period was conducted. Bed-side tests of physical fitness were compared to CPET, and their ability to measure change following a 4-week exercise progamme assessed, in two healthy older volunteer studies. A RCT determining the feasibility and impact on physical function of a 6-month home-based exercise programme following major non-cardiac surgery in older patients was undertaken. Surveys of older patients and the health care providers were used to assess patient need.

Results.

The systematic review established that post-operative exercise programmes can lead to improvement in physical function in the older population. However, this was limited by the significant clinical heterogeneity in the small number of studios included. The results support the use of HGS as a bed-side test in the assessment of physical fitness, with predictive models derived. However, none of the bed-side tests or derived models were able to measure the elicited change in CRF following 4 weeks of exercise training. The RCT showed that it was not feasible to implement a home-based exercise training programme post-operatively in the older surgical population. The surveys,

limited by poor response rates, showed a disparity in the recovery experiences of cognition and fatigue between patients and health care professionals, with an “expectation mismatch” highlighted by the GPs.

Conclusions.

As a body of work this has demonstrated the need for, and potential value of addressing physical function through the use of exercise interventions in the post-operative period for the older patient. With alternative tests of physical fitness, such as HGS, useful clinical tools. However, due to limitations experienced, further work is required in this field. This thesis has highlighted the need for greater collaboration between health care disciplines in order to understand patients’ needs along-side clinical outcomes, to improve patient and health care engagement in research ensuring future work leads to meaningful and better outcomes.

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List of Abbreviations II

AA	Amino Acid
AET	Aerobic exercise training
ALS	Advanced Life Support
AT	Anaerobic threshold
ATP	Adenosine Tri-Phospate
BCT	Bag and Carry Test
BGS	British Geriatrics Society
BMI	Body mass index
BNI	British Nursing Index
BP	Blood pressure
bpm	Beats per minute
BTT	Bruce Treadmill Test
CAD	Coronary artery disease
CES-D scale	Centre for Epidemiological Studies Depression scale
CHS	Cardiovascular Health Study
CI	Confidence interval
CINHAL	Cumulative Index to nursing and allied health literature.
CGA	Comprehensive geriatric assessment
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CRF	Cardiorespiratory fitness
CRP	C-reactive protein
CSHA	Canadian Study of Health and Aging
DASI	Duke activity status index
DHA	Docosahexaenoic acid
ECG	Electrocardiogram

EAA	Essential amino acid
EET	Endurance exercise training
EFS	Edmonton Frail Scale
EMBASE	Excerpta Medica dataBASE
EQ-5D-5L	EuroQoL standardised assessment of generic health status
EPA	Eicisapentaenoic acid
ERAS	Enhanced recovery after surgery
EWGSOP	European Working Party on Sarcopenia in Older People
$_{F}$L	Fasicle length
FBC	Full blood count
FITT-VP	Frequency, Intensity, Time and Type with Volume and Progression: principles of exercise programmes.
g/L	Gram per litre
GDPR	General Data Protection Regulation law
GDS	Geriatric depression scale.
GFI	The Groningen Frailty Indicator
GP	General Practioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
Hb	Haemoglobin
HIFE programme	High-Intensity Functional Exercise Programme.
HR	Heart rate
HR-QoL	Health related quality of life
HGS	Hand grip strength
HIIT	High intensity interval training
ID	Identification
IGF-1	Insulin-like growth factor

IL-6	Interleukin-6
IHD	Ischaemic heart disease
IPAQ	International physical activity questionnaire
Kcal	Kilocalories
kg	Kilogram
Kg/m^2	Kilogram per meter squared
L/kg	Litres per kilogram
LoS	Length of stay
MD	Difference in means
MDT	Multidisciplinary team
MEDLINE	The online counterpart to the MEDical Literature Analysis and Retrieval System (MEDLARS)
MET	Metabolic equivalent to task
MI	Myocardial infarction
MID	Minimal important difference
ml/kg/min	Millitres per kilogram per minute
mmHg	Milimetres of mercury
m/s	Metres per second
MOCA	Montreal Cognitive Assessment
MPB	Muscle protein breakdown
MPS	Muscle protein synthesis
MRI	Magnetic Resonance Imaging
$_{M}T$	Muscle thickness
MUST	Malnutrition Universal Screening Tool
NHS	National Health Service
NICE	National Institute for Health and Care Excellence.
NSCA	National Strength and Conditioning Association
OA	Osteoarthritis

O_2	Oxygen
OT	Occupational Therapy
${}_pA$	Pennation angle
PAH	Pulmonary artery hypertension
PECR	Privacy and Electronic Communication Regulations
PEDro	Physiotherapy evidence database
POCD	Post-operative cognitive dysfunction.
PIS	Participant information sheet
PRISMA	Program of Research on Integration of Services for the Maintenance of Autonomy.
PROSPERO	International prospective register of systematic reviews.
PTH	Parathyroid hormone
QoL	Quality of life
RCoA	Royal College of Anaesthetists
RCS	Royal College of Surgeons
RCT	Randomised controlled trial
RDH	Royal Derby Hospital
REC	Research ethics committee
REFS	Reported Edmonton Frail Scale
RER	Respiratory exchange ratio
RET	Resistance exercise training
rpm	Repititions per minute
SF-36	Short form health survey
SPPB	Short physical performance battery
SSTWT	Single-Stage Submaximal Walking Test
TFI	The Tilburg-Frailty Indicator
TNF-alpha	Tumour necrosis factor-alpha
TRIP database	Turning Research into Practice
TSA	Trial sequential analysis

TUGT	Timed up and go test
UK	United Kingdom
UN	United Nations
US	United States
USS	Ultrasound scan
VCO_2	Carbon dioxide output
VE	Minute ventilation
VL	*Vastus Lateralis*
VO_2	Oxygen consumption
VO_2 max	Maximum oxygen consumption
VO_2 peak	Peak oxygen consumption
W/min	Watts per minute
WHO	World Health Organisation
1-RM	1 repetition maximum
6MWT	6-minute walk test
12MWT	12-minute walk test
%	Percentage

Although sometimes used interchangeably, for the purpose of this thesis physical fitness will be used to describe aspects related to cardiorespiratory fitness (CRF), while physical function will be used more holistically and will refer to the ability to perform activities of daily living, including exercise-based tasks, which may include the step-box test used in this thesis, HGS or, for example, the ability to rise from a chair.

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1 Chapter One:

Setting the scene.

1.1 Introduction

Since the establishment of the National Health Service (NHS) in 1948, life expectancy has increased from 66 to 78 years of age for men and from 70 to 82 years of age for women(14). The National Office for Statistics projected in 2010 that the United Kingdom (UK) population would increase from an estimated 62.3 million in 2010 to 67.2 million in 2020, with the median age expected to rise from 39.7 years to 39.9 years in 2020(1). This increase in the ageing population is apparent across the world, with global reports in 2017, anticipating the expected number of older people to double to 2.1 billion by 2050(15). Within this aging population, in the UK the numbers of those over 85 years of age, are increasing at the fastest rate (reflected in Figure 1), with the number of centenarians expected to increase from 13,000 in 2010 to 110,000 in 2035(1).

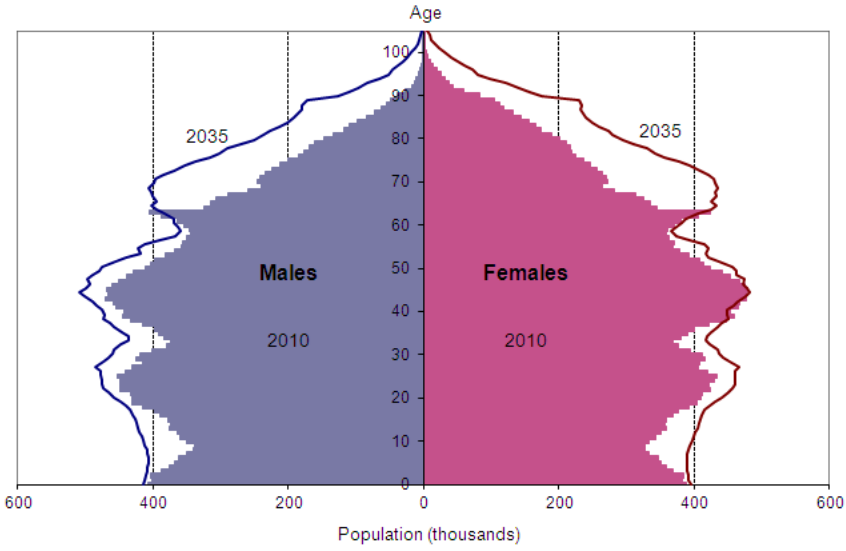


Figure 1.1: Estimated and projected age structure of the UK population, mid-2010 and mid-2035. Taken from the National Population Projections – Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/bulletins/nationalpopulationprojections/2011-10-26(1).

With a greater number of individuals living longer and more productive lives, this positively contributes to society through the experience and support they can offer. The success of the NHS has enabled individuals to live longer lives both with and without co-morbidities, and as

such clinical decision making should be more focused on the individuals biological age, which takes into account physiological age plus lifestyle factors, as compared to their chronological age(14)(16). However, the prolongation of life expectancy does represent challenges for the health service and for those providing care to an aging population in the perioperative period. As we age, we are more likely to suffer from common medical conditions such as Chronic obstructive pulmonary disease (COPD), diabetes, dementia and Ischaemic Heart Disease (IHD)(17), with in parallel geriatric syndromes which are common, multifactorial conditions associated with poor outcome, reflecting global reductions in physical and mental function, such as frailty, delirium, depression and incontinence(18). Of which, frailty is an independent risk factor for morbidity, mortality and length of stay (LoS)(4)(5).

The health care system therefore needs to adapt in order to meet the needs of this aging population. A shift is required to move away from the traditional approach of tailoring secondary care specialties' around single organ disease, to a more multi-disciplinary approach in-line with this populations tendancy to suffer from multiple conditions and geriatric syndromes as described above(19). Whereas there has been a tendancy to focus public health planning on the younger and working generations, greater focus is now needed on the public health of the older generation to meet their needs and address patient focused outcomes, such as the provision of good acute services, rehabilitation, high-quality residential care, person-centred co-ordinated care, and thereby address inequalities in life expectancy and premature mortality(19). However, this is not without cost. The revenue required to meet health care costs comes from a number of sources including income tax, property tax, tax related to goods and services plus social contributions, essentially taxation of the younger working members of the population(20). The ability of this revenue source to sufficiently meet the health care needs of the older demographic therefore depends upon the population age structure of the country(20), as such in line with the required changes to health care provision, and public health focus as described, changes in health care financing may be required to meet demand and ensure equitability(20).

This increase in the ageing population lead to the establishment of the Madrid International Plan of Action on Ageing (MIPAA) in 2002(21) which aims to improve the lives of the older

global population, with amongst a number of its core issues, “Health”; advocating that the older population “should have the same access to preventative and curative care and rehabilitation as other groups”(22). Within the UK NHS, a ban on age discrimination came into force in 2012(23), with recommendations on the delivery of surgical care in the older population outlined in the ‘Access all Ages’ document produced by the Royal College of Surgeons (RCS) in partnership with Age UK and Major Health Partners (MHP) Health Mandate in 2013(14).

Around 5.1 million surgical operations are performed each year in the NHS(2) with a greater proportion of these procedures being undertaken in the older population, with one in five of the population over the age of 75 years undergoing surgery as compared to 1 in ten of the population aged between 15 and 59 years(2). Of these 5.1 million cases, approximately 12.5% are high-risk(2) and although this group of patients represents a minority of those who present for surgical procedures, 80% of all post-operative deaths come from this group(24). As the age of the surgical population is increasing, the proportion falling into this high-risk group is therefore increasing in turn. In the past efforts have been focused on the surgical procedure as a way to reduce the risk these patients run in the time period around operation. However, the majority of complications which occur after surgery are medical, such as chest infections and heart attacks, and not associated with failings in surgical technique or the operation itself(25).

It is anticipated that the cost of surgical procedures in those aged over 75 years of age in England will be in excess of 3.2 billion Euros by 2030(2). Although there is evidence to suggest that the post-operative mortality rates are declining, this data could not determine whether this was due to improved patient centred care or due to a shift in the number of low-risk surgical procedures taking place(26)(2). With postoperative complications contributing significant financial cost(25) to an NHS system striving for more financial sustainability in a difficult economic climate.

In the Royal College of Anaesthetists (RCoA) document on Perioperative medicine: ‘The Pathway To Better Surgical Care’, it states “Perioperative medicine aims to deliver the best care possible for patients in the time before during and after surgery and to address the

patients' needs facilitating long-term post-operative recovery"(27). With the age of the surgical population increasing, a greater clinical focus on the patients' needs during recovery is required to improve their outcomes and ensure fair access to health care rehabilitation.

The United Nations Compendium of Recommendations on Population and Development (28) states within the actions outlined in Chapter 8: Health, Morbidity and Mortality "All countries should make access to basic health care and health promotion the central strategies for reducing mortality and morbidity" with one objective to "increase the healthy life-span and improve quality of life of all people…"(29). Morbidity describes "a state of being symptomatic or unhealthy for a disease or condition"(30) whilst mortality refers to the number of deaths as a result of a health event(30), specifically with regards to surgery mortality at 30 days post-surgery(31) is a frequent outcome measure. As such, these outcome measures are used to monitor health status and equity at local, national and international levels (32), and form part of the good surgical practice guidelines as outlined by the RCS(33). It is therefore commonplace when reviewing health services and the effect of health strategies and interventions that these are often evaluated by their impact on the patient outcomes of morbidity, mortality and quality of life (QoL), with length of stay (LoS) specific to secondary care practise(34). Throughout this thesis, these patient outcomes are referred to, however, they do not necessarily reflect what matters to the patient on a personal level, such as symptom management and functional ability, what can be loosely referred to as the patients needs. Consequently, more emphasis is being placed on these patient specific outcomes, with reference to patient needs in the RCoA statement on the aim of perioperative medicine as stated above (27).

This thesis has focused on the geriatric syndrome of frailty to determine if through rehabilitative exercise (described below) it can be addressed, potentially improving patient outcomes and addressing their needs.

1.2 Frailty

1.2.1 Frailty and the ageing process.

The Oxford dictionary defines ageing as "the process of growing old; the process of change in the properties of a material occurring over a period, either spontaneously or through deliberate action"(35). In turn, frailty reflects a process of change, negative changes or deficits(6), in the individuals physiological state. Therefore, rather than a separate consideration, frailty may be an integrated part of the continuum of the ageing process.

Frailty has developed from a relatively vague concept(36) to a recognised syndrome(3). Frailty has been defined as a lack of physiological reserve, which confers a vulnerability, such that older frail individuals are at risk of a sudden deterioration in their health due to a potentially minor event, with susceptibility to stressors such as acute illness and surgery(37). It is established as an independent risk factor for morbidity, mortality and increased LoS in hospital(4)(5) and can lead to a reduced quality of life (QoL) for the individual.

In the surgical setting, severity of an individual's frailty has been shown to correlate with post-operative complications(38), with frailty increasing the likelihood of post-operative complications, increased LoS, higher morbidity and mortality and the likelihood that the patient will be discharged to an institution rather than their home(4).

The CGA is a comprehensive multi-disciplinary clinical management tool and is considered the gold standard means of assessing the frail older patient by the BGS(39). It covers several domains: assessment of physical symptoms, mental health symptoms, level of functional daily activity, frailty, social support and environmental factors. Each domain is assessed individually, and the results brought together to form a global picture of the individual's health and well-being. CGA is associated with improved clinical outcomes, for instance the employment of CGA in acute geriatric units leads to a reduction in functional decline on discharge from hospital and an increased likelihood the patient will return to their home on discharge(40), even after emergency admission to hospital(41). As such, it is recommended for use clinically(42)(4), particularly in dedicated units for the older patient(40)(41). For

example, when used pre-operatively the CGA has been demonstrated to predict post-operative complications and increased hospital LoS following elective laparoscopic cholecystectomy in the older patient(5). However, it does require experienced individuals to undertake the assessment process and it is relatively time consuming in the often time consuming surgical setting(43).

Despite the growing recognition of frailty as a syndrome, there remains considerable misunderstanding in its definition and what it implies. This misunderstanding arises through lack of distinction clinically between frailty and multi-morbidity(44) and as a consequence, there is a negative connotation associated with the word frail. Given that the word is defined in the Oxford Dictionary as an adjective to describe "1. (especially for an old person) physically weak and thin, 2. weak; easily damaged and broken", it is therefore of little surprise that many older individuals would not wish to be described by this word(44).

1.2.2 The Models and assessment of frailty.

Frailty as a syndrome has been defined through its assessment using two main models: the Phenotype model(7) and the Cumulative Deficit model (also known as the Frailty Index)(6). Further, various scoring systems are currently in use to assess and chart the impact of frailty in the older population. The most commonly used scoring systems are:

- The Edmonton Frail Scale (EFS).
- PRISMA-7.

These models and scoring systems are discussed in detail below.

1.2.2.1 *The Phenotype Model:*

In 2001, Fried et al(7) proposed and validated the Phenotype model as a definition of Frailty based on the Cardiovascular Health Study (CHS)(45). CHS was a prospective observational study of 5201 individuals over 65 years of age (65 to 101 years of age) from across America aimed at identifying risk factors for cardiovascular disease and stroke(45). Fried had conducted this study in 1991(46) and although it had not been designed to study frailty, it provided an age appropriate data set from which the Phenotype model and its five criteria for defining frailty were derived. The five criteria for defining frailty are described below:

- weight loss: unintentional loss of 10 pounds or more in the last year or on follow-up, or weight loss of greater than 5% of their body weight in the previous year (actual body weight measurements required)(7).
- exhaustion: self-reported exhaustion has been demonstrated to be an indicator of VO_{2max} and predictive of cardiovascular disease. It is identified by questions from the Centre for Epidemiological Studies Depression scale (CES-D scale)(7).
- weak grip strength: grip strength in the lowest 20% at baseline (adjusted for gender and body mass index (BMI))(7).
- slow walking speed: determined by measuring the time to walk 15 feet, and following adjustment for gender and BMI establishing if they fall within the slowest 20% of the population(7).
- low physical activity: a weighted score of kilocalories (Kcals) expended per week. Males less than 383 Kcals/week, females less than 270 Kcals/week(7).

with a patient classed as frail if they meet 3 out of these 5 criteria.

The model supports the idea of frailty as a cyclical process, with intermediate (those at increased risk of frailty) and advanced irreversible stages. As a simple and easy to apply model, it has linked frailty as an independent risk factor for the outcome measures; disability, hospitalisation, incident falls, worsening mobility and death. However, probably as a consequence of using data generated for an alternative purpose, there are limitations in the model design and its derivation. For example, the five criteria on which the model is based upon are not particularly comprehensive, limiting the generalisability of the model. Subsequent evidence has demonstrated only three of the model variables; weight loss, slow gait speed and low physical activity to have independent associations with mortality, LoS and chronic disability(47), whilst cognitive impairment(48) a variable not included in the model, has been linked with these three model variables(49) (see section 1.2.3.).

1.2.2.2 *The Cumulative Deficit Model: Frailty Index and the Clinical Frailty Scale.*

The Frailty Index is a deficit accumulation model of frailty(50) which initially incorporated 92 potential clinical deficits but has since been reduced to 30, including: disease, physical deficits and deficits in the ability to undertake activities of daily living. Cognition, and mental health changes (including depression) were also included, ensuring a more comprehensive

evaluation of the individual assessed as compared to the Phenotype model(7) described above. The Index was derived from the results of the Canadian Study of Health and Aging (CSHA) which was a prospective 5-year cohort study aimed at assessing the epidemiology of cognitive impairment and other health issues in Canadians over 65 years of age(6). This comprehensive method of assessing deficit accumulation is likely to be more sensitive to the dynamic process of frailty, tracking the transition of individuals between frailty states, from non-frail to frail and potentially the reverse(51). However, the number of variables assessed makes the Frailty Index a cumbersome assessment in clinical practise, therefore the CSHA Frailty Scale (Rockwood Frailty Scale) was developed and validated against the Frailty Index(6). The Frailty Scale is a more subjective form of assessment and categorises the individual into one of seven descriptors (outlined below in Table 1.1) and is often presented as simple poster with pictorial images of how patients corresponding to each category may appear.

1.	Very Fit - robust, active, energetic, well-motivated and fit
2.¤	Well - without active disease, but less fit than in category 1
3.¤	Well - with treated comorbid disease
4.	Apparently vulnerable - although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms
5.	Mildly Frail - with limited dependence on others for instrumental activities of daily living
6.	Moderately frail - help is needed with instrumental and non-instrumental activities of daily living
7.	Severely frail - completely dependent on others for activities of daily living

Table 1.1: The seven descriptors associated with the Rockwood Frailty Scale(11).

The Frailty Index has been validated in a number of studies based in the primary care setting, secondary analysis of data from the Canadian Study of Health and Aging (CSHA-2)(52) and analysis of the Survey of Health, Aging and Retirement in Europe (SHARE)(53) both validated the Frailty Index, whilst de Vries et al.(54) demonstrated validity in their smaller community and residential care based study evaluating a frailty index for physical activity. With regards to secondary care, the Frailty Index has been shown to predict poor

outcomes in hospitalised patients(55). However, the predictive validity of the Frailty Index and Scale are equal, with the Frailty Scale demonstrated to show good criterion validity(6): as such due to its relative brevity, it is a more useful tool. Consequently, its use in acute medical units(56) and emergency departments(57) is proving useful and becoming more commonplace. However, the British Geriatrics Society (BGS) recommend the Frailty Scale is only used in conjunction with a formal comprehensive geriatric assessment(58).

As frailty assessment has grown in the clinical setting, review of the growing literature has revealed that the Phenotype assessment tool has often undergone modification(59) and such modifications have not been limited simply to the Phenotype model(60). With the impact on the validity of these measures such modifications pose, and the consequent effect on the reliability of the data generated, this has raised the call for a consensus agreement on a single, uniform frailty assessment method.

1.2.2.3 *The Edmonton Frailty Scale.*

The EFS is a tool which can be easily used in the clinical setting and is validated for use by non-geriatricians(4)(37)(61), based on the non-subjective nature of composite tests. As with the CGA, it is recognised by the BGS as a frailty tool(58). It provides a holistic approach(62), assessing the various domains reported to be relevant to frailty such as cognition, medication use, general health, social support, mood and nutrition(3). To assess functional performance, the timed up and go test (TUGT) is used. The TUGT involves measuring the time taken to stand up from a chair and walk a distance of 3 metres before turning and returning to sit in the chair(63). For individuals that are unable to complete the TUGT a modified version of the EFS has been developed. In this form, known as the Reported Edmonton Frail Scale(REFS)(64), TUGT is replaced with a report of the participant's physical function prior to their current illness.

Despite, as stated, the EFS providing a clinical non-subjective assessment tool, as compared to the subjective Frailty Scale described above. The Frailty Scale, due to its relative brevity, continues, as stated above, to be the tool most commonly used within acute medical units(56) and emergency departments(57).

1.2.2.4 *PRISMA-7.*

PRISMA stands for the Program of Research on Integration of Services for the Maintenance of Autonomy, with PRISMA-7(12) referring to the self-reported assessment of frailty based on 7 questions. This is a questionnaire formed of seven yes/no questions covering factors which identify frailty (Table 1.2), with frailty determined if the individual scores (answers yes) on three or more questions.

1.	Are you aged over 85 years?
2.¤	Do you have health problems that limit you to the home?
3.¤	Do you need extra support?
4.	Do you use mobility aids?
5.	Do you have social support?
6.	Are you male?
7.	Do you have any health problems that mean you need to limit your activities?

Table 1.2: The seven yes/no questions of PRISMA-7(12).

Although the self-reported assessment method has been demonstrated to be accurate for identifying frailty in the community(65), it has also been shown to over-screen for frailty, with limited specificity indicating a high false positive rate(66). As a tool it has been recommended by the BGS for self-assessment or as a means of assessing the likelihood of frailty in an individual too ill to undertake any form of assessment with a physical component to it(58).

1.2.2.5 *The Groningen Frailty Indicator (GFI).*

The GFI was developed to provide a global frailty assessment tool covering physical, social, psychological and cognitive domains, which at the time were felt to be lacking from other assessment tools(67). It is a self-assessment questionnaire comprised of 15 questions covering each of these domains, with a score of greater than 4 on a spectrum from 0 to 15 with 0 no frailty and 15 completely disabled, denoting frailty. It is validated for use both in the primary and secondary care settings(67)(68) There is evidence to suggest that the GFI could be used alongside the Frailty Index to enable a two-step identification process optimising the management of frail individuals in the primary care setting(69). However

despite this, to date, this tool has mainly been used in the Netherlands where it was developed(60).

1.2.2.6 *The Tilburg-Frailty Indicator (TFI).*

The TFI is also a self-reported questionnaire based tool developed in the Netherlands for use in the assessment of frailty in the community(70). Comprised of 15 questions covering a broad range of categories including health, psychological and social factors, it allows for a comprehensive assessment of the individual along with the physical aspect of the assessment focusing on mobility, weight loss, balance, vision, hearing, tiredness and grip strength. Good validity and reliability has been demonstrated(60)(71), along with good predictive ability for adverse outcomes(72), in particular predictive ability for disability, health care utilisation and falls in the older community based Dutch population(71).

Further work to validate these tools in communities out with the Dutch population may lead to greater widespread uptake of both the GFI and TFI tools.

1.2.3 Cognitive Impairment and Frailty.

Cognitive impairment describes the decline in intellectual functions such as reasoning, remembering, learning and planning(73). Many of the risks factor for cognitive impairment are shared with frailty; such as systemic disease(74), cardiovascular disease(74) affecting CRF, inflammatory processes and hormonal changes(73) (refer to section 1.2.3.). In section 1.2.2.1. it describes how cognitive impairment is linked with the Phenotype model variables; weight loss, slow gait speed and low physical activity, further demonstrating a common thread linking frailty and cognitive impairment together. Despite this, cognitive impairment is not specifically included in the Phenotype model for the assessment of frailty, however, it is included in the Frailty Index (section 1.2.2.2.) and EFS (section 1.2.2.4.) and is embedded within the CGA (section 1.2.2.3.). Acknowledging the inter-relationship between frailty and cognitive function, in turn acknowledges that interventions designed to ameliorate one, may also have a positive impact on the other(73).

1.2.4 The pathophysiology of frailty.

The definitive process leading to frailty is unclear, however multi-system involvement is evident, with endocrine, musculoskeletal and inflammatory processes all contributing. Consequently, a detailed explanation of the proposed pathophysiology of frailty is out-with the scope of this thesis. However, in relation to the three aforementioned body systems, chronic low-grade inflammation and oxidative stress are considered to be key in the development of frailty(75), with a number of inflammatory biomarkers linked to frailty (see section below). In relation to the endocrine system, hormonal changes are inextricably linked to ageing(76), with parathyroid hormone (PTH), insulin-like Growth Factor 1 (IGF1) and the gonadal hormones, in particular known to negatively impact the musculoskeletal system with advancing age(77). These consequent changes on the musculoskeletal system present in the form of sarcopenia(78) - a major modifiable condition closely associated with frailty in older adults(78)(79).

1.2.4.1 *Biomarkers of frailty.*

The lack of a clear understanding of the pathophysiology underpinning frailty, with the added complication that individuals may also suffer from other multi-morbidities alongside their frailty, make the identification of a clear biomarker(s) with adequate sensitivity and specificity challenging. For example, one review of the literature has shown a correlation between the inflammatory marker C-reactive protein (CRP) and frailty in the older population(75). However, CRP is an inflammatory marker which is already widely used as a clinical tool in the assessment of both acute and chronic inflammation and infection, and as such the specificity for CRP as a biomarker for frailty may be limited. Similarly, Interleukin-6 (IL-6) is another common inflammatory biomarker, which has also been shown to demonstrate a significant association with frailty(80). Beyond these two well-established inflammatory markers, a range of other biomarkers including; tumour necrosis factor-alpha (TNF-alpha), IGF-1, Vitamin D, albumin and the coagulation factor VIII have all be found at higher levels in frail patients(61)(81), and as such have all been postulated as potential candidate biomarkers of frailty. Improved mortality prediction has been demonstrated through the use of a combination of biomarkers (including a combination of those listed above), as compared to measuring single biomarkers(82), in some way combatting the lack of specificity and sensitivity which comes with many individual biomarkers.

As frailty is a dynamic process(51), there is evidence to suggest that biomarkers could be particularly useful in the early stages of frailty prior to any clinical deficit being overly apparent(82). As such, biomarkers are likely to form an integral part of the battery of frailty assessments, particularly if they can assist in the early detection of frailty enabling potential treatments and management strategies to be instigated early, leading to frailty modulation and improved outcomes.

1.2.5 Sarcopenia and Frailty.

Sarcopenia describes the loss of skeletal muscle mass and strength(83) in advancing age, which consequently has multi-system effects, including reduced mobility, and as such is strongly linked with frailty and adverse outcomes(7)(8). Sarcopenia is associated with numerous clinical situations and conditions, including chronic malnutrition and cancer(84). Muscle depletion, which includes a loss of muscle mass, is an independent prognostic factor for cancer survival in a number of patient groups (colorectal patients for example)(85), with sarcopenia associated with major post-operative complications and increased LoS(84).

As with frailty, the risk of developing sarcopenia has been linked with the endocrine system. For example, low gonadal hormone and IGF-1 levels have both been implicated in the development of sarcopenia(86). Low vitamin D levels, high levels of inflammatory markers, a pro-coagulative state and poor nutrition are all associated with sarcopenia and frailty(86)(80).

Through targeted management including exercise and nutrition support, sarcopenia is a potentially modifiable condition and as such provides a means by which patient outcomes can be improved. This notion underpins a large part of the theory behind pre-operative prehabilitation programmes(79).

Techniques for assessing sarcopenia include simple measures such as the mid-upper arm circumference, and the Malnutrition Universal Screening Tool (MUST) which is designed to assess those underweight and at risk of malnutrition. Specialist imaging techniques (i.e. magnetic resonance imaging (MRI) can also be used to assess muscle mass and muscle

quality, however, the feasibility of the use of some methods in the clinical environment is questioned(87).

1.2.5.1 *Imaging techniques for the assessment of muscle mass.*

Non-invasive imaging techniques such as ultrasound scans (USS) and MRI can be used to assess both muscle mass and muscle architecture(88), with evidence to support the pre-operative radiological assessment of sarcopenia as a prognostic tool(84). USS is particularly useful as although it involves equipment costs these are far lower than those associated with MRI scans and USS imaging equipment is more accessible and portable.

Skeletal muscle, which is the focus of sarcopenia, is a form of striated muscle consisting of muscle fibres which run either in series or in parallel. These fibres are composed of sarcomeres, (the smallest functional and basic contractile unit in skeletal muscle) which collectively form myofibrils, with a group of myofibrils forming a muscle fibre (Figure 1.2).

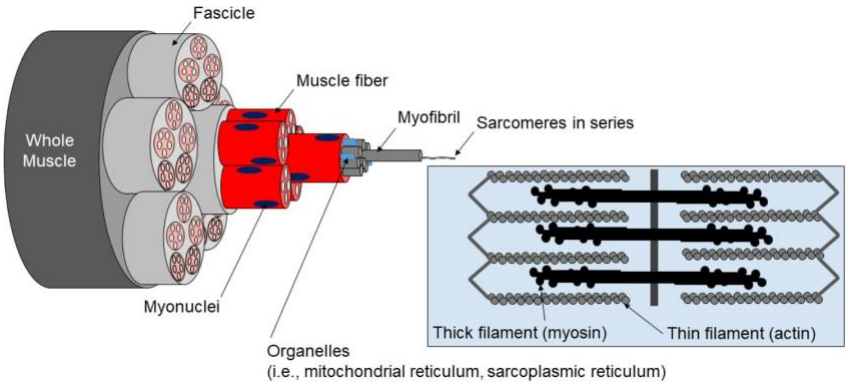


Figure 1.2: Hierarchical structure of skeletal muscle. Taken from Haun *et al.* https://www.frontiersin.org/articles/10.3389/fphys.2019.00247/full(89).

The muscle fibres either run in parallel to the direction of action (parallel fibres) or run obliquely to it (pennate fibres), attaching to the tendon at an angle (pennation angle). The shortening velocity of a muscle fibre is affected by the number of sarcomeres in series (the muscle fibre length) and by the pennation angle. Work assessing the soleus and gastrocnemius muscles of the cat has shown that significant differences exist in the peak isometric tension generated and the force velocity relationship between the two muscles, however, when muscle volume, pennation angle and fibre length are taken into account,

these differences are reduced, demonstrating the influence of muscle architecture on muscle function(90). Similarly, in human studies, resistance exercise training (RET) which results in muscle hypertrophy has been shown to be linked with an increase in pennation angle. As the number of muscle fibres attached to the tendon increases, as the tendon does not alter in length, the pennation angle must therefore increase to accommodate fibres(91).

Two-dimensional (2D) USS imaging of muscle fascicle length and pennation angle has been demonstrated to be reliable when the muscle is either relaxed or contracted(88) and formal sonographic training is not required(88). As such, measuring muscle fibre length and pennation angle provides a means of monitoring muscle mass (and therefore sarcopenia) and architecture and can contribute to the assessment of frailty(90)(92).

1.2.6 Physical function and frailty.

As discussed in section 1.1.1.3., the CGA is a comprehensive multi-disciplinary clinical management tool(39) covering the domains of physical symptoms, mental health symptoms, level of functional daily activity, frailty, social support and environmental factors which when brought together form a global picture of the individual's health and well-being. The CGA ensures that appropriate management plans can be implemented to address the findings across the various domains resulting in a multi-disciplinary integrated approach to the individuals care needs. Consequently, older patients who have undergone CGA have been found to be more likely to be alive and in their own home following emergency admission to hospital as compared to those who had undergone standard medical assessment(93). Further the impact of the role of the ortho-geriatrician, resulting in improved mortality in those older patients undergoing surgical hip repair(94), underscores the importance of an integrated multi-disciplinary approach to patient care in the perioperative period.

Part of the CGA process is to enable management strategies to be implemented that can enable deficits in the patient's physiological state to be addressed. Physical function and sarcopenia (described above as a loss of skeletal muscle mass and strength)(8)(10) are key components of frailty, included in all the various frailty assessments which are available(6)(7)(8)(9)(10). Therefore, there is the potential to address some aspects of frailty

through the implementation of exercise interventions, potentially enabling an individual to alter their frailty status due to its dynamic nature(51).

1.3 Assessment of Physical Function.

The CGA and other various frailty assessment tools attempt to assess physical function via various means. The sections below outline the main physical fitness assessment tools used in these assessments.

1.3.1 The Cardiopulmonary Exercise Test (CPET) and its outcome measures.

CPET measures the function of the cardiorespiratory system and is often described as the "gold-standard" measure of physical fitness(95)(96)(97)(98). It is a precise and comprehensive assessment(99)(100)(101) which can predict all-cause mortality(102), five-year survival after major surgery(103) and early mortality from cardiac failure(103). Given this predictive utility, the use of CPET pre-operatively as a tool to predict risk has increased over recent years, with more than 30,000 CPETs now conducted in the UK for clinical purposes each year(96).

The gold-standard measure of cardiorespiratory function (CRF) and one that can be determined by CPET is VO_{2max}; the maximal oxygen uptake during an incremental exercise protocol(104). VO_{2max} is an assessment of an individual's cardiopulmonary and muscular systems maximal capacity to take up, transport and effectively utilise oxygen. CPET involves exercising at increasing incremental work-loads, most commonly on a cycle ergometer or treadmill (Figure 1.3). Whilst exercising, non-invasive measurements of gas exchange are collected such that the VO_{2max} is recorded(98). The VO_{2max} is identifiable as a plateau in the VO_2 trace with increasing work-loads(99). The effort required to achieve VO_{2max} requires a level of physical ability which is often unattainable by untrained individuals and this is evident if no plateau in the VO_2 trace is reached. If the exercising individual reaches volitional exhaustion and cannot continue exercising any further, the VO_2 at this point is referred to as the VO_{2peak}(99). Although, VO_{2max} remains the gold-standard measurement, a low VO_{2peak} is associated with frailty(105) and is the parameter most commonly used in pre-operative risk stratification(106).

Figure 1.3: An individual about to undertake a CPET on a cycle ergometer.

An in depth discussion regarding the metabolic processes and principles underpinning CPET is beyond the remit of this thesis, further detail can be found in the article on the metabolic response to exercise(107) and in the textbook Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Application(108). In simple terms, during a CPET energy is generated via two metabolic pathways, aerobic and anaerobic metabolism. While aerobic metabolism occurs in the presence of oxygen, anaerobic metabolism (glycolysis) is the process by which the body generates energy independent of oxygen. During exercise, if the cardiopulmonary and oxygen transfer and delivery systems fail to meet the oxygen demands of the muscles, then energy production will switch from predominately aerobic metabolism to anaerobic metabolism. At this point lactate is formed as a product of anaerobic metabolism, and as the production of lactate outstrips its clearance a metabolic acidosis develops(109), which in turn is buffered by bicarbonate. This

buffering reduces the bicarbonate concentration and increases the carbon dioxide (CO_2) output(110). The change in metabolism pathway at this point is referred to throughout this thesis as the anaerobic threshold (AT)(98), although other terms are also used to refer to this such as the lactate threshold, ventilatory threshold and gas exchange threshold(95). The AT can be determined in a number of ways through CPET testing, each based upon changes in the pulmonary carbon dioxide production (VCO_2)(95)(98)(111) (Figure 1.4).

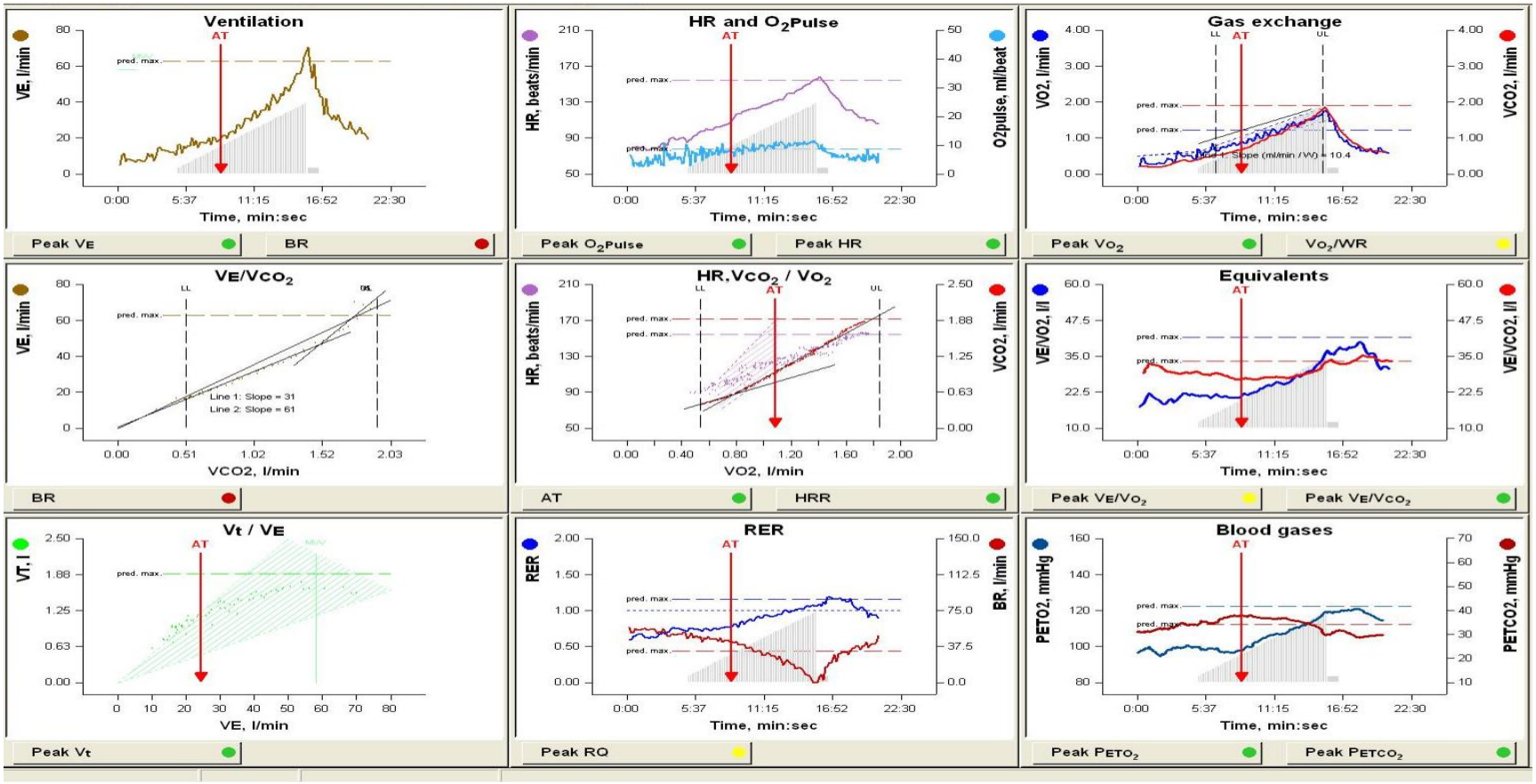


Figure 1.4. This figure is a screen shot of the CPET data as it is presented during the test and for analysis. It shows the variables measured, of those the (heart rate) HR VCO_2/VO_2, Equivalents, RER and VE/VCO_2 were the focus of our anaylsis. On a number of the graphs a red arrow labelled AT is present, this could be used to help facilitate analysis, in this figure it is not indicating the AT.

As with $VO_{2peak,}$ AT is a submaximal measure of CRF(109) and for certain surgical specialties including intra-abdominal, liver and pancreatic, it provides the best indicator of outcome(112). As AT is reached at work-loads which are approximately 47-64% of the VO_{2max}(99), this is a more achievable goal when conducting CPET with an untrained or physically limited (for example by obesity or osteoarthritis) individuals(113). In addition, AT is a less subjective measure of CRF than VO_{2peak} due to its physiological basis and lack of reliance on participant effort/exercise tolerance.

As with almost all clinical assessments there are time, equipment and personal costs to be considered with CPET(114)(115). However, where the economic impact compared to clinical outcome has been evaluated, both clinical and financial benefit was achieved through pre-operative risk stratification of patients due to the appropriate clinical management decisions which were guided by the CPET results(116).

1.3.2 Alternative measures of physical fitness.

Although CPET is the gold-standard assessment of physical fitness, as outlined above its use is limited for individuals with physical constraints and the associated equipment and personnel costs must be considered. Therefore, alternative measures to CPET using different submaximal exercise tests have been developed. These tests mainly rely on extrapolation of data or regression analysis to estimate VO_{2max} and are discussed below.

1.3.2.1 *Walking tests.*

The Bruce Treadmill Test (BTT)(117) was initially designed to assess coronary artery disease (CAD), with a modified version(118)(119) that utilises a gradual incremental increase in work-load making it more suitable for the older individual.

The Single-Stage Submaximal Walking Test (SSTWT)(120) combats the problem of fatigue, which may be a factor in the BTT, as the individual is required to walk at a constant speed and set gradient for a defined period of time. However, both of these tests have the same time, equipment and personal cost implications as the CPET.

Walking tests such as the 6MWT(121)(122), 12-minute walk test (12 MWT)(121), the Self-Paced Walking Test (SPWT)(123), the Rockport fitness test (a one-mile track walk test)(124) and the Modified Shuttle Walking test(125) are all based on the principle that VO_2 parameters will be correlated to either the distance covered in a specific period of time (6MWT, 12MWT) or the time taken to cover a set distance (Rockport fitness, SPWT). The 6MWT is widely used and has been validated as correlating with VO_{2peak} measured by CPET in healthy and non-healthy individuals(126).

Walking speed, also referred to as gait speed, is a recognised method for assessing frailty(66)(127)(62). The Gait Speed Test measures the time taken to walk 4 metres, where a speed of less than 0.8m/s is diagnostic for frailty with a high sensitivity and specificity(66) and is the cut-off speed in the European consensus definition of sarcopenia(78). These time, distance and gait speed walking-based exercises mainly utilise space such as corridors and do not require specialised equipment such as a treadmill or cycle-ergometer as such these tests are easy and practical to complete.

Slightly more complicated tests which are still primarily based on walking include the Bag and Carry Test (BCT) and the TUGT(63). The BCT involves carrying a weight which is gradually increased over a set distance and up and down steps. It is designed to provide a test of both endurance and muscle force(128). In the TUGT the individual is required to rise from a standard chair, walk 3 meters, return and sit down(63). The time taken to complete this series of actions is recorded with a time greater than 10 seconds shown to be diagnostic for frailty, with high specificity and sensitivity(66). This test is validated in the older population and is a recognised test for assessing frailty(62)(78). It forms a part of the EFS system(37) and is a simple test to perform requiring only a chair and a small amount of space.

1.3.2.2 *Step-Box testing:*

Various methods for assessing physical fitness via step-box testing have been published. Originally developed in 1961 as The Young Men's Christian Association (YMCA) test, the original step-box testing involved a 12-inch step that the individual stepped on and off at a predetermined rate for 3 minutes. The heart rate (HR) after one minute of recovery was

then used to predict VO_{2max}(129). Since that time, the various step-box methods published generally fall into one of two categories: single-stage or multi-stage step tests. While the single-stage tests involve a fixed stepping rate, the multi-stage step test methods utilise various rates of stepping often using a metronome to set the pace. For example, 17, 26 and 34 steps per minute are thought to be approximations of different stages of the BTT protocol(130). Across the literature the height of the step-box reported is not consistent(131), and as such it is difficult to interpret data across different studies. This led Culpepper & Francis to develop an equation to ensure the height of the step was based on the ideal hip angle for those undertaking the test(132), a set-up that has been adopted by a few research groups since(133)(134)(135)(136). However, preliminary work revealed that the height of the step based on the Culpepper & Francis equation resulted in a step height which many older individuals found challenging and unnerving, particularly at the determined stepping rates, fearing a loss of balance and requiring additional supports. As such, Petrella et al.,(137) devised a step-box test specifically to predict aerobic fitness in the older individual. The step height was 60cm for all and the stepping rates were "slow", "normal walking pace" and "fast" as determined by the individual. Predictive models using this test, based on step time, HR, age, body mass index (BMI) and oxygen pulse, correlated well with measured VO_{2max} for both men and women, although no significant difference was found between the normal paced and fast paced stepping rates(137). This test method was also demonstrated to show no significant test-retest differences over 2 to 4 weeks and was found to be sensitive to change when utilised following an exercise intervention(137). An example of the step-box used throughout this thesis is shown in figure 1.5.

Figure 1.5: This figure shows an example of the Reebox step-box (Reebok step, group fitness equipment) as used in the studies of this thesis, and its 3 height settings.

1.3.2.3 *Hang Grip strength (HGS) testing.*

HGS is known to decline with advancing age(138) and the European Working Party on Sarcopenia in Older People (EWGSOP) recommend the use of the HGS test as a measure of frailty in the older individual(66). As well as being known to decline with age(138), HGS is also predictive of prolonged LoS(139), all-cause mortality(138), cardiovascular and non-cardiovascular mortality(140), cognitive decline and impaired health related quality of life (HR-QoL)(139). Given these predictive strengths and that HGS can be simply measured using a hand-grip dynamometer (Figure 1.6), HGS is therefore a good, low-cost assessment method.

Figure 1.6: Example of a hand dynamometer used for assessment of HGS.

1.3.3 Strategies for the improvement of muscle function.

As explained above, sarcopenia arises not simply through a lack of muscle use, but also as a consequence of inflammatory, hormonal and nutritional factors. Therefore, to address sarcopenia a multi-system approach is ideally required, tackling its progression through exercise, improved nutrition and the treatment of conditions leading to inflammatory and hormonal change. Although the main focus of this thesis is the use of exercise to address age-associated reductions in physical function, a short synopsis of nutritional and hormonal tools that may also be used is provided in the sections below.

1.3.3.1 *Nutrition.*

For the maintenance and growth (when combined with exercise) of muscle mass, there is one key nutritional strategy that is established and widely accepted, that being the provision of adequate dietary protein(141)(142)(143). More specifically, it is the provision of adequate amino acid (AA) that is key for muscle mass maintenance(142)(143)(144), with essential AA (EAA) shown to have the most potent anabolic (stimulating muscle protein synthesis and

attenuating muscle protein breakdown(143) via insulin(145)) properties(146). Indeed, the single EAA leucine, is now established as the nutritional regulator of muscle mass maintenance(147)(148). It must however be acknowledged that nutrition alone cannot stimulate muscle hypertrophy, nutrition combined with contractile activity (exercise) is required to passage the dynamic equilibrium between muscle protein synthesis (MPS) and muscle protein breakdown (MPB) into positive net balance(143).

Another aspect of macronutrient (protein, fats and carbohydrate) intake, which is associated with physical function, through muscle contractile properties rather than muscle mass regulation, is that of glycogen availability(149). Glycogen is a substrate used for the production of adenosine triphosphate (ATP) which provides energy for multiple molecular processes, including muscle contraction(150). As glycogen is a glucose polysaccharide its availability is regulated by dietary carbohydrate intake(151). Therefore, poor dietary intake can lead to reduced glycogen stores which in turn significantly negatively impacts on muscle performance(152). Further there is continued debate as to whether co-administration of glycogen (or carbohydrate) alongside supplementary protein in the diet can improve MPS (and reduce MPB(153)) and facilitate greater muscle hypertrophy when nutritional strategies are combined with RET(154).

As a result of the evidence for these macronutrient-based strategies improving aspects of muscle health, there are numerous glycogen- and protein-based nutritional supplements available on the market targeted at individuals aiming to improve their muscle function and exercise capacity. Indeed, sports/exercise nutrition is a rapidly growing market which had a global market value of 50.84 billion US Dollars in 2018(155). Although the key focus of this market is to improve sports performance through nutrition, background research in this field has led to findings showing that some of these ‘sports supplements’ may also have potential in clinical situations (i.e., those of muscle wasting). For example, the Omega-3 fatty acids, Eicisapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) which are found naturally in fish oil, are marketed as improving many aspects of sports performance (including oxygen utilisation and recovery) have also been shown to improve muscle mass and function in conditions of wasting(156). However, to date, there is no standardisation in the dosing or timing of the supplement required to elicit clinical benefit.

1.3.3.2 *Hormones.*

As an anabolic hormone, insulin stimulates glucose storage in skeletal muscle following meals, and is also linked to the inhibition of MPB and therefore increased muscle mass(157). Other anabolic hormones have also been linked to muscle mass and function, including; Growth Hormone, IGF-1, Testosterone and Thyroxine(157). Indeed, a recent study in older men showed that testosterone supplementation during 8-weeks RET increased skeletal muscle mass and performance, beyond that seen in a placebo control group(158). The literature supporting the role of these hormones in muscle-related parameters has led to individuals attempting to maximise their physical fitness for sport and exercise gains by abusing hormone supplementation(159)(160). However, these hormones have wide ranging physiological effects with consequences well-beyond their impact on muscle function(161) and as such beyond clinical prescription should not be advocated.

1.3.3.3 *Exercise.*

Despite some suggestions of blunted physiological adaptation in older age(162) exercise training has been demonstrated to improve CRF, physical function, sarcopenia, physical activity participation and cognition in the older, frail population(163)(164)(165). Therefore, following the discussion on frailty in the sections above (1.1.1.1. and 1.1.1.2.), one means by which to modulate frailty could be through the use of exercise interventions(166)(167)(168). There are a number of considerations as to what form of exercise intervention is best. The type of exercise is clearly important, with for example, high intensity exercise improving strength more compared to low intensity exercises(169) and resistance and multicomponent exercise programmes improving physical function(165)(170). However, the choice of exercise programme must also take into account the specific characteristics of the end user, for example health concerns such as the physical limitations secondary to OA, and co-morbidities such as IHD, therefore, the programme must be designed around what is realistically achievable to expect of the target population.

1.3.3.3.1 Principles of exercise training programmes.

The framework for exercise programmes can be built around the FITT -VP principles of exercise training (The initial four FITT principles of Frequency, Intensity Time and Type, with Volume (the total amount of exercise) and Progression)(171)(172)(173). Broadly, the type of exercise is either aerobic or resistance in nature. Aerobic exercise (also referred to as endurance exercise) describes activity, which is characterised by high repetition and low output, for example swimming, cycling and running(174). Whilst resistance exercise is the converse, characterised by low resistance and high output(174). Whilst, aerobic exercise is linked with CRF, RET is accepted as the most effective strategy by which to improve muscle mass and function(175). Combining both forms of exercise to form multi-component training programmes, is beneficial, although the strength gains made during these programmes are not greater than those achieved with RET alone(176). However, such multi-component training programmes are a means by which to target the numerous aspects of physical function in the frail older adult (CRF, muscle strength and power, balance)(163).

Regarding exercise intensity, this has a dose response relationship with CRF(177). With the intensity level required to increase VO_{2max} dependent upon the baseline physical activity of the individual i.e. the deconditioned individual compared to the highly trained athlete. Intensity can be determined by its percentage of that required to achieve VO_{2max}, such that light exercise reflects 30-40% of VO_{2max}, moderate, 40-60% of VO_{2max} and vigorous 60 to 90% of VO_{2max}(177). Other methods of defining intensity can be used, such as equating the intensity to a percentage of the maximum HR, absolute oxygen uptake, metabolic equivalents (METs) and caloric expenditure(177). However, the benefit of basing intensity on $\%VO_{2max}$ is that it takes into account the individual's physiological characteristics such as baseline activity and age(177).

Programmes incorporating exercise sessions three times per week, with each session lasting 30-45 minutes and running for longer than 5 months have demonstrated the greatest gains(172)(173)(177). However, the data looking at the duration of the programme is biased by a healthier population, as in frail, older individuals longer duration studies suffer from a higher dropout rate due to morbidity and mortality as compared to studies utilising shorter duration training programs(165).

Progression is a key component of the FITT -VP principles of exercise training, for it to occur, there is required engagement and adherence to the other principles. Aside from the impact of morbidity and mortality in the older population on exercise intervention adherence as explained above, adherence and engagement with exercise is subject to behavioural beliefs, perceived benefits both emotionally and physically alongside both positive and negative attitudes to exercise(178)(179)(180)(181). In addition, socioeconomic factors, education, logistical factors such as access to facilities, time, and social support enabling exercise, play important roles(182)(180)(181). For example, the opposing beliefs, acknowledging the positive impact of exercise on health, and the negative perception of a lack of time to undertake the exercise, have been proven to be significant predictors of exercise behaviour amongst older women(183). Although, in general, adherence to exercise programs has been demonstrated to be good in the older frail population(165), within this population the benefit achieved is affected by age and gender, with the older frail female gaining the greatest benefit from exercise(165). This is attributed to a lower baseline functional ability(184) enabling greater scope to improve further, compared to the younger frail male(165).

Pulling the FITT-VP principles together, when considering aerobic exercise training (AET) to improve CRF, the evidence suggests that training programmes which incorporate the FITT principles; sufficient exercise intensity (greater than or equal to 60% of pre-training VO_{2max}), appropriate frequency (a minimum of 3 days per week) and duration (a minimum of 16 weeks) should significantly increase the VO_{2max} of the older individual(163). As such these principles are seen to form the framework of exercise recommendations detailed as part of national guidelines on health. The NHS guidelines on physical activity for older adults(185) state that adults aged over 65 years should undertake daily activity with the aim to do at least 150 minutes of moderate intensity activity or 75 minutes of vigorous activity each week. It provides examples of moderate and vigorous exercise and advocates a multi-component programme of aerobic activities such as brisk walking, cycling with resistance exercises to improve strength, balance and flexibility. This guideline formed the basis of the exercise training intervention used in Chapter 3. Whilst, the exercise intervention used in Chapter 5 to explore the feasibility and effectiveness of delivering an 8-week home-based exercise programme following major abdominal surgery, was based upon the High-Intensity

Functional Exercise Programme (the HIFE programme) used in the Swedish Frail Older People Activity and Nutrition Study (FOPANU) in Umea(186) and the Help the Aged (now Age UK) Exercise Programme for Preventing Falls(13), both adhering to FITT-VP principles.

1.4 Thesis Aims.

Section 1.1. describes the increasing aging population, how this demographic brings with it broad comprehensive health care needs, challenging the NHS, driving a review of public health strategies, to eliminate age discrimination and ensure fair access to health care provision, including acute services such as surgery and rehabilitation, with the focus of this care centred around the patient and their needs.

With Frailty (see section 1.2.) identified as a syndrome which is an independent risk factor for morbidity, mortality and increased LoS, correlating with post-operative complications, leading to a reduced QoL, impacting a patient's likelihood of successful discharge to their own home. Targeting this through public health rehabilitative measures such as exercise interventions following surgery to establish if this could improve patient outcomes, was the impetus for the work outlined in this thesis. Consequently, Chapter 2 of this thesis presents a systematic review of the evidence underpinning the use of exercise-based therapies in the post-operative period.

If exercise is to be used as a peri-operative intervention, its impact on physical function must be measurable. As can be seen from the sections above, the assessment of physical fitness, particularly in the older adult is neither simple nor uniform. Given the challenges (personnel, equipment, physical capability) associated with the gold-standard (CPET) assessment of fitness, Chapter 3 of this thesis explores the utility of more feasible bed-side assessments of physical fitness in the older adult both at a single timepoint and as a tool to track change (i.e. intervention effectiveness).

As stated, a more holistic approach, placing the patient at the centre of their care, is paramount. Therefore, in addition to understanding the best exercise interventions to elicit physiological adaptations in a specific clinical population, the view of these patients and the

associated clinical team must be better understood. This is the aim of the work presented in Chapter 4 of this thesis.

Pulling together the various chapters of this thesis, Chapter 5 aims to determine the acceptability, feasibility and effectiveness of delivering an 8-week home-based exercise programme following major abdominal surgery in the older patient population, through a clinical intervention trial.

2 Chapter Two:

Physical exercise programs following major non-cardiac surgery in the older patient: systematic review, meta-analysis and trial sequential analysis.

2.1 Introduction.

In 2018, the Office of National Statistics(187) recorded a 23% percentage increase over the previous 10 years in the population aged 65 to 84 years, and a similar increase in those over 85 years(188). With this population trend, as described in section 1.1, there is an impact on health service provision, part of which is an anticipated increase in the number of older patients accessing surgical services(189). This change in the surgical population, brings new challenges to perioperative medicine which aims to improve the patients care pathway through surgery to facilitate recovery(27). It is recognised that older surgical patients are associated with higher risks of morbidity and mortality for both elective and emergency surgery(190). This population is associated with an increased prevalence of age-related co-morbidities and increased risk of cancer(191), further those over 65 years of age suffer significantly worse post-operative outcomes(192) which detrimentally impact the ability of these patients to return to their baseline function(193) with consequent implications for their long term health and QoL.

Recently the concept of frailty has gained favour as a term for describing age-related declines in physical and mental function. Frailty, discussed in detail in section 1.2., is defined as a lack of physiological reserve, with increased susceptibility to stressors such as acute illness and surgery(3). It has also been linked with an increased risk of post-operative complications(4), with such complications shown to corelate with the severity of the individuals frailty(194). Further, Frailty is an independent predictor for increased LoS, and higher morbidity and mortality(4)(5). It is therefore not surprising that frailty is also linked with a greater likelihood that the patient will be discharged from hospital to an institution rather than their own home(4).

As stated above and discussed in section 1.1, perioperative medicine aims to address the patients' needs in order to facilitate long-term post-operative recovery, these needs encompassing the delivery of best clinical care and ensuring fair access to health care services to enable rehabilitation, improving morbidity and mortality outcomes. Specifically, the older surgical patient presents distinct challenges for perioperative management as a consequence of age-related changes such as the geriatric syndromes and increased

prevalence of certain common medical conditions such as COPD, IHD, dementia and diabetes(17) as described in section 1.1, along with Frailty which is discussed in section 1.2. One means by which the patients' needs may be addressed is through the use of exercise, which has been demonstrated to improve CRF, physical function, sarcopenia, physical activity participation, depression and cognition in the older frail population(166)(167)(168)(195) thereby potentially conferring a positive effect on morbidity, mortality(196) and QoL outcomes(195). With the possibility of introducing exercise interventions pre-operatively (prehabilitation), or post-surgery (rehabilitation), there is an increasing body of work assessing exercise programmes in the perioperative period. Prehabilitation has grown as one part of a multi-modal approach, to improve patient surgical outcomes and QoL across various surgical specialities, including cancer surgery, and older surgical patients(197)(198)(199)(200)(201). However, although rehabilitation programmes are a common feature of clinical pathways, and of research attention, it is limited in the main to cardiac surgery(202). Cardiac surgery is a highly specialised surgical discipline, the nature of the surgery itself is complex with unique physiological consequences to the patient which are in addition to those of the cardiac disease leading to surgery. Patients therefore undergoing cardiac surgery are not representative of the general surgical patient population and therefore are not included in this systematic review. However, the evidence available from rehabilitation following cardiac surgery may shed light on the outcomes and challenges of rehabilitation following non-cardiac surgery. For instance, early mobilisation following cardiac surgery has been shown to improve functional capacity, reduce post-operative complications and hospital LoS(203). With exercise rehabilitation shown to reduce mortality and reinfarction following myocardial infarction (MI)(204) and improve QoL measures, particularly in the physical domain reflecting physical fitness, for patients with coronary artery disease(205). However, participation and adherence to cardiac rehabilitation programmes is affected by gender, co-morbidities and socio-economic factors such as low income, and education(206). No significant improvement in outcomes was found for supervised centre-based exercise rehabilitation programmes as compared to home based programmes for low risk cardiac patients(207) and in assessment of QoL(205). However, when reviewing the evidence available, generalising the findings is limited by the clinical heterogeneity in the intervention

strategies(203)(207), a limitation also evident in the systematic reviews of prehabilitation evidence noted above(201).

A preliminary scoping review of the evidence base for exercise interventions in the post-operative period in the older surgical population highlighted minimal available literature, with an apparent lack of consensus in exercise intervention design and use of assessment tools for physical function and QoL measures. As described above, there is a clear rationale for the use of post-operative exercise intervention as a means to improve morbidity, mortality and QoL outcomes in the older surgical population, with the evidence available from rehabilitation following cardiac surgery, as described above, going some way to support this. To establish if the evidence found in the preliminary scoping review could provide a quantitative answer with regards to whether post-operative exercise interventions in the older surgical population positively impact on patient outcomes, or whether further evidence is required to ascertain this, a systematic review of the available evidence was undertaken.

2.1.1 Aim of this systematic review:

This systematic review aimed to evaluate the evidence base for post-operative exercise interventions to improve physical function and QoL in the older non-cardiac surgical population.

2.2 Methods

2.2.1 Search strategy.

This review followed the Program of Research on Integration of Services for the Maintenance of Autonomy (PRISMA) checklist(208) and was registered on the International prospective register of systematic reviews (PROSPERO) database (CRD42017072477).

The NICE interface was used to search the Cumulative Index to nursing and allied health literature (CINAHL), Medline, and Excerpta Medica dataBASE (EMBASE) databases. Searches of; PubMed, TRIP, British Nursing Index (BNI), Physiotherapy evidence database (PEDro), OT seeker, Google Scholar, Science.gov and Microsoft Academic Search were also undertaken

up to 4th December 2020. The subject heading, syntax and searching strategy were tailored to each database. The searches utilized the subject headings; “Aged”, “Aged 60 and over”, “Ambulatory surgical procedures” “Biliary tract procedures”, “Colorectal surgical procedures”, “Cystoreduction surgical procedures” “Digestive system surgical procedures”, “Elective surgical procedures”, “Endocrine surgical procedures”, “Exercise therapy”, “General surgical procedures”, “Gynaecological surgical procedures”, “Urological surgical procedures”, “Rehabilitation” “Renal surgical procedures”, “Vascular surgical procedures” , “Orthopaedic surgical procedures”, “Postoperative period”, “Therapeutic exercise” with text words; “Aged”, “Elderly”, “Older”, “Exercise”, “Post-operative/postoperative/”post-operative””, “Post-surgical/postsurgical/”post-surgical””, “Rehabilitation”, “Surgery”.

2.2.1.1 *Inclusion and exclusion criteria*

Randomised controlled trials (RCTs) with participants aged over 65 years of age (mean age of >65 years accepted), involving the administration of a post-operative exercise intervention incorporating global (whole-body) exercise with some form of physical function and QoL assessment were included. The review was limited to RCT studies only as these represent the highest level of evidence(209). Only literature published in English was included and to ensure the studies incorporated the most up to date forms of exercise interventions and physical function assessments, only literature from 2010 up to the completion of the review in December 2018 was included.

The exclusion criteria included studies focusing on limb or trunk exercises only or rehabilitation following organ transplantation, or cardiac surgery. Due to the specific complexities of cardiac surgery and the physiological consequences of cardiac disease, patients undergoing cardiac surgery are not representative of the general surgical patient population and therefore, this patient group are not included in this systematic review.

2.2.2 Risk of bias and data extraction.

The studies were screened for eligibility based on the title and abstract. Of those included, the bibliographies were scrutinized for other eligible studies. The risk of bias was assessed independently by two reviewers (B.D. and L.C.) using the Cochrane risk of bias tool(210). The Cochrane handook (section 7.3.2.)(211) does not recommend that the extent to which

assessments by multiple reviewers match be statistically determined, therefore, statistical measures of agreement between the two reviewers has not been undertaken.

The data extracted from the studies included: details of the intervention (type of exercise, frequency and duration of exercise, supervision of exercise, location of exercise), control conditions, study methodology, recruitment and completion rates, outcomes, form of physical function assessment, quality of life assessment methods, time of measurement and indicators of feasibility and acceptability of the intervention.

2.2.3 Data analysis.

Clinical heterogeneity was substantial across the included studies with multiple surgical disciplines, disparate exercise programmes and variable outcome assessments. Where the studies used the same physical function assessment and QoL outcome measure, data was extracted for meta-analysis. As a consequence of the clinical heterogeneity, the data was aggregated using a random-effects model and the effects estimates presented as difference in means (MD) with 95% confidence interval (CI). Statistical heterogeneity was determined using the p-value derived from the Chi square statistic and the I^2 statistic, with a $p<0.10$ or a $I^2>50\%$ taken as evidence of statistical heterogeneity. Where possible, change standard deviations were calculated using methods from the Cochrane handbook or estimated from other studies in the analysis. Due to the limited number of included studies, meta-regression to investigate heterogeneity and assessment for publication bias was not possible. To reduce type I and II errors in analysis trial sequential analysis (TSA) with an alpha of 0.05 and a 1-beta of 0.80 was performed. Empirical measures of diversity (D2), variance and effect estimates using a random effects model were used. Quality of evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations)(212). All analyses were conducted using Stata Version 15 and TSA software from the Copenhagen Trial Unit.

2.3 Results

2.3.1 Description of the included and excluded studies.

Of 1060 studies identified (Figure 2.1), after the removal of duplicates, 1007 did not meet inclusion criteria, leaving 5 studies for analysis(213)(214)(215)(216)(217) (Refer to Tables 1 and 2 below). The predominant inclusion criteria which failed to be met by the studies reviewed were the age criteria and the lack of global exercise intervention and physical function assessment.

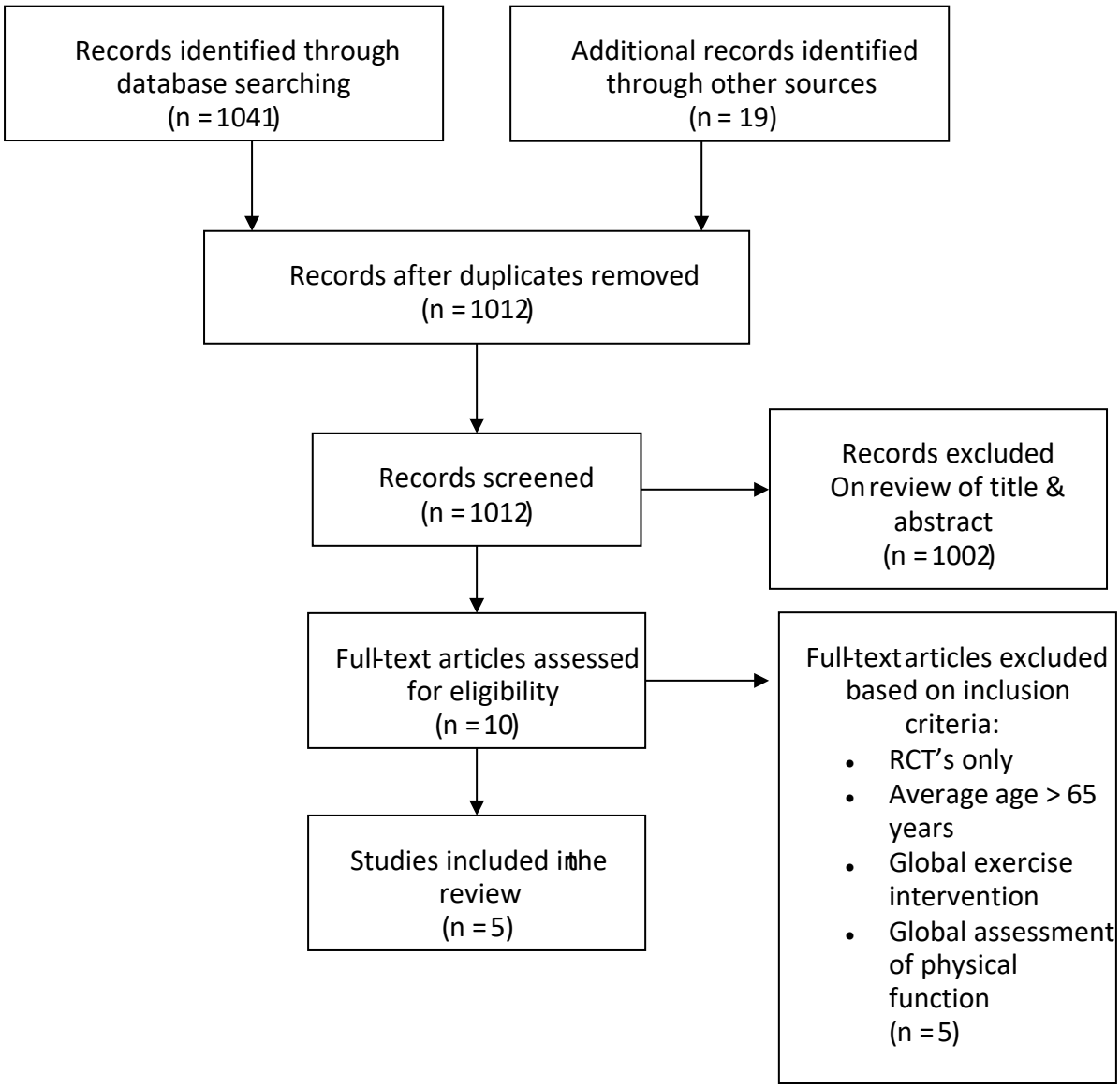


Figure 2.1: PRISMA diagram depicting the different stages of the systematic review.

AUTHORS *(& sample size overview)*	**STUDY DESIGN**	**INCLUSION/ EXCLUSION CRITERIA**	**PATIENT DEMOGRAPHICS**	**PHYSICAL FUNCTION MEASURES**	**QUALITY OF LIFE MEASURES**
Arbane et al. 2011 (213) *Control group n = 26, Included in results analysis n = 22* *Intervention group n = 27 Included in results analysis n = 21*	Hospital and home based 12-week exercise programme Supervised and un-supervised component Tests (T): T1 pre-op, T2 5 days post-op, T3 12 weeks post exercise	Inclusion: • Adults with NSCLC (non-small cell lung cancer) • Referred for lung resection (lobectomy and/or pneumonectomy) via open thoracotomy or video-assisted thorascopic surgery (VATS) Exclusion: • Thoracotomy procedure where no lung resection performed (e.g. pleurectomy) • Patient undergoing pneumonectomy • Admission > 48 hours to the intensive care unit post-surgery	Mean (SD) *Control (n = 25):* Age range (years): 62.6 (32 – 47) BMI: 25.7 (4.8) FEV_1: 1.9 (0.8) *Exercise (n = 26):* Age (range) years: 65.4 (47 – 82) BMI: 25.5 (3.6) FEV_1: 1.9 (0.6) No significant difference between the two groups for each of the above	Exercise tolerance: • 6MWT – the best of two recorded Quadriceps muscle strength: • Magnetic stimulation of the femoral nerve with a junior load cell to measure force The best of 3 measurements was recorded	EORTC-QLQ questionnaire: integrated system for assessing health related QoL in cancer patients QLQ-LC13 questionnaire: specifically designed for lung cancer patients QoL was not measured 5 days post-operatively as this would not reflect the patient's usual state
G. Arbane et al. 2014 (214) *Control group n = 67 Primary outcome analysis n = 38* *Intervention group n = 64*	Hospital and 4 week home based exercise programme Supervised and un-supervised components Tests (T): T1 pre-op, T2 pre-exercise 5 days post-op,	Inclusion: • Adults with NSCLC • Referred for lung resection (lobectomy and/or pneumonectomy) via open thoracotomy or video-assisted thorascopic surgery (VATS) Exclusion: • Received exploratory surgery, considered unsuitable for resection • Required admission to the intensive care unit for >48 hours after surgery	Mean (SD) *Control (n = 67):* Age (years): 68 (11) Female n (%): 24 (36%) BMI: 26 (4.7) FEV_1: 2.5 (1.1) *Exercise (n = 64):* Age (years): 67 (11) Female n (%): 35 (55%)	Exercise tolerance: *Primary outcome:* • Physical activity was recorded using a Respironics Actiwatch, worn 48 hours pre-op, followed by 24hours/day for at least 5 days after surgery, then for 1 week prior to 4-week post-operative assessments. This	EORTC-QLQ questionnaire: integrated system for assessing health related QoL in cancer patients QLQ-LC13 questionnaire: specifically designed for lung cancer patients QoL was not measured 5 days post-operatively as this would not reflect the patient's usual state

Primary outcome analysis n = 40	T3 12 weeks post exercise	• Received >72 hours of supplementary oxygen at rest to maintain oxygen saturations >90%	BMI: 26 (4.4) FEV_1: 2.3 (1.2) No significant difference between the two groups for each of the above, bar the number of females per group (p = 0.03)	recorded time spent undertaking sedentary, low and moderate intensity activity. *Secondary outcome:* • Incremental Shuttle Walk Distance (ISWT): 10-minute walk test. The best of 2 tests was recorded before surgery and then one test for each assessment post-operatively Quadriceps muscle strength: • The best of 3 maximum voluntary contractions with force measured using a junior load cell <u>Subgroup analysis performed in patients with airflow obstruction</u>	Short Form-36 questionnaire: a generic multipurpose health survey
Latham et al. 2014 (215) *Control group n = 112 Primary outcome*	6 month home based exercise programme Unsupervised only Tests:	Inclusion: • Primary diagnosis of hip fracture • Greater than or equal to 60 years of age • Discharged from rehabilitation services within 20 months of the baseline assessment	Mean (SD) *Control (n = 112):* Age (years): 78.9 (9.4) Female n (%): 77 (69%)	Primary outcome measure - Physical function at 6 months: • SPPB – standing balance, gait speed and chair rise.	Not measured

analysis at 6 months n = 95, at 9 months n = 85 *Intervention group n = 120 Primary outcome analysis at 6 months n = 100, at 9 months n = 94*	T1 pre-op T2 6 months post-op	• Understand and communicate in English • Be able to safely and independently move from sitting to standing with or without the aid of a mobility device • All had to have a functional limitation, defined as a limitation in at least 1 of the tasks listed in the Short Form 36 physical function scale Exclusion: • Significant cognitive deficits (i.e. Mini-Mental State Examination score of < 20) • Severe depression (i.e. score of greater than or equal to 10 on the short form of the Geriatric Depression Scale) • A terminal illness (survival expected to be < 1 year) • Significant pulmonary or cardiovascular contraindications • Pre-existing conditions that precluded participation in an exercise programme • Legally blind • Currently receiving rehabilitation therapy • Resident outside the study's catchment area in New England • Bilateral hip fracture • Hip fracture due to malignancy	*Exercise (n = 120):* Age (years): 77.2 (10.2) Female n (%): 83 (69%) No significant difference between the two groups for each of the above	• Activity measures for post-acute care (AM-PAC): patient reported measure. *Secondary outcomes:* • Lower extremity isometric muscle strength – measured bilateral knee extension force • Balance assessed using the Berg Balance Test • Falls self-efficacy assessed using the Modified Falls Self-Efficacy Scale • The Self-Efficacy for Exercise Scale • Outcome expectations for Exercise Scale	

		• More than 24 months since the hip fracture at enrolment in the study • Rapidly progressive neurological disease			
Park et al. 2012 (216) *Control group n = 33 Included in analysis n = 25* *Intervention group n = 33 Included in analysis n = 26*	12-week progressive exercise training programme Programme commenced 3 weeks post-surgery Exercise programme was supervised Tests: T1 1-week pre-op, T2 3 weeks post-op before exercise T3 15 weeks post exercise post-op	Inclusion: • Male • Greater than or equal to 65 years of age • Clinically localised prostate cancer (cT1-T2) • Eastern Cooperative Oncology group performance status 0 or 1 • Written informed consent • Laproscopic radical prostatectomy Exclusion: • Adjuvant or neoadjuvant therapy • Severe postoperative complications • History of intrapelvic surgery • Diseases that can affect voiding function • Limitations for exercise intervention such as serious cardiovascular events or spinal or articular disease	Mean (SD) *Control (n = 33):* Age (years): 69.4 (7.2) BMI: 23.8 (3.6) *Exercise (n = 33):* Age (years): 69.1(5.7) BMI: 23.8 (3.6) No significant difference between the two groups for each of the above	Primary outcomes: a • functional fitness • muscle strength, • endurance • flexibility • body composition • balance Functional fitness, muscle strength and muscle endurance via sit ups, chair stand, dominant grip strength, hip adduction, back lift and knee lift each performed for 2 minutes. Flexibility via sit-and-reach test Balance via body sway test Body composition via body composition analyser – measuring fat mass, skeletal muscle mass, BMI and waist/hip ratio	Short Form-36 questionnaire: a generic multipurpose health survey Beck Depression Inventory for the assessment of depression
Porserund et al. 2014 (217)	12-week hospital-based group	Inclusion: • Men and Women • Age 60-80 years	Mean (SD) *Control (n = 9):*	Functional capacity assessed by the 6 MWT,	Short Form-36 questionnaire: a generic multipurpose health survey

CONTROL GROUP N = 9 INTERVENTION GROUP N = 9. Baseline (T1) and assessments at 14 weeks (T2); control n = 8, exercise group n = 5. Baseline (T1), 14-week test (T2) and one year test (T3); control n = 6, exercise group n = 4.	exercise training programme Supervised training programme Baseline data was collected within a week after discharge from hospital or postoperative care clinic The exercise intervention commenced within a week following collection of the baseline data, therefore, the exercise intervention did not start immediately post-operatively Tests: T1 1-week post discharge from hospital T2 14 weeks T3 1-year post-op	• Understand Swedish • Resided in the Stockholm County Council area • Mobile with or without a walking aid • Surgery: Radical cystectomy with ileal conduit for urinary bladder cancer Exclusion: • Recurring malignancy • Scheduled for robot-assisted laproscopic surgery.	Age (years): 72 (4) BMI: 25 (3) *Exercise (n = 9):* Age (years): 72 (5) BMI: 23 (3) No significant difference between the two groups for each of the above	repeated twice with a 45-minute break in between. Balance assessed by walking two laps in a figure of eight Lower body strength assessed by 30-second chair stand test	

Table 2.1: Characteristics of the included studies. *6MWT*; *SPPB*; *AM-PAC,* Activity Measure for Post-Acute Care; *LOS*; *SF-36*; *QoL*, quality of life.

2.3.2 Quality assessment of the included studies.

Due to the nature of the exercise interventions, for all of the studies, the participants were not blinded, therefore all are at high risk of bias. Further, study design made it difficult to blind the assessment of the outcome data, further increasing the risk of bias(213)(214)(216). The high attrition rates also increased bias in the remaining studies(215)(217).Table 2.2 below depicts the summary of the risk of bias for each of the included studies below.

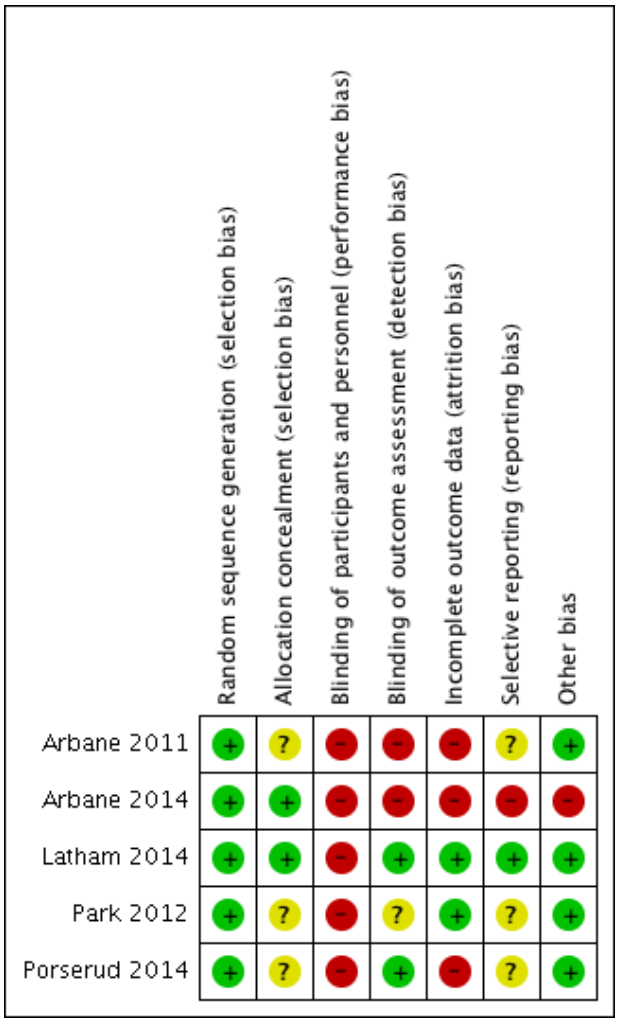


Figure 2.2: The table provides a summary of the risk of bias for the included studies. *Green* indicates low risk, *Yellow*, intermediate risk and *Red*, high risk(210).

2.3.3 Details of the exercise interventions.

Across the five studies reviewed (refer to Table 2.2) there was little uniformity in the exercise programmes, with differences in both modality and format. The study by Latham *et al*.(215) utilised a home-based exercise programme, whilst supervised exercise was the mainstay of the studies by Park *et al*.(216) and Porserund *et al*.(217) The remaining studies by Arbane *et al.*(213) and G. Arbane *et al*.(214) incorporated a mix of both supervised and unsupervised activity. The programmes all incorporated both strength and aerobic exercise training, however the nature of the exercise varied, including walking, cycling, resistance-based exercise and functional task-focused exercises. Only three studies(213)(214)(216) set target goals for the exercise. The programmes also had various starting points relative to surgery, some commenced immediately post-operatively(213)(214), with the longest gap between surgery and commencement of exercise being 3-weeks(216). Further, the duration of the exercise programmes ranged from 4-weeks(214) to 6-months(215) with individual exercise sessions lasting between 10(213) and 60-minutes(214)(215)

AUTHORS	STUDY DESIGN	INTERVENTION DETAILS
Arbane et al. 2011 (213)	Hospital and home based 12-week exercise programme. Supervised and un-supervised componenet. Tests (T): T1 pre-op, T2 5 days post-op, T3 12 weeks post exercise.	Day 1 – 5 post-op supervised twice daily strength & mobility training with additional physiotherapy sessions consisting of walking, marching on the spot and recumbent bike sessions. After day 5, 12 weeks of a home-based programme. Strength training involved seated leg raises with 2 – 4lb. Once discharged home participants were encouraged to continue with their walking exercise programme plus an adapted strength training programme. Home visits were individualised in accordance with the participants hobbies. Aim to work at 60 – 80% of max heart rate (using 220 – age to determine maximum HR) for at least 5 minutes up to a maximum of 10 minutes.
G. Arbane et al. 2014 (214)	Hospital and 4 week home based exercise programme. Supervised and un-supervised components. Tests (T): T1 pre-op, T2 pre-exercise 5 days post-op, T3 12 weeks post exercise.	Post-op day 1 – 5 (or until discharge home): one supervised cycling session plus strength training per day. The cycling session was 30 minutes in duration involving 2 minutes of familiarisation consisting of unloaded pedalling at 50-60 revolutions per minute (rpm). The intensity was then increased steadily during the third minute to reach a maximum of 60-90% of the calculated HR reserve [target HR range = HR_{max} – HR_{rest}) x percent intensity] + HR_{rest} (with a correction factor of 12 or25% reduction in pre-operative maximum load for lobectomy or pneumonectomy respectively). Participants were instructed to exercise at an intensity equating to a level of 3 or 4 on the Borg CR10 Breathlessness Scale (BBS) and 13 to 15 on the Borg Rating of Perceived Exertion (RPE). The pedalling rate was fixed between 50 and 60 rpm. There then followed at least 2 minutes of cooling down which consisted of unladed pedalling until the HR returned to within 10 beats per minute of resting baseline value. The strength training programme involved the use of ankle weights and was based on the 10 maximum REP principle (maximum weight which can be lifted for 10 repititions). The Home based componenet of the exercise programme consisted of unsupervised walking sessions adapted from the SPACE walking programme for individuals suffering from chronic obstructive pulmonary disease (COPD). Each participant was provided with a pedometer and a daily walking target of 30 minutes of continuous activity.
Latham et al. 2014 (215)	6 month home based exercise programme. Unsupervised only. Tests: pre-op and at 6 months.	Participants were instructed to complete the home training 3 times per week for 6 months. The participants were provided with 3 home visits, each 1 hour long, to undergo training on how to complete the exercises and a 4^{th} teaching session provided if health or other problems required additional modifications to the programme. A DVD (plus DVD player) of the training programme was supplied for reference. The exercises focused on repeating functionals tasks based on the Strong for Life programme using Thera-bands for resistance. Standing exercises using steps of varying height with weighted vests to provide load based on the INVEST and Sherrington & Lord hip fracture programmes were also incorporated into the training programme. Cognitive & behavioural strategies used to positively enhance the attitudes & beliefs of each study participant.

Park et al. 2012 (216)	12-week progressive exercise training programme. Programme commenced 3-weeks post-surgery. Exercises programme was supervised. Tests: 1-week pre-op, 3-weeks before exercise post-op and at 15-weeks post exercise post-op.	Participants were requested to exercise 2 times each week, for 60 minutes daily. The exercises included: resistance exercises using an elastic band (Theraband, Hygenic, Akron, OH), pelvic flexibility and Kegel exercises. The intensity of the exercises with the elastic band was set at 50-70% of 1 repetition maximum. Exercise intensity was det to reach 45-75% of the heart rate reserve maximum (based on the use of a heartbeat clock, Polar-400) and 9-13 on a perceived exertion scale of exercise intensity. This exercise programme was developed by Sports science experts and had been previously demonstrated to be beneficial. The details of the exercise programme: Weeks 1-4, adaptation period: • Education about postoperative symptoms. • Performing Kegel exercises – learn about parapelvic muscles. • Pelvic floor flexibility fitness: pelvic exercises while sitting on a ball. Weeks 5-8, ball exercises: • Pelvic exercises sitting on a ball. • Lower extremity exercises using a ball against a wall. • Lifting a heel on the ball while standing face-to-face with the wall. • Lifting up and down on the ball while spreading and bending the legs. • Performing flank exercises while having a ball in the hand. • Squeezing the ball with the adductor muscles while lying on a table. Weeks 9-12, elastic band exercises: • Lifting the object with an elastic band lateral, anterior and posterior to the patient's arms. • Lifting the legs and then spreading them while attaching an elastic band to the foot.
Porserud et al. 2014 (217)	12-week hospital-based group exercise training programme. Supervised training programme. Baseline data was collected within a week after discharge from hospital or postoperative care clinic. The exercise intervention then commenced within a week following collection of the baseline data. Therefore, the exercise intervention did not start immediately post-operatively. Tests: baseline data 1-week post discharge from hospital, then at 14-weeks and 1-year post-op.	The training was led by a physiotherapist with 2 sessions per week, each session 45 minutes in duration. The programme consisted of strength and endurance training for the lower extremities, such as walking. Balance and mobility training with stretching exercises were incorporated. Participants were instructed to walk for at least 15 minutes 3 to 5 times per week at a self-selected pace.

Table 2.2: This table provides specific details of the intervention and the study design for each of the 5 studies in this review.

2.3.3.1 *Adherence to the exercise programmes.*

For the non-supervised exercise interventions, various techniques for monitoring exercise adherence were adopted, these are described, with adherence rates in Table 2.3 below. Arbane *et al.*(213) included monthly visits, Porserund et al.(217) used participant diaries, whilst G.Arbane *et al*.(214) and Latham *et al*.(215) contacted the participants by telephone

Latham *et al*.(215) reported a 70% exercise adherence rate, completing on average 2.1 exercise sessions per week of the 3 required. The exercise intervention duration was 6 months, the number of weeks not documented, no raw data was provided quantifying the exact number of exercise sessions completed against the required number to be undertaken (assumed to be 72 based on 3 sessions per week, 4 weeks per month for 6 months). The Latham *et al*.(215) study was the only study to target participant beliefs and perceptions of exercise by using cognitive and behavioural strategies to facilitate adherence. Porserund *et al*.(217) reported a 76% (median reported, range 67%-95%) attendance rate at the supervised group exercise sessions and 87% (median reported, range 56%-100%) adherence for the home-based component of the exercise programme, based on self-report. The study did not clarify the minimum number of exercise sessions which had to be completed, for the unsupervised activity the participants were instructed to undertake walks 3 to 5 days per week for a minimum of 15 minutes. The raw data is provided in Table 2.3 below, this shows that for the intervention group as a whole, a mean of 16.17 (-/-2.714) sessions out of 24 were completed (as a mean percentage figure this is 67%), with a minimum of 12 and a maximum of 20 sessions completed by a patient. This raw data does not marry with the attendance rate range of 67% to 95% as reported in the paper, described above. For the reported walking activity, a mean of 4.57 (+/- 3.53) hours were completed by the group as a whole, as the minimum required was 15 minutes, 3 times per week, for the 12 weeks, this would equate to 5.4 hours, no maximum was clearly stipulated in minutes, although participants were requested to walk up to 5 days per week. The only attempt to quantitatively measure home-based activity was made by G.Arbane *et al*.(214) through the use of a pedometer, in which they found that step count supported self-reported data. Arbane et al. (213) assessed adherence through the use of home visits, however, the service input was minimal and insufficient data on adherence to the home-based exercise

programme was collected to provide any meaningful assessment of this. Adherence is not discussed in the Park et al. study(216).

Despite supervised exercise training programmes, Porserud *et al*.(217) and Park *et al*.(216) suffered from high drop-out rates in both the control and exercise groups which were attributed to patient factors. G.Arbane *et al*.(214) also reported a high drop-out rate with 6 out of 13 withdrawals from the exercise group during the intervention period. Both Arbane et al.(213) and Latham et al.(215) suffered a number of dropouts and withdrawals from both the control and intervention arms, with no bias reported towards the intervention arm in each study.

AUTHORS *(& sample size overview)*	**ADHERENCE RATES**	**DROP-OUT RATES**
Arbane et al. **2011** (213) *Control group n = 26* *Intervention group n = 27*	No adherence data relating to the exercise componenet collected.	Control arm: 2 during the control period. Intervention arm: 1 during the exercise period.
G. Arbane et al. **2014** (214) *Control group n = 67* *Intervention group n = 64*	Adherence monitored using a diary and pedometer step counts, was reported to have corroborated the of activity undertaken as described by the participant.	Control arm: 2 during the control period. However, 4 were lost to follow up/monitor failure. Intervention arm: 6 during the exercise period.
Latham et al. **2014** (215) *Control group n = 112* *Intervention group n = 120*	Participants self-monitored their progress using an exercise calendar. Reported 70% adherence rate to the exercise programme across 26 weeks.	Control arm: *At 6 months (Primary endpoint):* 10 Refused to continue or unable to schedule visit. 4 unable to contact *At 9 months:* 11 Refused to continue or unable to schedule visit. 6 unable to contact • Total: 31 patients Intervention arm: *At 6 months:* 7 Refused to continue or unable to schedule visit. 3 unable to contact *At 9 months:* 10 Refused to continue or unable to schedule visit. 3 unable to contact • Total: 23 patients.
Park et al. **2012** (216) *Control group n = 33* *Intervention group n = 33*	Exercise programme was supervised.	Control arm: 8 during the control period. Intervention arm: 7 during the exercise period.
Porserud et al. 2014 (217) *Control group n = 9* *Intervention group n = 9*	Supervised group sessions: A total of 24 group sessions (2 per week for 12 weeks). A mean of 16.17 (+/-2.714) sessions were completed, minimum number of 12, maximum 20 (1 patient) The patients reported their daily walks in an exercise training diary. A mean of 4.57 (+/- 3.53) hours per week was recorded, minimum of 2, maximum of 11.50 hours per week.	Control arm: 3 during the control period. Intervention arm: 5 during the exercise period.

Table 2.3: This table details the measurements and results of adherence plus the dropout rates per study. The dropout rates are reported for the control and intervention arms, they include reported withdrawals where no reason is provided, and numbers were follow-up was not achieved for an unknown reason. Mean values reported with Standard deviation values in brackets

2.3.4 Outcome assessments.

2.3.4.1 *Assessment of physical function.*

There was no consistency in the assessment of physical function across the five studies, as shown in Table 2.4 below. Two studies(213)(214) showed that 5-days following surgery there was a deterioration in patient walking distance (which was significant (p=<0.0001) in the Arbane *et al*.(213) study (466.6 to 336.7 metres), using the 6MWT; a validated measure of physical function(218), with a return to baseline by the end of the exercise training (4-weeks(214) and 12-weeks(213)) for both the control and exercise groups. In contrast, although Porserud *et al*.(217) also found a significant increase in the 6MWT at the end of the (12-weeks) exercise training compared to the baseline 6MWT assessed on discharge from postoperative care, for both the control and exercise groups (p=0.012 and p = 0.043 respectively), the increase was significantly greater in the exercise group (p = 0.013). In addition, on assessment at one-year post-surgery, 6MWT performance had significantly decreased in the control group (p=0.002) but further increased in the exercise group (p =0.018). Using a short physical performance battery (SPPB) test(219), Latham *et al*.(215) found a significant (p < 0.001) increase in physical function after 6 months of exercise training and this was consistent with improved mobility, self-efficacy for exercise and daily activity scores (AM-PAC questionnaire). Using a variety of assessment methods to assess functional fitness, Park *et al*.(216) found significant improvements in functional physical fitness as assessed by sit ups and the chair stand (p < 0.001 for both assessments) but not by hand grip strength. There was also a significant increase in flexibility (sit and reach flexibility test) (p = 0.027) and balance (body sway test) (p = 0.015) following 12 weeks of exercise, and this was reflected in the short form health survey (SF-36) physical domain questionnaire which was observed to decrease immediately following surgery in both the control and intervention groups but return to pre-operative levels in the exercise group at the end of the study.

Lower body strength was assessed by all five studies (refer to Table 2.4 below); however, a variety of tests were utilized making direct comparison difficult.

AUTHORS	ASSESSMENT OF PHYSICAL FITNESS	RESULTS	SIGNIFICANCE
Arbane et al. 2011 (213)	Exercise tolerance: • 6MWT Quadriceps muscle strength: • Magnetic stimulation of the femoral nerve with a junior load cell to measure force	Exercise tolerance via 6MWT (m (SD)) *Exercise:* • Pre-op: 466.6 (102.10) • 5 days post-op: 336.7 (84.1) • 12 weeks post-op: 480.2 (110.0) *Control:* • Pre-op: 455.7 (98.0) • 5 days post-op: 308.7 (124.8) • 12 weeks post-op: 448.2 (95.1) Quadriceps muscle strength (kg): *Exercise:* • Pre-op: 33.2 • 5 days post-op: 37.6 • 12 weeks post-op: 34.2 *Control:* • Pre-op: 29.1 • 5 days post-op: 21.5 • 12 weeks post-op: 26.4	Exercise tolerance: p=<0.0001 for pre-operative vs. 5 day (paired t tests) 6MWT repeated measures analysis: within subjects change over time p=<0.001, group effect p=0.47, between subject's time effect p=0.89 Quadriceps strength repeated measures analysis: within subjects change over time p=0.70, group effect p=0.38, between subjects' time effect p=0.04

G. Arbane et al. 2014 (214)	Exercise tolerance:
	• Physical activity was recorded using a Respironics Actiwatch.
	
	• Incremental Shuttle Walk Distance (ISWT).
	
	Quadriceps muscle strength:
	• The best of 3 maximum voluntary contractions with force measured using a junior load.
		Exercise tolerance via Respironic Actiwatch (minutes per day (SD)):
		Exercise:
		• 200(86.7).
		
		Control:
		• 197(69.5)
		
		Categorised 4-week activity count (% (SD)):
		• Sedentary:
		  ○ Exercise group 36.9 (14.1)
		• Low:
		  ○ Exercise group 63.0(3.9),
		  ○ Control 64.0(17.9)
		• Moderate:
		  ○ Exercise group 0.1(0.3),
			Exercise tolerance:
			Exercise compared to control group physical activity (minutes per day via Respironic Actiwatch):
			• Mann-Whitney test, p = 0.71, ANCOVA test p = 0.46
			
			Categorised 4-week activity count (%):
			Sedentary:
			• Mann-Whitney p =.34, ANCOVA p = 0.96
			Low:
			• Mann-Whitney p =.37, ANCOVA p = 0.61
			Moderate:
			• Mann-Whitney p =.90, ANCOVA p = 0.95

	SUBGROUP ANALYSIS PERFORMED IN PATIENTS WITH AIRFLOW OBSTRUCTION.	○ control group 0.1(0.2) Exercise tolerance via ISWT: Raw data not presented. Diagrammatically presented as a graph. *Exercise:* • A decrease (not quantifiable from graph) in the walking distance was demonstrated 5 days post-operatively (or at discharge if earlier) • Return to baseline levels at 4 weeks post-operatively. *Control:* • A decrease (not quantifiable from graph) in the walking distance was demonstrated 5 days post-operatively (or at discharge if earlier) • Return to baseline levels at 4 weeks post-operatively. Quadriceps muscle strength: *Exercise:* • A mean increase in quadriceps muscle strength of 4.7Kg at 4 weeks post-surgery. *Control:* • At 5 days post-surgery/time of discharge there was no difference in quadricep muscle strength between the groups.	Exercise tolerance via ISWT: No significant difference between the baseline and the 4-week post-operative data p> 0.05 Quadriceps muscle strength: *Exercise:* • Mean change 4.7kg (95% CI 0.18 to 0.20) p= 0.04.
Latham et al. 2014 (215)	Physical function at 6 months: • SPPB – standing balance, gait speed and chair rise. • Activity measures for post-acute care (AM-PAC): patient reported measure. Secondary outcome measures:	Primary Outcome analysis at 6 months: *Exercise:* • SPPB: 0.8 (0.4 to1.2) • AM-PAC mobility: 1.3 (0.2 to 2.4) • AM-PAC daily activity: 3.5 (0.9 to 6.0) *Control:* • SPPB: 1.0 (0.6 to 1.4).	Primary Outcome analysis at 6 months: SPPB p < 0.001, unadjusted and adjusted for age and sex. AM-PAC mobility p = 0.01 unadjusted and adjusted for age and sex.

	• Lower extremity isometric muscle strength – measured bilateral knee extension force. • Balance assessed using the Berg Balance Test. • Falls self-efficacy assessed using the Modified Falls Self-Efficacy Scale. • The Self-Efficacy for Exercise Scale. • Outcome expectations for Exercise Scale.	• AM-PAC mobility: 1.7 (0.5 to 2.8). • AM-PAC daily activity: 2.8 (0.3 to 5.4). Secondary outcome measures: *Exercise:* • Leg strength fractured leg (lb): 1.5 (-0.9 to 4.0) • Leg strength nonfractured leg (lb): Exercise 0.9 (-1.5 to 3.2) • Berg Balance Test: 2.3 (1.1 to 3.5) • Self-Efficacy for Exercise Scale: 3.4 (-1.4 to 8.2) • Modified Falls Self-Efficacy Scale: 3.4 (-2.5 to 9.2) • Outcome Expectations for Exercise Scale: -1.0 (-2.1 to 0.2) *Control:* • Leg strength fractured leg (lb): 2.3 (-0.3 to 4.8). • Leg strength nonfractured leg (lb): 3.5 (1.0 to 5.9). • Berg Balance Test: 2.7 (1.4 to 3.9). • Self-Efficacy for Exercise Scale: 6.6 (1.7 to 11.5). • Modified Falls Self-Efficacy Scale: 1.0 (-5.0 to 7.0). • Outcome Expectations for Exercise Scale: -1.1 (-2.3 to 0.1).	AM-PAC daily activity p = 0.02 unadjusted and p = 0.01 adjusted for age and sex. Secondary outcome measures: Leg strength fractured leg (lb) p = 0.19 unadjusted and p = 0.16 adjusted for age and sex. Leg strength nonfractured leg (lb)p = 0.02 unadjusted and adjusted for age and sex. Berg Balance Test p = 0.01 unadjusted and adjusted for age and sex. Self-Efficacy for Exercise Scale p = 0.03 unadjusted and adjusted for age and sex. Modified Falls Self-Efficacy Scale p = 0.52 unadjusted and p = 0.53 adjusted for age and sex. Outcome Expectations for Exercise Scale p = 0.12 unadjusted and p = 0.13 adjusted for age and sex.
Park et al. 2012 (216)	*Primary Outcome assessment:* • Muscle endurance: sit ups, chair stand, dominant grip strength, adduction ability, back lift and knee lift performed for 2 minutes. • Flexibility: sit-and-reach flexibility test.	Results were graphically presented; no raw data was available.	Exercise group: Improved functional physical fitness (p< 0.001), flexibility (p=0.027) and balance ability (p = 0.015). No improvement was found in the hand grip strength for the exercise group. No changes were found for fat mass (p = 0.353), skeletal muscle mass (p = 0.263), BMI (p = 0.514) or waist/hip ration (p = 0.586).

	• Balance function: Body sway test using a Balance D&T. • Body composition measured using a body composition analyser – measuring fat mass, skeletal muscle mass, BMI and waist/hip ratio.		
Porserud et al. 2014 (217)	Functional capacity: • 6MWT, • Balance assessed by walking two laps in a figure of eight. • Lower body strength assessed by the means of the 30-second chair stand test.	Baseline (T1) and 14-week assessments (T2), median (range) values provided: *Exercise:* • T1: 438 (359-598) • T2: 539 (478-707) *Control:* • T1: 495 (217-558) • T2: 556 (282-606) Baseline (T1) and 14-week assessments (T2) and 1-year (T3), median (range) values provided: *Exercise:* T1: 435 (359-455) T2: 526 (478-608) T3: 554 (498 – 627) *Control:* T1: 495 (432-558) T2: 558 (519-606) T3: 537 (488 – 600	Baseline (T1) and 14-week assessments (T2): *Exercise:* P = 0.043 *Control:* P = 0.012 *Exercise:* P = 0.018 *Control:* P = 0.002

Table 2.4: This table details for each of the 5 studies included in this review, the data pertaining to the number of participants in the control and intervention groups, also the details of the assessments of physical fitness completed, the results and the significance of these findings. Mean values reported with Standard deviation values in brackets.

2.3.4.2 *Meta-analysis of the 6MWT data.*

Extracting and pooling the 6MWT data from the studies by Arbane *et al*.(213) and Porsreund *et al*.(217) (Figure 2.3), demonstrated a MD of 32.83m (95% CI 4.93m to 60.73m) metres, depicting a positive gain in distance covered for those completing exercise training. The I^2 of 22% indicates a small amount of statistical heterogeneity. TSA showed that the results did not cross the monitoring boundaries or reach the required information size (74 participants) indicating future research is required. The quality of evidence was very low being downgraded due to risk of bias, inconsistency and imprecision.

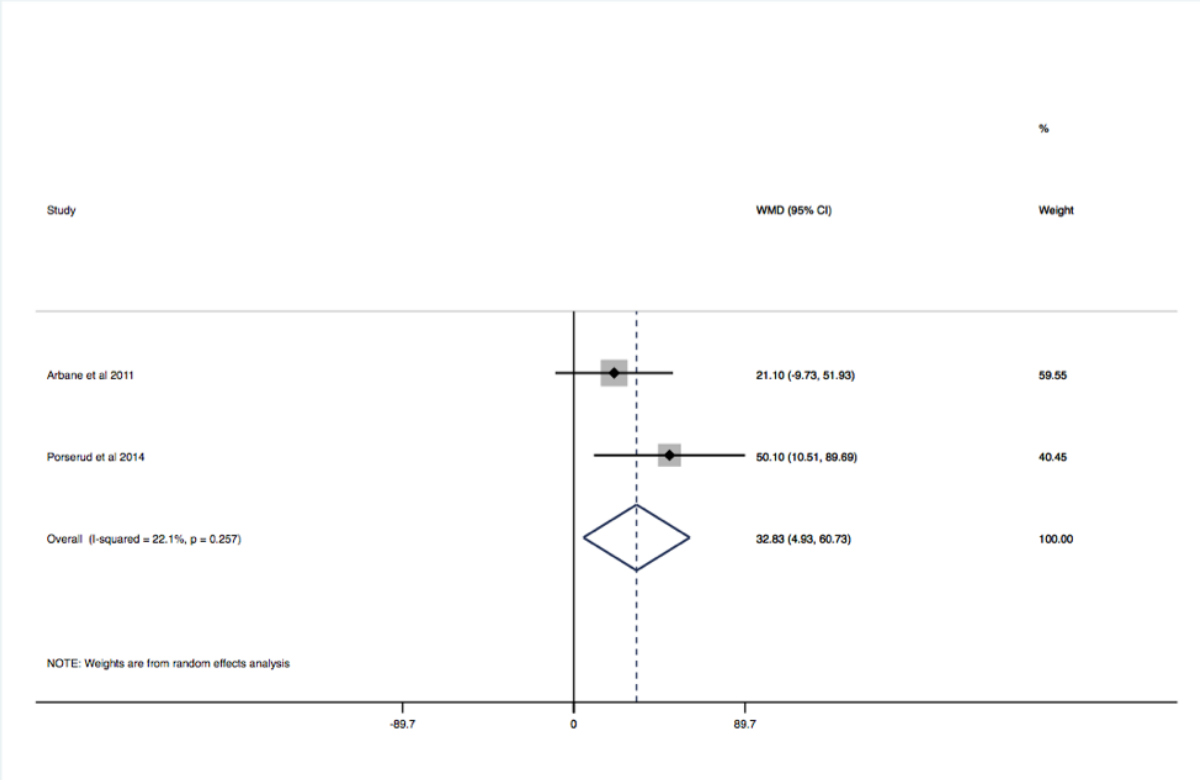


Figure 2.3: Forrest plot data for the 6MWT data extracted from the studies Arcane et al.[(213)] and Porserud et al.[(217)] Pooled WMD 32.83 meters; 95% CI 4.93 to 60.73 meters. The I^2 is 22.1%. p = 0.257

2.3.5 Assessment of quality of life.

For QoL assessment, three of the studies(215)(216)(217) used the SF-36 health survey (Table 2.5) which covers eight domains (general health perceptions, physical functioning, pain, mental health, emotional, social and physical role functioning and vitality) broadly divided into physical and mental health categories. The remaining two studies(213)(214) used the ECORT-QLQ-LC13 (Table 2.5), a survey specific for the assessment of QoL in patients suffering from lung cancer.

Authors *(& sample size overview)*	**Quality of life assessments used**	**Quality of life findings**
Arbane et al. **2011** (213) *Control group n = 26,* *Included in results analysis n = 22* *Intervention group n = 27* *Included in results analysis n = 21*	EORTC-QLQ questionnaire: integrated system for assessing health related QoL in cancer patients QLQ-LC13 questionnaire: specifically designed for lung cancer patients. QoL was not measured 5 days post-operatively as this would not reflect the patient's usual state	*Control:* EORTC-C30 (functional): Mean difference 2.0 (95% CI -5.5 to 9.3) EORTC-C30 (symptom): Mean difference -2.5 (95% CI -7.8 to 2.9) EORTC-C30 (global health): Mean difference 6.5 (95%CI -7.7 to 20.7) *Exercise:* EORTC-C30 (functional): Mean difference 2.7 (95% CI -4.7 to 10) EORTC-C30 (symptom): Mean difference 3.2 (95% CI -8.3 to 2.1) EORTC-C30 (global health): Mean difference 2.2 (95%CI -5.2 to 9.6) No significant differences over time or differences between the groups found
G. Arbane et al. **2014** (214) *Control group n = 67* *Primary outcome analysis: n = 38.* *Intervention group n = 64* *Primary outcome analysis: n = 40*	EORTC-QLQ questionnaire: integrated system for assessing health related QoL in cancer patients. QLQ-LC13 questionnaire: specifically designed for lung cancer patients. QoL was not measured 5 days post-operatively as this would not reflect the patient's usual state. SF-36 questionnaire.	There were no significant differences between the control and exercise groups found for the EORTC QLQ-LC13 and SF-36 QoL data. SUBGROUP ANALYSIS OF THE PATIENTS WITH AIRFLOW OBSTRUCTION: This analysis showed that the exercise group demonstrated a significant benefit in QoL 4 weeks post-operatively. No decline in the mental and physical componenet of the SF-36 data for the exercise group was evident as observed in the control group. • Physical domain: mean difference between groups (95% CI): 12 (0.5 to 23.0) p-value 0.04 (ANCOVA). • Mental domain: mean difference between groups (95% CI): 20 (4.6 to 34.6) p-value 0.01 (ANCOVA). No significant differences were found between the control and exercise groups with the EORTC QLQ-LC13 questionnaire.
Latham et al. **2014** (215) *Control group n = 112* *Primary outcome analysis at 6 months n = 95* *Analysis at 9 months n = 85.*	Not measured.	

Intervention group n = 120 *Primary outcome analysis at 6 months n = 100* *Analysis at 9 months n = 94.*		
Park et al. 2012 (216) *Control group n = 33* *Included in analysis n = 25.* *Intervention group n = 33.* *Included in analysis n = 26.*	SF-36 used to assess QoL. Beck Depression Inventory for the assessment of depression.	A significant decrease in the physical domain SF-36 score was found for both the control and exercise groups following surgery ($p < 0.001$). The physical domain SF-36 score did not recover to the pre-op level in the control group at 12 weeks ($p = 0.225$). The mental domain SF-36 score showed significant improvement after 12 weeks in the exercise group ($p = 0.017$), with no change in the control group ($p = 0.773$). The depression score significantly decreased at 12 weeks in the exercise group ($p = 0.013$).
Porserud et al. 2014 (217) *Control group n = 9* *Intervention group n = 9.* *Baseline (T1) and assessments at 14 weeks (T2):* • *control n = 8* • *exercise group n = 5* *Baseline (T1), 14 week test (T2) and one year test (T3):* • *control n = 6* • *exercise group n = 4.*	SF-36 used to assess QoL.	No significant difference was found between the control and exercise groups for any of the SF-36 domains.

Table 2.5: This table details for each of the 5 studies included in this review, the data pertaining to the number of participants in the control and intervention groups, also the details of the QoL assessments and their findings. Mean values reported with Standard deviation values in brackets.

Porserud *et al*.(217) demonstrated a significant improvement only in the SF-36 physical function score in the exercise group at the end of the exercise training, with no change in the overarching domain of physical health. Park *el al*.(216) found that for both the control and exercise groups the physical health score significantly decreased following surgery with a return to the pre-operative baseline level in the exercise group only. The mental health score was found to significantly improve after 12-weeks in the exercise group only, with no change observed in the control group.

The ECORT-QLQ-LC13 questionnaire has three categories: general health, function and symptoms. In the two studies using this questionnaire(213)(214), no significant changes in any of these categories were reported in the control or exercise groups when baseline pre-operative data was compared to that at the end of the intervention period.

2.3.5.1 *Meta-analysis of the QoL SF-26 physical and mental health domains.*

The data reflecting the physical and mental health of the patients assessed using the SF-36 questionnaire has been extracted and pooled from the studies, Park *et al*.(216) and Porserund *et al*.(217). Although Arbane *et al*.(213) also utilized the SF-36 as an outcome measure of QoL, on review of the data, the reported data was for a subgroup of patients with airflow limitation only. Further, the scoring system had been altered such that the scores provided reflected a value derived from subtracting the final outcome data from the baseline data, therefore this study was excluded from this data analysis.

The meta-analysis for the pooled SF-36 overall physical health domain is shown in Figure 2.4. The pooled MD of 6.87 (95% CI: 4.14 to 9.59) demonstrates a significantly positive improvement in physical health for those completing exercise training. The I^2 of 0.0% indicates no statistical heterogeneity. There were too few data to conduct TSA. The quality of evidence was low, being downgraded due to risk of bias and inconsistency.

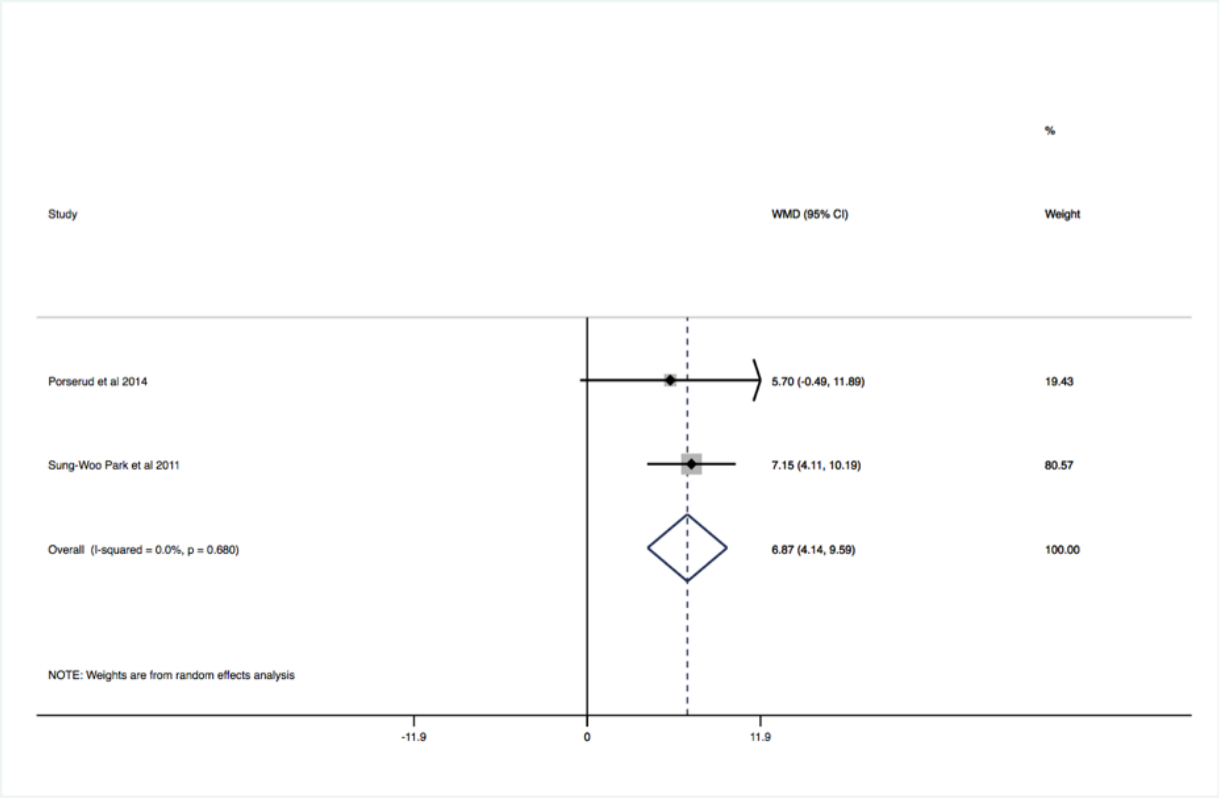


Figure 2.4: Forrest plot of the SF-36 physical health QoL data. The pooled WMD is 6.87, 95% CI 4.14 to 9.59. I^2 0.0%, p = 0.680.

The meta-analysis results for the pooled SF-36 overall mental health domain is shown in Figure 2.5. The pooled MD of 2.84 (95% CI: -3.69 to 9.36) demonstrates no significant difference in mental health for those completing exercise training. The I^2 of 0.0% indicates no statistical heterogeneity. There were too few data to conduct TSA. The quality of evidence was low, being downgraded due to risk of bias and inconsistency

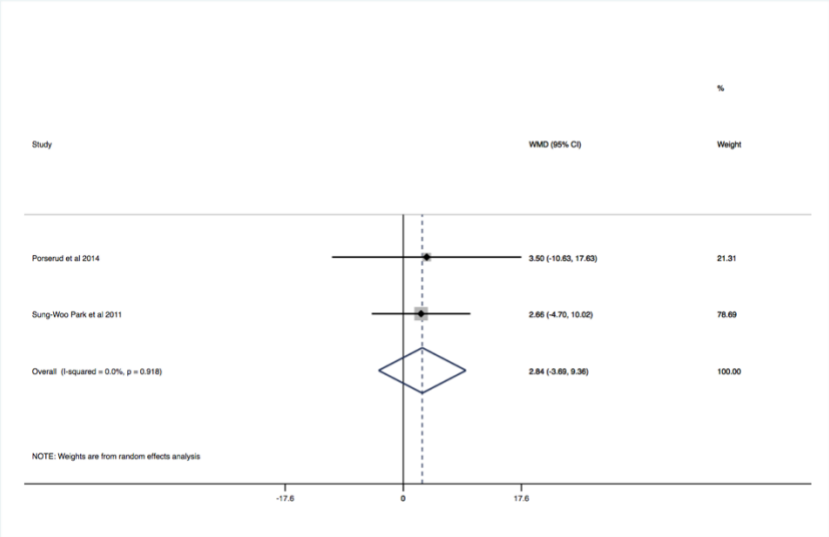


Figure 2.5: Forrest plot of the SF-36 mental health QoL data. The pooled WMD is 2.84, 95% CI -3.69 to 9.36. I^2 0.0%, p = 0.918

2.3.6 Post-operative outcomes.

One study(214) looked at the effect of post-operative exercise on hospital length of stay and post-operative complications. The percentage of complications reported was similar overall between the control and exercise groups, with 33% of the control participants and 31% of those in the exercise programme suffering post-operative complications. However, 8% of these were classified as cardiac complications in the exercise group, yet no cardiac complications were reported for the control group. No significant difference was evident in the hospital length of stay between the two groups.

2.4 Discussion

This review found that for the older surgical population (greater than 65 years of age), post-operative exercise programmes, incorporating global (whole-body) exercise (with no distinction between supervised, unsupervised or mixed design), can lead to improvement in physical function as assessed using the 6MWT and the physical aspect of QoL assessment, however, with too few data points these findings cannot be considered conclusive, which is reflected in the low quality of evidence when assessed using GRADE(212).

As the five studies(213)(214)(215)(216)(217) included in this review cover colorectal, breast, thoracic and orthopaedic surgery, the anticipated effect of these disease processes upon the baseline function of the patient and their ability to exercise will be varied. Furthermore, although all five studies incorporated both strength and aerobic exercise training in line with NHS England recommendations(220), the training programmes were highly diverse in their design. These factors render comparison of the outcome data for the exercise interventions difficult and potentially unclear.

Of the studies, two(213)(214) assessed physical fitness immediately post-operatively, and both found that physical fitness had deteriorated, with Arbane *et al*.(213) recording a significant fall in muscle mass in the control group. For both of these studies, an in-hospital exercise programme had been undertaken between the operation and the post-surgery assessment of physical fitness which was conducted on day-5 post-surgery. Arbane *et al*.(213) found a significant difference in muscle strength between the exercise and control groups for the 5-day period of in-hospital training following surgery, potentially reflecting how a short-term, immediately implemented exercise intervention may counteract the negative impact of surgery on strength. However, this suggestion is not supported by the findings of G. Arbane *et al*.(214) and ultimately for both studies, as by the end of the intervention period (4 weeks(214) and 12 weeks(213)) the physical fitness had returned to baseline pre-operative levels for both control and exercise groups. In contrast, in the remaining three studies(215)(216)(217), improved physical fitness with the exercise interventions was observed. Further, Latham *et al*.(215) and Porserud *et al*.(217) documented long-term gains in physical fitness after the exercise programmes had finished.

Overall, this improvement in physical fitness with exercise is supported by the meta-analysis of the 6MWT in this review. The results of the meta-analysis in this review show a gain in the distance covered on assessment using the 6MWT to be 33meters.

The minimal important difference (MID) reflects the smallest change in a measured outcome perceived by either the patient or a clinician to warrant a change in current management(221). For the 6MWT this was quantified in a group of older patients (mean age of 70 years SD 9 years) with COPD as a change in distance of 25 metres (95% CI 20-61m) or as a 14% change in baseline value(221). Whilst for patients suffering from diffuse idiopathic parenchymal lung disease, with a mean age of 69 years (SD 9 years) a MID in the range of 29-34 metres is significant(222). Comparatively, for patients with chronic heart failure, and a mean age of 57 years (+/-12) a MID of 35 metres was established for follow up after 180 days and 37 metres for follow up after 365 days. Whilst, for patients studied with pulmonary artery hypertension (PAH), a MID of 33 metres(223) has been demonstrated which is consistent with other similar studies in patients with cardiopulmonary disease(223). The reported increase by 33 metres (95% CI 5-61m) in the distance covered during 6MWT for those who had undertaken an exercise intervention in this review, seems a comparable value to the MID figures quoted as outlined in these previous papers. However, to conclude that an increase of 33 meters would represent a MID for those participants of the studies included in the meta-analysis is a generalisation, it is not taking into account the specifics for the individuals; their gender, age, weight or height; the demographic data used to determine the reference values for MID(224). An increase in 33 meters may have justified the exercise intervention to some of the study participants or clinicians involved in these studies, however, this is an assumption based on evidence and normative data. Whereas, a more personalised analysis would reflect a more accurate MID(225) and ensure the cost of exercise interventions to the individual and the training provider are warranted.

Depending upon the individuals baseline function, an increase of 33 metres in walking distance may reflect only a small percentage change. However, a small percentage change could potentially be attributable to a learning effect as compared to a true change in functional capacity. The learning effect is typically evident when the test is repeated on the same day, with evidence to support that such an effect would not be anticipated to exist

beyond a 2-month period(226). Also, there is evidence indicating that the learning effect is not of significant impact in clinical studies whereby the 6MWT is conducted as a baseline measure and not repeated until follow up assessment(225). Both of the studies included in this meta-analysis(214)(217) conducted the 6MWT assessments over a period of time greater than 2-months, with the comparative data collected at baseline and then at follow up assessment sessions only, supporting the result of the meta-analysis as a true change in distance covered .

Despite the meta-analysis in this review favouring multi-modal (resistance and aerobic) post-surgery exercise for eliciting improvements in physical fitness, the impact of these interventions on mental health is less clear. Indeed, the meta-analysis in this review showed no improvement in the mental health domain of the SF-36 questionnaire with exercise training, however, this is only based on data from two conflicting studies(216)(217).

The feasibility of post-operative exercise training was not addressed by any of the studies in this review. Three studies(214)(216)(217) suffered from high drop-out rates, and although these were largely attributable to patient specific factors (e.g., illness due to comorbidities and changes in personal circumstances), one of these studies(214) did report that a reasonable proportion of the withdrawals occurred during the exercise training. Exercise adherence rates were reported in two studies(215)(217), both demonstrating good adherence, suggesting that the exercise interventions were well tolerated by patients. As discussed in section 1.3.3.3.1. behaviours and beliefs impact on engagement and adherence with exercise regimens, despite this only one paper reviewed, Latham et al.(215), employed cognitive and behavioural strategies to facilitate adherence.

Whether supervised or unsupervised exercise programme design impacts on participant adherence, could not be determined. Although, of the studies included, a mix of design was present; 2 entirely supervised(216)(217) one entirely unsupervised(215), and two a mix of supervised and unsupervised sessions(213)(214), without feasibility addressed by any of the studies, and with good adherence rates reported in both the unsupervised(215) and supervised studies(217), no conclusion can be drawn on this. However, this is consistent with the findings in cardiac rehabilitation work as discussed in section 2.1, were no

significant improvement in outcomes based upon supervised centre-based exercise rehabilitation programmes as compared to home based programmes for low risk cardiac patients was found(207)

2.4.1 Limitations of this study.

The lack of evidence available to be included in this review, impacts the ability to draw firm conclusions from the results. Of the literature included, it suffers from high risk of bias and clinical heterogeneity and as a consequence, the meta-analysis is limited. Regarding future work, exercise intervention studies will, by design, remain at high risk of bias due to the inability to blind the participant to the intervention. Further, when comparing studies covering differing surgical specialties' clinical heterogeneity will always arise due to the nature of the surgical insults and associated comorbidities, and these factors in turn limit the ability to standardise exercise interventions. However, greater consistency in the choice of physical fitness and QoL assessment methods may be attainable, providing a more robust evidence base on which to construct post-operative exercise recommendations.

2.4.2 In summary.

Despite the significant clinical heterogeneity and lack of intervention consistency across the five studies, this review suggests that post-operative exercise programmes incorporated into the perioperative pathway of the older surgical patient may confer physical benefit. Although the gain demonstrated in physical fitness by increased walking distance during a 6MWT in this review was consistent with previously reported MID values, this is a generalisation of the data. Further research is required to establish the benefit of post-operative exercise training programmes on physical function and thereby frailty and the outcome measures of post-operative morbidity, mortality and QoL. In turn, establishing whether this is an interventional tool that could be potentially incorporated into public health planning of rehabilitation strategies going forward to lessen the consequent socioeconomic burden on the NHS and address inequalities in life expectancy and premature mortality in the older population (see section 1.1 for discussion on public health and the aging population).

3 Chapter Three:

Determining the suitability of bed-side assessments to determine cardiorespiratory fitness and exercise induced changes in older adults.

Poster presentation at the Pre-operative Association Conference 2016: L.Carrick., J.Blackwell., B.E.Phillips., J.N.Lund & J.P. Williams. Assessing the validity of accessible measures of physical function in the older population.

3.1 Introduction.

The systematic review in Chapter 2 supported the use of post-operative exercise programmes to improve physical function, and therefore potentially address frailty and improve morbidity, mortality and QoL outcomes. Amongst the studies reviewed, there was a lack of intervention consistency and various physical fitness outcomes measures were employed, with only two studies included in the meta-analysis of the 6MWT data. The review supported the need for further work to address whether exercise interventions in the post-operative period are associated with positive patient outcomes. Consequently, Chapter 5 of this thesis describes a RCT looking at the feasibility and impact on physical fitness of such a post-operative exercise intervention. For the RCT, assessments of physical fitness that could be undertaken by patients who have undergone major cavity surgery were required. CPET as a robust method for measuring physical fitness, and as a predictive tool of peri-operative risk, is described in detail in section 1.3.1. However, due to the physicality of the test as detailed in section 1.3.1. and below in 3.1.1. it is not an appropriate assessment tool post abdominal surgery. Further as apparent in figures 1.3 and 3.4 CPET is not a mobile bed-side tool. Therefore, alternative measures of physical fitness were needed for the RCT described in Chapter 5. HGS and the step-box test were chosen as measures of physical fitness as both of these methods have been widely used to assess aspects of physical fitness in the older adult(66)(136)(137)(138) and in various clinical cohorts, such as community groups(130), healthy(131)(227) and those with chronic lung disease(131), and those with neurological, musculoskeletal or systemic conditions(227). This study aimed to assess if these alternative (to CPET) tests were reliable measures of physical fitness in the target older population for the clinical study (Chapter 5) by comparing CPET-derived physiological variables with HGS and step-box test data in an older population, age-matched to those most commonly presenting for major cavity surgery (see Chapter 5).

3.1.1 Cardiopulmonary Exercise Testing (CPET).

Work linking exercise testing and CRF measures can be traced back to as early as 1964(228). As described in detail in section 1.1.2.1.1, since then a considerable body of literature has been published in the field, and CPET is now a well-established, “gold-standard” measure of physical fitness(95)(96)(97)(98)(100). Despite this however, the equipment to perform this is

not available in all clinical units(96), it has significant equipment and personal costs (114)(115). In addition, CPET, is physically demanding (described below) and as such the ability to perform the test may be prohibited by physical constraints. For example, osteoarthritis, a condition affecting approximately 7.3 million individuals in the UK, with increasing prevalence with age(229), is the main cause of pain worldwide, leading to reduced function and disability(229), and as such those suffering with this condition would physically not be able to perform a CPET.

3.1.1.1 *CPET Physiological Variables.*

CPET involves exercising at, or near to a maximal level of exertion whilst specific physiological variables are measured (see section 1.1.2.1.1. for details). Further to the manual collection and assessment of breath gas as used in early CPET set-ups, integrated (to the CPET cart) computer analysis of breath-by-breath data has been developed, with software programs facilitating the analysis of breath-based physiological variables in most modern CPET equipment. These physiological variables, and options associated with their analysis are described in the sections below.

3.1.1.1.1 $VO_{2peak.}$

As discussed in section 1.1.2.1.1., VO_{2max} determined using CPET is often referred to as the gold standard measure of CRF(104). However, in the older population due to both physical and mental constraints, attainment of VO_{2max} may not be realistically achievable. As such, VO_{2peak}, is an acceptable alternative clinical measure of CRF(230) which can predict morbidity and mortality outcomes post-operatively(106)(100). In the studies presented in this thesis, including in this chapter, VO_{2peak} was used as the primary measure of CRF.

VO_{2peak} is a metabolic rate defined as "the highest VO_2 attained on a rapid incremental test at end-exercise"(231). To establish that the participant has reached a level reflective of their best effort, other factors must be considered in order to reliably determine that the individual has indeed reached their VO_{2peak}. The consensus clinical guidelines on CPET indications, organisation, conduct and physiological interpretation(231) were referred to for the conduct and analysis of CPET in this study. The criteria for VO_{2max} include volitional

exhaustion and sustained oxygen consumption despite an increase in exercise intensity, these do not form the criteria for VO_{2peak}, instead the below criteria for VO_{2peak} are included:

- a HR which is equal to or greater than their maximal estimated HR(231) (calculation: Maximum HR = 208 – (0.7*Age)(232))
- a peak respiratory exchange ratio (RER) of above 1.10(231).

Based on these criteria, participants underlying co-morbidities and medications can affect the reliability of HR and RER measurements(231). However, in this study such factors influencing these parameters, for example beta-blocker medication (affecting HR) and severe COPD were exclusion criteria. In addition, given that VO_{2peak} is known to be affected by the participants own will(233) appropriate, adequate and consistent encouragement was provided to participants during the CPET.

3.1.1.1.2 3.1.1.3 Anaerobic Threshold.

AT is a submaximal measure of CRF(100) and is discussed in detail in section 1.1.2.1.1, assessment of AT can be determined through serial measurements of blood lactate levels looking for a sharp rise in concentration(234). However, this method is invasive, requiring multiple venous blood samples and therefore has a physical cost to the individual participant and an economic cost for the assessment of multiple biological samples. More commonly AT is determined via the assessment of physiological variables of gas exchange measured via CPET. Defined as the point at which "during exercise, the oxygen consumption above which anaerobic emergency production is supplemented by anaerobic mechanisms, causing a sustained increase in lactate and metabolic acidosis"(235), AT is commonly reported using a combination of the V-slope and the ventilatory equivalents methods (as described below) to reduce interobserver variability and improve accuracy(231).

3.1.1.1.2.1 The V-slope Method.

The V-slope(236) method for determining AT is based on analysis of the slopes of gas volume curves for Oxygen (VO_2) and Carbon Dioxide (VCO_2)(236). Initially at the start of a CPET the rise of VCO_2 is slower, compared to the rate of rise of VO_2. However, as the work rate incrementally increases, the rise in the VCO_2 becomes linear with the rate of rise of VO_2, with the linear regression line of the VCO_2-VO_2 relationship termed S_1. At the point of AT,

the VCO_2-VO_2 relationship changes as the increase in VCO_2 exceeds that of VO_2 resulting in a steeper linear regression line; this is termed S_2. At the point the two linear regression lines intersect, this is the AT(231) (see figure 3.1). However, if there is no clear intersection point, the AT can be determined as the point at which the first clear marked rise in VCO_2 occurs.

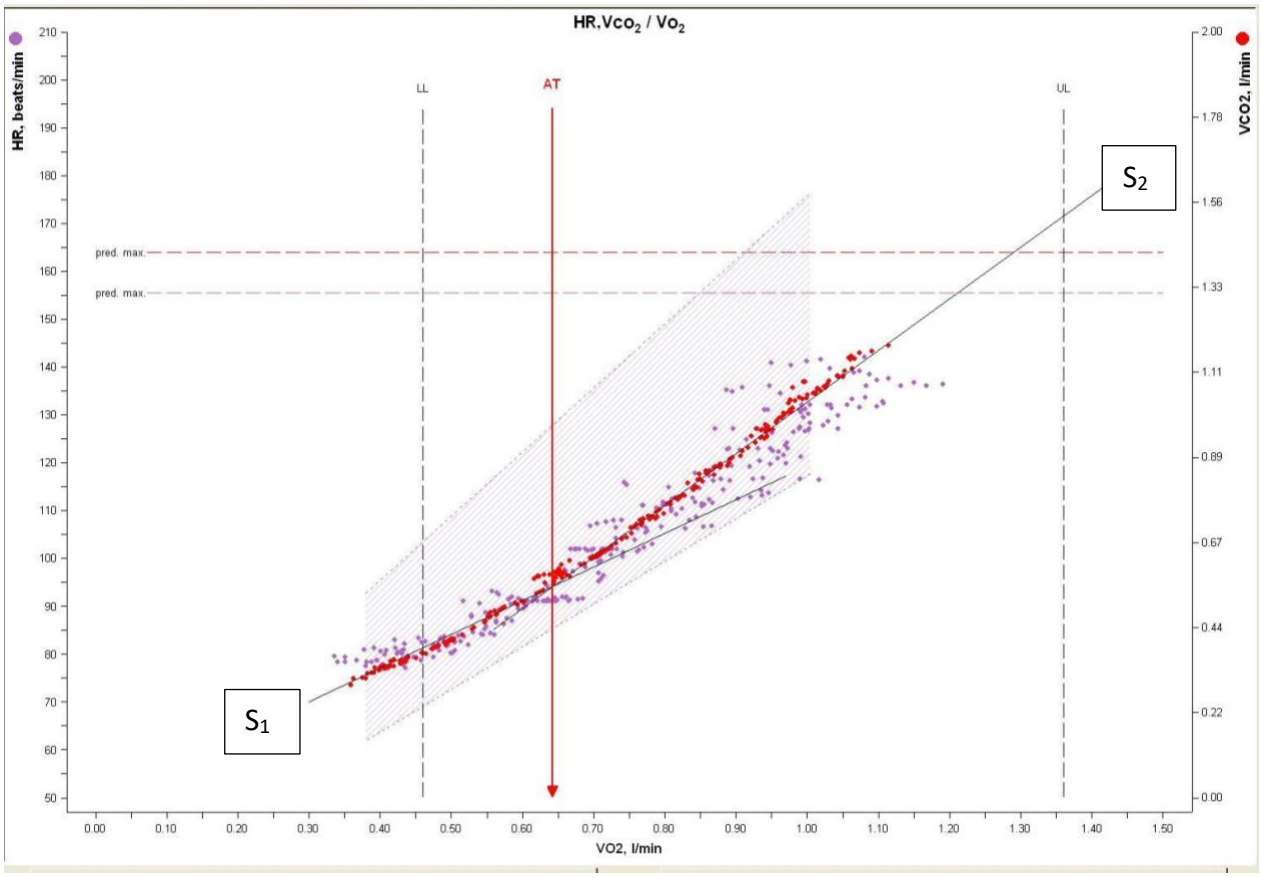


Figure 3.1: The VCO_2-VO_2 relationship graphically depicting the v-slope method for determining AT. With incremental increases in the work rate, the linear regression line of the VCO_2-VO_2 relationship is labelled S_1. Following AT, the steeper linear regression line is labelled S_2, the point of intersection of these two lines is the point of AT(231) and this point of intersection on this graph is represented by the red line labelled AT.

3.1.1.1.2.2 The Ventilatory Equivalents Method.

Prior to AT, the ventilatory response (VE) is proportional to VCO_2, therefore the partial pressure of CO_2 in the alveolus ($P_{ET}CO_2$) is similar to that in the arterial blood (PCO_2). At the point of AT there is a delay of several minutes in the respiratory mechanisms which drive hyperventilation to compensate for the increasing metabolic acidosis due to exercise and lactate production(231). Therefore, with no compensatory increase in ventilation, the VE/VCO_2 should remain constant or decrease and there should be no decrease in $P_{ET}CO_2$ as there is no hyperventilation relative to the CO_2. However, at the point of AT there will be hyperventilation relative to O_2, with VE/VO_2 increasing (see figure 3.2).

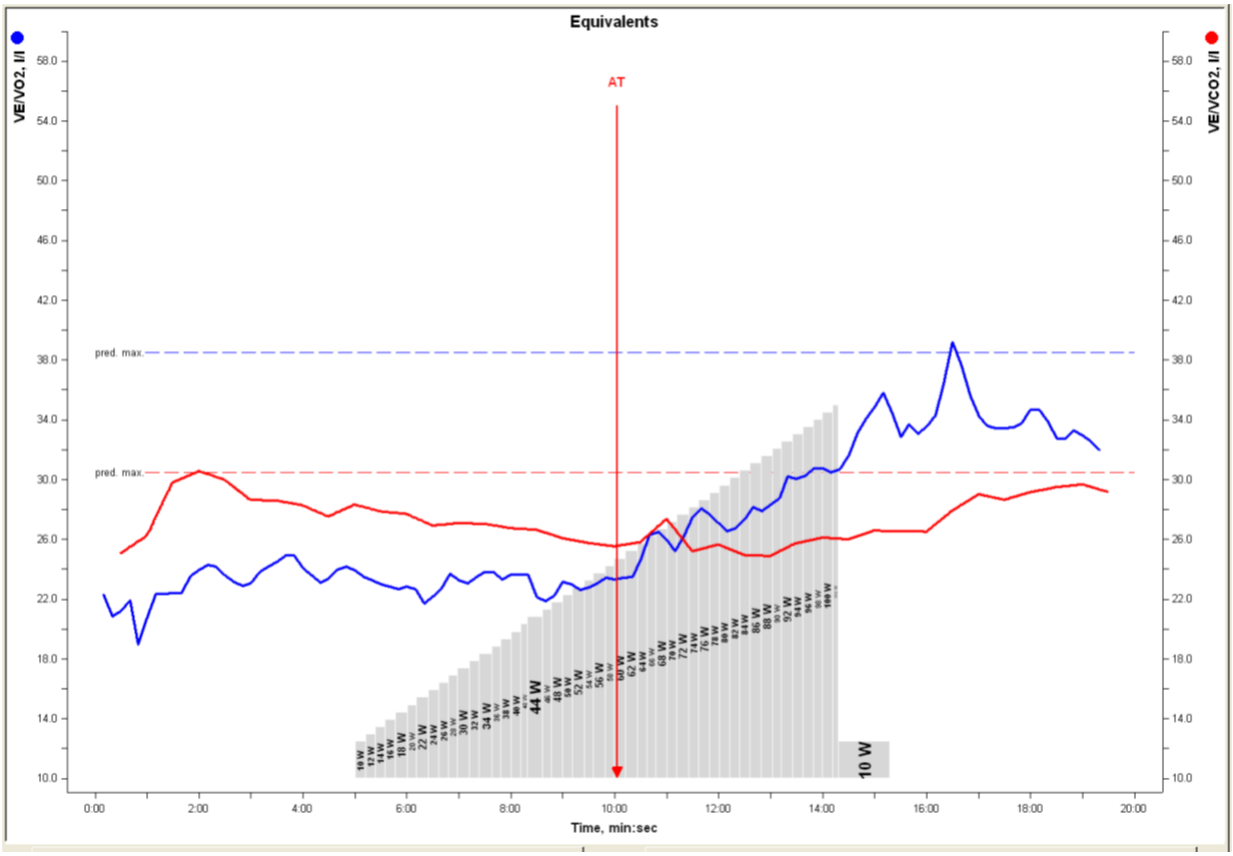


Figure 3.2: This demonstrates graphically the ventilatory equivalents method for determining AT. This shows the increase in VE/VO_2 which occurs following a relatively flat period, whilst the VE/VCO_2 demonstrates no significant change. The red line labelled AT denotes the point at which the VE/VO_2 begins to increase, equating with AT.

3.1.1.1.3 Blood Lactate levels.

Although blood lactate levels are included as a measured CPET physiological variable[234], this requires numerous repeated blood tests in short time succession and therefore have a personal cost to the participant as they can be painful and are not without risk, and also a personal and equipment cost as they required trained personal and special biochemical analysis. Blood lactate levels are not included in the Consensus clinical guidelines(231) which have been the reference used in this study to guide the conduct and physiological interpretation of CPET.

3.1.1.1.4 Normal values for CPET Variables.

Common reference values for CPET used in clinical practice are available(237)(238), however, these are not specific to the older population (Hansen et al. participants mean age of 54 years(237); Jones et. al. age range from 15 to 71 years(238)), with the values as determined by Jones et al.(238) derived from a group of healthy participants, with an equal gender split, whilst although those provided by Hansen et al.(237) arise from a population with co-morbidities such as hypertension and obesity, including some smokers, the group was all male. The consensus clinical guidelines on indications, organisation, conduct and physiological interpretation(239) therefore recommend that in interpreting a response result, the measured VO_{2peak} is related to the reference value (as chosen by the exercise laboratory), such that if the measured VO_{2peak} is >80% of the reference value it indicates this result is not abnormal (or within 95% CI), if it 71-80% of the reference value it is mildly reduced, 51-70% reflects moderation reduction and < 50% is severely reduced(239). Despite this, absolute values of AT and VO_{2peak}, indexed to body weight are commonly quoted for preoperative risk assessments, however, such values need to be treated with caution at the extremes of weight, unless ideal body weight is used(239). Reference values for VO_{2peak}, both in absolute (L/min) and relative (ml/kg/min) have been determined by Rapp et. al.(240) using a cycle ergometry based CPET (as used throughout this thesis). This study involved 10,090 healthy German individuals (6462 men and 3628 women), over an age range of 21 to 83 years (mean age 46 years). The paper provides nomograms of percentile reference values for VO_{2peak} by gender, however, they only extend up to the age of 69 years.

When CPET is used as a risk predictor for surgery to facilitate the optimisation of the patient's perioperative care, cut-points for VO_{2peak} and AT are used to relate physical fitness to morbidity, mortality and LoS outcomes for surgical specialty, these cut-points indicate values below which there is increased risk of poor outcomes in these domains, and are therefore used to guide surgical decision making and perioperative care planning, such as admission post-operatively to the intensive care unit (ITU)(112). These cut-points are specific to the type of surgery the individual is to undergo, such that for intra-abdominal surgery; increased risks associated with mortality occurs at a AT of less than 10.9 ml/kg/min, increased risk of morbidity at a AT of less than 10.1 ml/kg/min, with those patients with a AT between 10.1 and 12 ml/kg/min recommended to be treated with caution(112). Comparatively, for pancreatic surgery, increased morbidity risk is associated with a AT of less than 10-10.1 ml/kg/min(112) and for abdominal aortic aneurysm (AAA) repair surgery, a $VO_{2\ peak}$ of less than 15ml/kg/min predicts increased risk of a poor survival outcomes at 90 days post- surgery(112).

3.1.2 Alternative Measures of Physical Fitness.

The alternative measures of physical fitness to be compared to CPET in this study are the Step-box test and HGS, with muscle mass (*m. vastus lateralis* (VL) muscle architecture) also explored. Although both of these methods are commonly used in research(130)(131)(139)(140), and in some-settings in clinical practice(134)(138), review of the published data used to validate these tests, indicates that the majority of the participants involved were below 65 years of age. It is not uncommon for older participants to be excluded from research and clinical studies(241)(242), with subsequent extrapolation of findings being applied to the older population. However, the older population have physiological challenges and co-morbidities which are distinct from the younger population, therefore questioning the appropriateness and validity of these extrapolations. For example, the physicality of performing the Step-box test may impact its validity in the older adult(137).

3.1.3 Sarcopenia and Muscle Mass.

Sarcopenia, the age-associated loss of muscle mass and function(78) is, independent of CRF, linked with frailty(7), increased LoS and major post-operative complications(84), as described in more detail in section 1.2.5. However, despite low muscle mass being an independent risk factor for poor clinical outcomes(84)(243), a relationship between CRF and muscle mass has been shown across the life-course(244)(245)(246), with some evidence of this in pre-operative patient cohorts also(247). Of the various techniques used to assess the muscle mass component of sarcopenia, there is evidence to support the use of radiological assessment as a pre-operative prognostic tool(84). However, as with CPET to determine CRF, this assessment technique has significant limitations, especially for certain patient populations. For example, in cancer patients needing radiotherapy, any additional radiation burden would want to be avoided. In addition, radiological services are in high-demand and are associated with significant specialist personnel and equipment requirements.

3.1.3.1 *Defining muscle mass by its architecture.*

Skeletal muscle is a highly pliable tissue which is capable of losing and gaining contractile tissue (atrophy and hypertrophy, respectively), primarily dependent upon its use(90) and the provision of adequate (amino acid) nutrition(248). Muscle hypertrophy is associated with increased muscle thickness ($_{M}T$) as well as an increase in the pennation angle ($_{p}A$, the angle at which the oblique muscle fibres attach to the muscle tendon)(90) of the muscle, with strength increases associated with an increased $_{p}A$(90). The length of the muscle fibres can also be altered in response to clinical (e.g. ageing(249)) and/ or environmental (e.g. exercise(250)) stimuli, and like $_{p}A$, has been shown to be associated with muscle function(251), with fascicle (muscle fibre bundle) length ($_{F}L$) affecting the shortening velocity of the muscle and the peak isometric tension(90). Therefore, by measuring $_{M}T$ (which is a validated indicator of muscle mass(252)), $_{p}A$ and $_{F}L$, the relationship between muscle architecture and measures of physical fitness can be determined.

As stated above non-invasive imaging techniques such MRI can be used to measure muscle architecture(88) however, USS offers both practical and cost advantages over MRI, with MRI facilities expensive and not commonly available. In addition, many users find the MRI tubes claustrophobic and noisy. A relatively simple, cheaper and less burdensome assessment of

the aforementioned muscle architecture parameters via USS has been shown to be highly correlated to MRI(253). As such, USS assessment of muscle architecture is advocated as a safe and efficient tool for assessing aspects of muscle architecture that may be related to strength and functional capacity in older individuals(254). However, the relationship between USS-derived measures of muscle architecture and CRF is yet to be explored.

Retaining the focus on bed-side appropriate assessments, throughout this thesis muscle mass (and other aspects of muscle architecture) has been measured using USS. The method of USS assessment of muscle mass and architecture (described in detail in section 3.2.4.1.) has been shown to correlate well with MRI (the gold-standard assessment of muscle mass)(88).

3.1.4 Study aims.

The primary aim of this study was to determine the suitability of alternative, 'bed-side' methods of assessing physical fitness (HGS and step box test) as compared to the gold-standard method of physical fitness assessment (CRF by CPET) and whether these measures were sensitive enough to measure change following a 4-week partly-supervised exercise training intervention in those over 70 years of age.

The secondary aim of this study was to determine if parameters of muscle architecture ($_{M}T$, $_{p}A$, $_{F}L$) known to be associated with different aspects of physical performance, correlated with CRF determined by CPET and if changes in these parameters measured by USS reflected changes in CRF as measured by CPET following an exercise intervention.

3.1.5 Study objectives.

In order to achieve the above stated aims, the primary objective of this study was to document the relationship between simple measures of physical fitness (HGS and step-box test score), including muscle mass, with the CPET variables of VO_{2peak} and AT in healthy volunteers over 70 years of age and whether these measures could measure change in CRF in comparison to CPET following a 4-week training programme. With the secondary objective to explore the relationship between CRF and muscle mass as determined by USS.

3.2 Materials and Methods.

3.2.1 Ethical approval.

Ethical approval was granted through the University of Nottingham Faculty of Medicine & Health Sciences research ethics committee (REC) (REC reference: 16/EE/0137).

3.2.2 Participant screening and recruitment.

This study aimed to recruit healthy volunteers over the age of 70 years. Information about the study was distributed locally to various targeted groups such as the local hospital volunteers and various activity clubs (e.g. Bowls) where a high proportion of their members were aged 70 years and over. Interested participants were first provided with a detailed participant information sheet (PIS) and given a minimum of 48 hours to consider participation. For those wishing to proceed with participation after reading the PIS, they were first invited to attend a medical screening session to assess their eligibility to participate against the inclusion and exclusion criteria outlined below (Table 3.1). After providing written informed consent for the study, this screening session involved: a medical history questionnaire, a clinical examination (cardiorespiratory examination, height and weight, blood pressure (BP) and resting HR), a blood sample for haematology and biochemistry profiles, and an electrocardiogram (ECG).

INCLUSION CRITERIA

- **Male and female participants over 70 years**
- **Sufficient capacity to consent for the trial**

EXCLUSION CRITERIA

- **Participants under the age of 70 years**
- **Significant past medical history, including:**
  - **Recent myocardial infarction (within last 6 months)**
  - **Unstable angina**
  - **Heart failure (New York Heart Association class III/IV)**
  - **Uncontrolled hypertension (BP>160/100)**
  - **Taking beta blocker medication***
  - **Severe respiratory disease, including: known pulmonary hypertension (>25 mmHg), forced expiratory volume in 1 second (FEV1) <1.5 litres, brittle asthma, exercise induced asthma**
  - **Known cerebral aneurysm or abdominal aortic aneurysm**
  - **Previous stroke**
- **Metabolic disease including untreated hypo- and hyperthyroidism, hypo- or hyperparathyroidism, Cushing's disease and type I or II Diabetes**
- **Musculoskeletal, rheumatoid or neurological disorders, limiting the participants ability to undertake exercise training or study fitness assessments**
- **Body weight greater than 160kg (due to equipment limitations) and/or BMI >35kg/m^2**
- **Cognitive impairment which may reduce an individuals' ability to provide informed consent**

Table 3.1. Study inclusion and exclusion criteria. **As one method of physical fitness assessment of used in this study was the step-box test which relies on measures of HR responses to exercise, taking beta-blocker medication which affects HR variability and responses to exercise was deemed an exclusion criteria.*

As outlined in the introduction section of this chapter, older participants were the target population for this study, therefore the lower age limit was set at 70 years of age but with no upper age limit. The definition of old age is not universal or well-defined, but dependent upon context. Defining age by chronological years lived as compared to function within society, the United Nations (UN) defines old age as greater than 65 years(255), however, this only fits in a westernised society, in Africa, the World Health Organisation (WHO) describe the start of old age occurring at 50 to 55 years(256). In developed countries the notion of old age has commonly been linked to retirement age which was traditionally 60 to 65 years of age, although recently this has changed with life expectancy increasing(255) and the retirement age altering(257). Old age sub-groups such as young-old (60-69 years), middle-old (70-80 years) and very-old (80+ years)(258), provide a more realistic reflection of the ageing process in society. Therefore, by setting the lower age limit for this study to 70 years with no upper limit this allows us to include all eligible individuals defined as middle-old and very-old and falls in line with recent changes in UK retirement age(259).

3.2.3 Study visits.

If results of the screening session confirmed eligibility to participate in the study, participants were invited to attend for an assessment day on a date that was mutually convenient for the participant and the research team. On this visit each participant completed three assessments of physical function: the gold-standard CPET and the two alternative assessments of HGS and the step box test. An USS assessment of VL muscle architecture was also conducted at this visit.

3.2.4 Exercise Intervention sub-group.

The baseline study visit (V1) took the form of the study visit as described above, the data collected was included in the group analysis for comparison of the assessment measures to CPET and as the baseline data for the exercise intervention study arm. Participants then repeated these assessments on their second study visit (V2) which took place after they had completed the exercise intervention.

A familiarisation effect has been documented between repeated CPET tests(260)(261), however, these tests have often been in quick succession, within hours to days of each

other(260). Further, there is evidence to suggest a familiarisation effect may depend upon the CPET variable measured(260), with evidence available to indicate such an effect does not occur when measuring VO_{2peak}(262)(263)(264). To minimise any potential for familarisation impacting upon the measurements, a standardised short period of time was built into the CPET protocol at the start of each test to ensure the participant was familiar with the cycle ergometer. Also, the CPET tests were a minimum of 4 weeks a part (duration of exercise training programme).

3.2.5 Measurements:

3.2.5.1 *Muscle ultrasound.*

The visit started with a muscle USS of the VL of each participants' (self-nominated) dominant leg.

The muscle architecture was assessed using the methods described in full by Franchi et al.,(252). In brief, the VL muscle architecture was assessed using B-mode ultrasonography (Mylab 70, Esaote Biomedica) with a 10-15mHz, 100mm, linear array probe (Esaote Biomedica, Modle: 9600184000), see figure 3.3 below.

Figure 3.3. This picture shows the USS machine, the Mylab 70 (Esaote Biomedica) with a 10-15mHz, 100mm, linear array probe (Esaote Biomedica, Modle: 9600184000), used for assessing muscle architecture.

The participant was positioned supine on a couch such that the knee was in full extension. Muscle architecture was assessed at the mid-point along the length of the VL measured from the greater trochanter of the femur to the knee joint-line and at the midsagittal line of the muscle(252). Sagittal images were used to delineate the anterior and posterior borders (superficial and deep tendon aponeuroses, respectively) of the muscle to enable the measurement of $_{M}T$ as calculated by measuring a perpendicular line between these borders (Figure 3.4(a)). The USS probe was then aligned along the plane of the muscle fascicles(265) and the $_{p}A$ was measured at the intersection of the muscle fascicle and the deep tendon aponeurosis (Figure 3.4(b)). The length of the fascicle was directly measured in most instances, however, if the length of the fascicle ($_{F}L$) exceeded the U/S window, using the aponeuroses defining the muscle anterior and posterior borders, with extrapolation of the muscle fascicle itself, an estimation of its length was derived(252) (Figure 3.4(c)). The analysis of the ultrasound images was performed using ImageJ software (Public domain

image processing programme, National Institutes of Health, Maryland, USA) with three images obtained for each time-point.

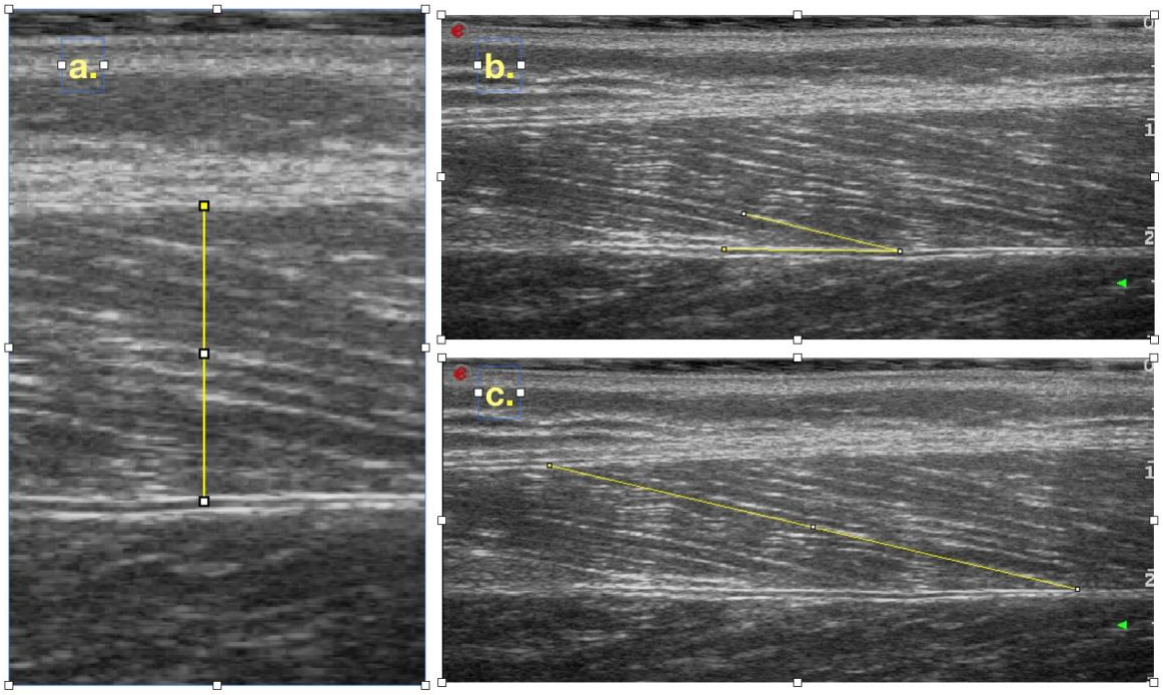


Figure 3.4.(a-c): This shows an example of the USS images obtained of the VL muscle and how these are processed using the Image J software to obtain the measurements of $_{M}T$, $_{p}A$ and $_{F}L$, (a). shows the measurement for $_{M}T$. (b). shows how the $_{p}A$ is derived and (c). shows how $_{F}L$ is measured.

3.2.5.2 *Step box test.*

The step-box test was the first physical fitness assessment conducted after the USS. The order of the tests during the assessment day was designed such that the most physically demanding test, the CPET, was completed last therefore not impacting on the ability to complete the step-box test to the best of the participants ability, also the step-box test helped to determine which ramp protocol to use for the CPET test (see section 3.2.4.4.). Various methods of using a step-box have been developed to assess physical fitness and these methods generally fall into two categories; a single stage step-test or a multi-stage step-test. A single stage step-test involves pre-determined step frequency rates which are fixed for the whole test, while the multi-stage step-test method incorporates various rates of stepping to generate a gradual increase in work rate (for example 17, 26 and 34 steps per minute as approximations of the stages in a Bruce Treadmill test protocol(130))(266). Based on the continued use of both, as reported in the literature, little consensus appears to have been reached on which, if either, of these approaches is superior(131)(130)(135)(136).

Petrella et al.,(137) devised a multi-stage step box test specifically to predict aerobic fitness in older adults, precisely the aim of this study. In this work by Petrella and colleagues, the step height was set at 60 cm for all participants and the stepping rates were “slow”, “normal walking pace” and “fast”, as determined by the individual. Predictive models based on step time, HR, age, BMI and oxygen pulse correlated well with measured VO_2max for both men and women, although no significant difference was found between the self-determined “normal” and “fast” paced stepping rates. The method was demonstrated to show no significant test re-test differences over 2 to 4 weeks and was found to be sensitive to change when utilised following an exercise intervention.

Based on the age-appropriateness of this test method, and the test re-test and sensitivity data, the step test as described by Petrella et al., was used in this study. The only difference to the step-box test described by Petrella et al., was that the step-box used in this study was a commercially available exercise step (Reebok step, group fitness equipment, designed and produced by Reebok with adjustability, and a textured surface to provide grip. Maximum user weight of 110kg) which had three height settings of 15, 20 and 25 cm, all of which are considerably lower than the 60 cm used by Petrella and colleagues (Figure 3.5). This was due to preliminary work which established that older participants found the height of the step (at 60 cm) challenging, fearing a loss of balance and were only comfortable to proceed if physical supports could be used which are not a feature of step box assessment equipment. Similarly, with an individualised step height as determined by the Culpepper and Francis equation, which accounts for height and gender differences in hip anatomy i.e.,

- **Male step height: 0.192 x height (cm)**
- **Females step height: 0.189 x height (cm)**(132)**,**

aiming for a hip angle of 73.3 degrees whilst stepping (which they found provided the optimal test conditions to derive aerobic capacity from heart rate recovery following stepping), many participants were still resistant to the step height (>30 cm).

Figure 3.5: A Reebok step box as used in this study. The figure depicts the three heights (a. 15, b. 20 and c. 25cm) that can be set.

Therefore, in this study, each participant was provided with a practice period before their assessment using the three various different step heights, after which they chose the height at which they felt most safe and comfortable. Participants were not allowed to use any aids to support their balance during the step test, although for safety a chair was placed directly behind the participants which they could use should they feel unsafe or unwell. In addition, two members of the research team were present to provide support should the participant become unsteady.

Prior to commencing the step-box test the participant's resting HR and cardiac rhythm were recorded using a three lead ECG (Mindray iMEC8 patient monitor). The participant was then asked to step at what they determined to be a "slow" pace, a "normal" pace and a "fast" pace. The slow pace for 20 steps provided familiarisation with the stepping after which they had 5 minutes rest before they commenced stepping at their normal pace. Each participant completed 20 steps at their normal pace and the time to complete this was measured (seconds) along with their maximum HR during the stepping. Their HR was also recorded in the recovery period once the participant had completed their last step; time intervals for this were 0, 5, 10, 15, 20, 25, 30, 35, 40 and 45 seconds. The participant then rested for 5

minutes or until their HR had returned to within 5 bpm of their resting value before commencing 20 steps at their self-determined fast pace with the same HR assessments as outlined above. HR was measured by a 3-lead ECG.

In order to maintain consistency of protocol across tests, members of the research team did not provide any form of encouragement during the test, they did however count the number of steps out loud.

If participants were unable to complete the step-box test due to physical difficulties, for example balance or orthopaedic comorbidities affecting the lower limbs, they were excluded from participation in the study.

3.2.5.3 *Handgrip strength.*

After a standardised 10 minutes rest, HGS was assessed using a handgrip dynamometer (Takei A 5401 hand grip dynamometer (GRIP-D, measuring range 0 – 500kg, produced by Takei, made in Japan), see Figure 3.6. Using a low-cost portable tool, HGS has been demonstrated to decline with advancing age(267) and has also been found to be independently predictive of all-cause mortality(267), cardiovascular and non-cardiovascular mortality(140), prolonged hospital LoS(139), cognitive decline and impaired health related QoL(139). As an assessment method, it has been recommended as a measure of frailty by the European Working Party on Sarcopenia in Older People (EWGSOP)(66) and therefore, was incorporated into the tests assessing physical fitness in this study.

Figure 3.6: A Takei digital handgrip dynamometer (GRIP-D, measuring range 0 – 500kg, produced by Takei, made in Japan) used to in this study.

To complete the HGS test, participants were seated with their shoulders adducted, elbows flexed at 90 degrees and forearm in the neutral position (as recommended by the American Society of Hand Therapists(268)). Three readings of maximal HGS by each hand were taken, each a minute apart and the maximum voluntary contraction for each hand recorded. The research team members did not provide any form of encouragement during the test.

3.2.5.4 *Cardiopulmonary Exercise Testing (CPET).*

After a further 10 minute rest, or until HR had returned to within 10bpm of baseline and remained at this rate for 10 minutes, the second and final physical fitness assessment completed by all participants was a CPET; the gold-standard method for assessing an individual's physical fitness(95)(96)(97)(98)(99)(100)(101). The CPET for this study was conducted using a cycle ergometer (Lode Corival Cycle ergometer, Lode, Groningen, see Figure 3.7) with an inline breath-by-breath gas analysis system (ZAN 680, nSpire Health, Colorado, USA), with breath acquisition via a tight-fitting face mask. After adjusting the mask and bike (seat height and handlebar distance) to fit, an initial rest period (3-minutes) was allowed to collect baseline data, followed 2 minutes of unloaded cycling to provide time for the participant to become familiar with the cycle ergometer and provide a physiological "warm-up". The test phase of the CPET then commenced. This test phase involved a gradual increase in work rate, with a uniform increase achieved through the use of a gradual incremental workload producing a ramp slope (Watts per minute (W/min)). As the aim for a CPET is for participants to reach their maximal effort level following 8-12 minutes of exercise(269)(270), an appropriate ramp slope for each individual must be chosen based on weight, height and reported habitual physical activity. For the participants in this study, a ramp of between 5-15W/min was considered appropriate; a lesser slope than the 25 W/min commonly used in the literature(231). As the step-box test was conducted by participants prior to CPET, it was found that the subjective assessment of the participants performance in the step-box test aided the appropriate designation of ramp slope for the CPET. Participants were instructed to maintain a cycling cadence of 50 to 60 repititions per minute (rpm) which was visually displayed to them and they were provided with verbal feedback on this throughout the test. Participants were verbally encouraged throughout the process with the aim of reaching a RER (VCO_2/VO_2) above 1.10(231) and a HR within 10 beats per

minute (bpm) of age predicted maximum *(Max HR = 208 - (0.7*Age)*(232)), as to meet the criteria for the measurement of VO_{2peak}(231).

The test was deemed complete once the participant had indicated that they had reached volitional exhaustion, which is defined as the point at which an individual is unable to perform a muscular contraction and voluntarily choose not to undertake muscular contraction(271), in this setting it was determined either by the participants inability to maintain the cadence of 50 to 60 rpm(231) or when the participant requested to stop due to an inability to continue. Once the test was completed, the load was removed, and a 5-minute recovery period commenced during which the participant continued to cycle against zero load. The participant was monitored until their HR was within 10 bpm of their baseline value and their BP had returned to baseline values.

Throughout the CPET, participants were monitored using a 12-lead ECG, non-invasive BP monitoring and pulse oximetry. As per local guidelines, CPET sessions were supervised by two individuals, at least one trained in Advanced Life Support (ALS), with termination criteria based upon the American Thoracic Society and American College of Chest Physicians statement on CPET(272).

Figure 3.7. Cycle ergometer and metabolic cart used for cardiopulmonary exercise testing (CPET).

Physiological variables measured from CPET were:

ii) VO_{2peak},

iI) AT,

iii) RER; equivalent to VCO_2/VO_2 at VO_{2peak},

iv) Ventilatory efficiency as determined by the relationship of minute ventilation (VE) to CO_2 production (VE/VCO_2) at AT and VO_{2peak}.

Two experienced assessors independently analysed the data to determine these parameters and where discrepancies arose the data was re-analysed jointly. If a consensus could not be reached a third independent assessor would review the data, although this was not required. To determine the AT, the V-slope method(236)(231) and the ventilatory equivalents methods (231)(273) were both implemented and the mean of these two values used as the final value for AT

3.2.6 Exercise training regime.

The NHS provides guidelines on physical activity for older adults(185)(274) which states that adults aged over 65 years should:

- Be physically active every day,
- Target activities which improve strength on 2 days per week,
- Incorporate physical activity to improve balance and co-ordination on at least two days a week if they are at risk of falling,
- Aim to do at least 150 minutes of moderate intensity activity or 75 minutes of vigorous activity (or a combination of the two) each week.

In relation to this, examples are given that moderate intensity activities include brisk walking, riding a bike, dancing, pushing a lawnmower, hiking, water aerobics and doubles tennis. Examples of vigorous intensity activities include running or jogging, fast swimming, singles tennis, football, hiking hills, martial arts, energetic dancing, aerobics and riding a bike fast or up hills. Although all of these activities can be performed at different intensities the NHS also provides a definition of vigorous activity being activity that "makes you breathe hard and fast… you will not be able to say more than a few words without pausing for breath". Older adults are also recommended to reduce the time spent sitting or lying down.

One point of contention around these guidelines is the lack of specificity of these to older adults(275), despite the well reported differences in physical capabilities, comorbidities and other limitations (e.g. fear of falling)(17)(276)(277) between young and older adults. To exemplify this, when comparing the government guidelines for those over 65 years to the general adult population (aged 19-64 years) the only difference is the inclusion of "older adults at risk of falls should incorporate physical activity to improve balance and co-ordination on at least two days a week" for those over the age of 65.

Despite this lack of specificity, the exercise training programme used in this study was devised based on the above government guidelines, with 4-weeks chosen as a time-frame that has been previously used to elicit gains in both muscle mass and CRF in older adults(278)(279) and also has prehabilitation potential given the pre-surgery time

constraints associated with some age-associated conditions (e.g., 31-days from decision to treat to surgery for cancer(280)).

As such, participants were required to undertake:

- 150 minutes of moderate AET per week (in the form of cycling or brisk walking), PLUS
- two sessions of supervised RET engaging all the major muscle groups, as used previously by the research group(162) (described in detail below).

An example weekly exercise schedule is shown in table 3.2.

	MON	**TUE**	**WED**	**THU**	**FRI**	**SAT**	**SUN**
ACTIVITY	RET + Supervised AET	Home-based AET	RET + Supervised AET	Rest Day	RET + Supervised AET	Home-based AET	Rest Day

Table 3.2. This table provides an example of the weekly exercise schedule for the training programme.

Rest days involved no formal physical exercise training, but activities of daily living were encouraged (e.g., house-work etc.).

The 150 minutes of AET were divided into 5, 30-minute sessions each of which could be split into minimum durations of continuous exercise of 10 minutes (e.g., 3 x 10-minute episodes). Three of the five sessions were fully-supervised by the research team with the remaining 2 unsupervised at/ from home and documented by self-report. The supervised sessions involved participants cycling at a wattage that was 50% of the wattage at VO_{2PEAK} as determined from their baseline CPET. The 2 unsupervised sessions required the participant to complete two 30-minute walks (or 60 min in >10 min episodes) across the week.

The RET programme involved 3 sets of 8 to 12 repetitions, with 90 seconds rest between each set of the same exercise(281). The exercises included were:

1) leg extension
2) leg curl
3) leg press
4) lateral pull down
5) chest press
6) chest row
7) abdominal crunches,

and was based on previous work by the group(162).

To ensure the participants trained at a sufficient intensity to elicit gains in muscle function(162) and potentially muscle mass(162)(277), the weight for each exercise was set at 70% 1 repetition maximum (1-RM) (with the exception of abdominal crunches which were unweighted), which was determined at the start of the 4-week programme and then reassessed half way through the programme to maintain training intensity with progression. 1-RM reflects the participants best single attempt at an individual exercise and is commonly measured directly(282). The direct method of assessing 1-RM, involved successive attempts, each separated by 90 to 120 seconds of rest, to lift the highest load through a full range of motion, before two failed attempts, for each exercise(281). However, for many of the participants in this study (and likely reflective of the older adult population), using weights was a new experience and there was some anxiety around this assessment, despite familiarisation. As such, some participants did not perform 1-RM for each exercise, instead this was calculated using the National Strength and Conditioning Association (NSCA)(283) training load chart from maximal attempts at a set number of repetitions, however, once confidence was gained with the equipment, the direct method for evaluating 1-RM as described was used. The supervised exercise sessions were supervised in accordance with the local divisional exercise supervision policy.

An intervention record: number of repetitions and weight per exercise, was kept for each participant with any deviations from the planned programme noted. At each supervised training session, the participants unsupervised activity was discussed and recorded.

3.2.7 Study size calculation.

3.2.7.1 *For comparison of CPET to the alternative measures of physical fitness:*

Based on previous data from the laboratory, which observed an AT <15ml/kg/min in 40% of those over the age of 75 years. Assuming an α=0.05 and a 1-β=0.80, with area under the ROC curve of 0.80 compared to the null hypothesis of 0.50, and considering the number of variables being used in the prediction model (n=5) it is estimated a minimum of 60 participants are required in order to build a model to predict CRF (VO_{2peak} and AT).

3.2.7.2 *Exercise Intervention sub-group.*

Based on a primary endpoint of change in CRF (AT) with exercise training, in order to be able to determine the ability of bed-side measures to detect these changes, an priori power calculation based on data from the laboratory suggested that to detect a minimum clinically important difference in CRF (1.5ml/kg/min)(284) with 80% power and significance at the 5% level 10 individuals would be needed to complete the pre- and post-exercise assessment visits and the intervention.

3.2.8 Statistical analysis.

Statistical analyses were performed using Prism version 9.0.2 (Graph Pad Prism 9.0.2. (134), Graph Pad Software, LLC.), with all data reported as median ± the standard error of the mean (SEM), with significance set at $p<0.05$. The muscle architecture data were correlated with the CPET-derived parameters with Pearson r correlation coefficients derived to determine the strength of the linear relationship with 95% CI and significance set at $p<0.05$. Two-tailed Student's *t* tests were used to compare before and after training values.

3.2.8.1 *The derivation of models to predicting CPET-derived VO_{2peak} and AT using alternate tests of physical function.*

To ascertain significant predictors of VO_{2peak} and AT and develop a model to determine these from the step-box test and HGS data, analyses were conducted using Stat Version 16 (TIBCO Data Science). As this was exploratory analysis, stepwise backward linear regression

was used to identify the significant predictors of VO_{2peak} and AT with $p<0.1$ required for retention in the model. Model fit is reported as R^2 with p-values for the model. Assumptions tested included linearity (via scatterplots), normality of residuals (via Shapiro Wilk test), outliers (studentised residual > 3) and homoscedasticity (Breusch-Pagan / Cook-Weisberg tests).

3.2.8.2 *Assessment of the VL architecture.*

The USS images were assessed using Image J (Image K 1.51s Wayne Rasband, National Institute of Health, USA, software in the public domain) and the raw data was entered into Microsoft Excel (Microsoft Excel version 16.43) files for calculation of mean values which were subsequently inputted into Prism version 9.0.2. (Graph Pad Prism 9.0.2. (134), Graph Pad Software, LLC.) for statistical analysis and graphical presentation.

3.3 Results.

3.3.1 Participant demographics and physiological parameters.

Sixty-four volunteers participated in the study: 35 Males and 29 Females. The median age of the participants was 74 years, with a minimum age of 65 and maximum age of 90 years. BMI was 25.9±0.44 kg/m^2. The cohort of participants was not matched for co-morbidities.

Of these 64, 18 participants were recruited to undertake the exercise intervention sub-section of this study. Of these 18, 4 did not complete the study. Of the 14 participants who completed the pre- and post-exercise training assessments and all of the training regime, the median age was 70 years, with the youngest in the group 66 and the oldest 80 years of age. The BMI and Haemoglobin (Hb) levels are provided in Table 3.3. The majority of the group were females, with only 3 males completing the study.

PHYSIOLOGICAL PARAMETER	MEDIAN	SEM
Age (years)	70	1.1
BMI	23.1	0.99
Hb (g/L)	132	2.79

Table 3.3: The participant demographics of age (years) and BMI (kg/m^2).

Of the 4 participants who did not complete the study, two were male and two were female. Two did not undertake any of the training programme, with one withdrawing after providing consent but before any tests were undertaken, and one withdrawing after the initial test session; both withdrew due to ill-health unrelated to the study. Of the remaining two participants one withdrew at the end of the first week of the training programme, citing the demand on personal time as their reason for withdrawal. The fourth participant withdrew in the final week of training due to ill-health as a consequence of vertigo, again not related to the study.

3.3.2 Main results:

3.3.2.1 *CRF as measured using CPET.*

All 64 participants completed a single CPET, with group data presented in Table 3.4 below:

PHYSIOLOGICAL PARAMETER	MEDIAN	SEM
Hb (g/L)	140	2.49
VO_{2peak} (L/min)	1.57	0.1
VO_{2peak} (ml/kg/min)	22.00	0.7
AT (L/min)	0.98	0.03
AT (ml/kg/min)	13.31	0.47
Wattage at AT	56	2.6
Wattage at VO_{2peak}	112	4.8
RER at VO_{2peak}	1.07	0.015
VE/VCO_2 at AT	26.7	0.43
VE/VCO_2 at VO_{2peak}	29.0	0.5

Table 3.4: Hb and CPET variables relating to exercise capacity. VO_{2peak} and AT are presented in units' L/min as opposed to ml/kg/min for comparison to HGS and VL architecture, both of which were not adjusted for the participants weight.

3.3.2.2 *HGS:*

All 64 participants completed a handgrip assessment. Only two of these participants were left hand dominant, the remainder were all right hand dominant. The median average grip strength for the dominant hand (average of three HGS assessments) was 29.45 (±1.11) kg, with the median value for maximum HGS 30.85 (±1.13) kg. For the non-dominant hand, the median average grip strength was 26.40 (±1.08) kg, and the median maximum grip strength

was 27.30 (±1.11) kg. Neither dominant nor non-dominant HGS was found to correlate with age or BMI (Table 3.5).

	AGE (years)	BMI (kg/m^2)
Maximum dominant HGS	R^2= 0.008 P= 0.476	R^2= 0.000 P= 0.972
Maximum non-dominant HGS	R^2= 0.023 P= 0.246	R^2= -0.000 P= 0.998

Table 3.5: Relationship between HGS and the participant demographics of age (years) and BMI (kg/m^2). R^2 and p-values presented from Pearson's correlation analysis. Dominancy assigned by each participant.

3.3.2.3 *Muscle ultrasound.*

All 64 participants had an ultrasound assessment of their VL, with MT, PA and FL obtained in all individuals (Table 3.6).

	Muscle thickness (MT) (cm)	**Pennation angle (PA) (degrees)**	**Muscle fibre length (FL) (cm)**
MEDIAN	1.918	13.58	7.190
SEM	0.058	0.390	0.127

Table 3.6. The median and SEM vales of MT, PA and FL for the 64 participants in the study.

As with HGS there was no relationship between age or BMI and any aspect of VL architecture (Table 3.7).

VL architecture:	AGE (years)	BMI (kg/m^2)
Muscle thickness (cm)	R^2= 0.108 P= 0.020	R^2= 0.075 P= 0.052
Pennation angle (degrees)	R^2= 0.278 P= 0.246	R^2= 0.001 P= 0.852
Fascicle length (cm)	R^2= 0.002 P= 0.774	R^2= 0.012 P= 0.774

Table 3.7: Relationship between the parameters of the VL architecture; MT, PT and FL determined using USS and the participant demographics of age (years) and BMI (kg/m^2). R^2 and p-values presented from Pearson's correlation analysis. Dominancy assigned by each participant.

3.3.3 Relationships between different assessments of physical function.

3.3.3.1 *CPET data and hand grip strength.*

The dominant and non-dominant HGS results significantly correlated with both VO_{2peak} and AT, with both the maximum grip strength value and the average value obtained over three assessments, demonstrating strong correlations. (Figure 3.8 a-d, Figure 3.9 a-d). The correlation between HGS and CRF was stronger for VO_{2peak} compared to AT when using data from both hands. Unsurprisingly given the relationship between VO_{2peak} and AT and the wattage at these time-points, significant correlations were evident between both the dominant and non-dominant HGS (average and maximum) and the wattage at AT (dominant maximum: $r^2 = 0.214$, $p = 0.0001$; non-dominant maximum: $r^2 = 0.242$, $p < 0.0001$) and at VO_{2peak} (dominant maximum: $r^2 = 0.409$, $p < 0.0001$; non-dominant maximum: $r^2 = 0.425$, $p < 0.0001$). There was no correlation between any aspect of HGS, irrespective of dominance or average/maximum, and the RER at VO_{2peak}.

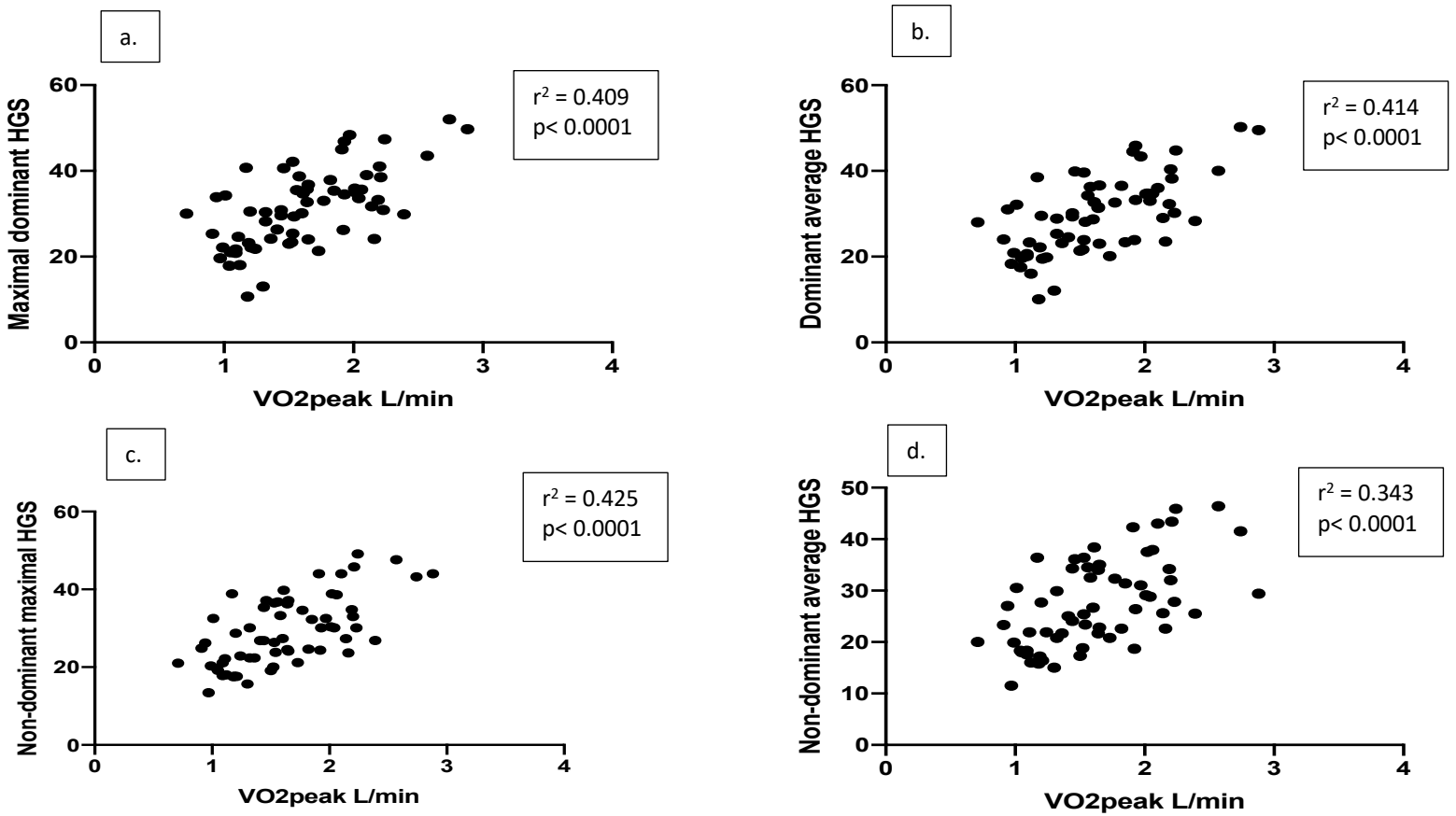


Figure 3.8: Graphical representation of the Pearson correlation between HGS and CPET VO_{2peak} (L/min). a) maximal dominant HGS and VO_{2peak}, b) dominant average HGS and VO_{2peak} c) non-dominant maximal HGC and VO_{2peak} d) non-dominant average HGS and VO_{2peak}. R^2 denotes the strength of the Pearson correlation and a $p< 0.01$ indicates the relationship is significant.

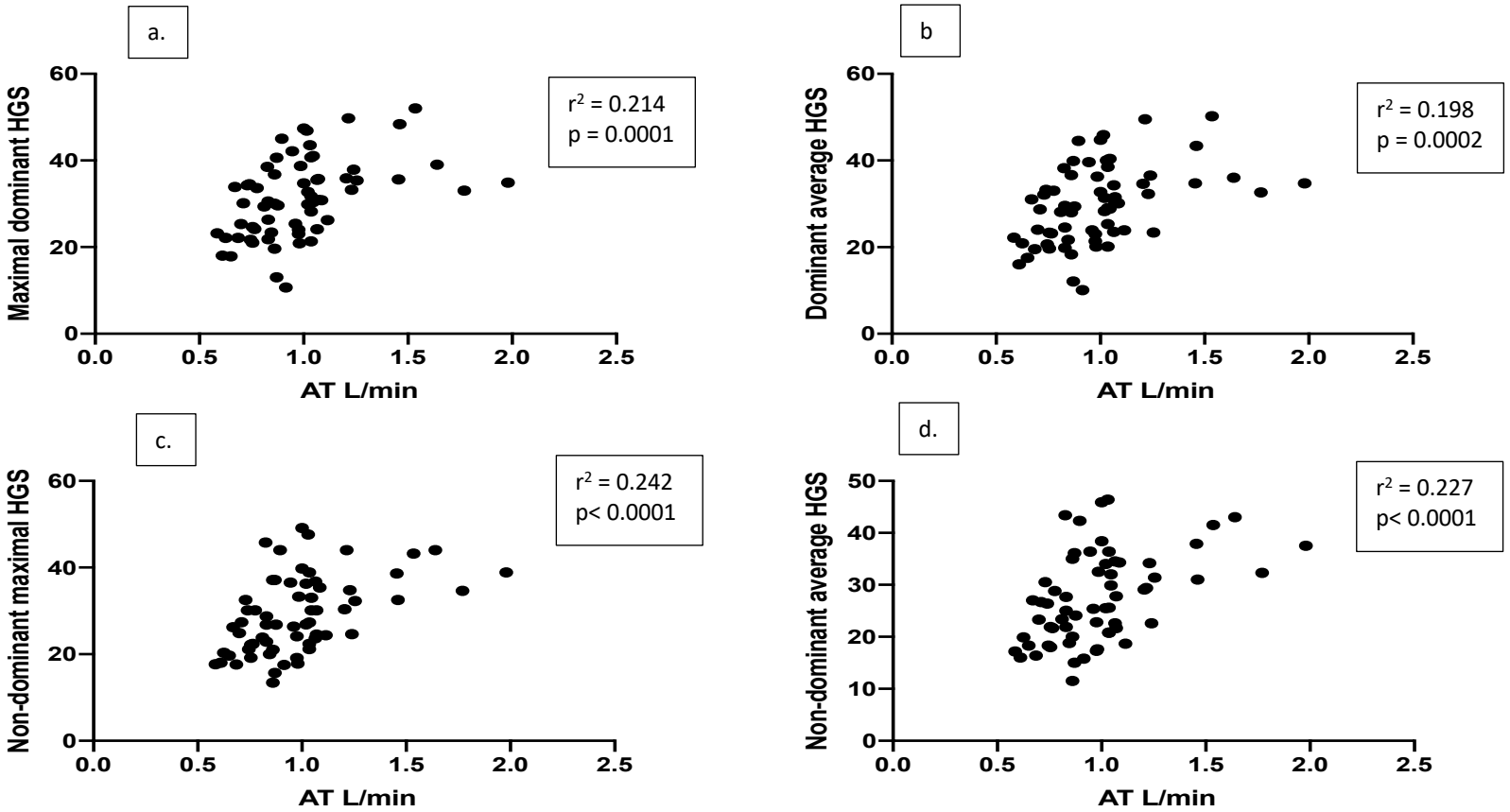


Figure 3.9: Graphical representation of the Pearson correlation between HGS and CPET AT (L/min). a) maximal dominant HGS and AT, b) dominant average HGS and AT c) non-dominant maximal HGC and AT d) non-dominant average HGS and AT. R^2 denotes the strength of the Pearson correlation and a $p< 0.01$ indicates the relationship is significant.

Considering parameters associated with respiratory function, there was no correlation between the any aspect of HGS and VE/VCO_2 at AT or at VO_{2peak} (Table 3.8).

	VE/VCO_2 at AT	VE/VCO_2 at VO_{2peak}
Dominant maximal HGS	R^2= 0.004 P= 0.662	R^2= 0.000 P= 0.998
Non-dominant maximal HGS	R^2= 0.000 P= 0.980	R^2= 0.009 P= 0.480
Dominant average HGS	R^2= 0.002 P= 0.723	R^2= 0.001 P= 0.809
Non-dominant average HGS	R^2= 0.000 P= 0.919	R^2= 0.012 P= 0.429

Table 3.8: Pearson correlation data for HGS and the CPET variables of VE/VCO_2 at AT or at VO_{2peak} reflecting respiratory function. R^2 is the Pearson correlation coefficient, the greater the number, the stronger the correlation. The p- value indicating significance if $p < 0.01$.

3.3.3.2 *CPET data and step-box test.*

The step-box test variables used as measures of CRF were the time taken for the participant to complete 20 steps at a fast pace (pace determined by the participant) (fast step-box time in seconds) and the HR recorded 45 seconds into the recovery period after completion of the 20 steps at fast pace (HR at t 45 seconds), based on previous validation of a step-box test protocol which demonstrated the HR at 45 seconds into the recovery period to be predictive of VO_{2peak}(135). On correlation with the CPET parameters, weakly significant relationships were evident between the HR recorded at 45 seconds into the recovery period of the step-box test and the CPET wattage at VO_{2peak} (R^2 = 0.002, p = 0.012) and the time taken to complete 20 fast steps and the wattage at AT, RER at VO_{2peak} and VE/VCO_2 at AT (R^2= 0.216 p = 0.0001, R^2= 0.169 p = 0.0016, R^2= 0.149 p = 0.0031).

	Fast Step-box time (s)	HR at t 45 seconds (bpm)
VO_{2peak} (L/min)	R^2= 0.070 P= 0.0360	R^2= 0.036 P= 0.134
AT (L/min)	R^2= 0.011 P= 0.590	R^2= 0.052 P= 0.145
Wattage at AT	R^2= 0.067 P= 0.0522	R^2= 0.029 P= 0.207
Wattage at VO_{2peak}	R^2= 0.216 P= 0.0001***	R^2= 0.002 P= 0.012*
RER at VO_{2peak}	R^2= 0.169 P= 0.0016**	R^2= 0.003 P= 0.896
VE/VCO_2 at AT	R^2= 0.149 P= 0.0031**	R^2= 0.000 P=0.916
VE/VCO_2 at VO_{2peak}	R^2= 0.009 P= 0.494	R^2= 0.002 P= 0.774

Table 3.9: Pearson correlation data for the step-box data (the time taken to complete the 20 steps at a fast pace, and the HR, 45 seconds into the recovery period) and the CPET variables. VO_{2peak} and AT are presented in units' L/min as opposed to ml/kg/min for comparison to HGS and VL architecture, both of which were not adjusted for the participants weight. R^2 is the Pearson correlation coefficient, the greater the number, the stronger the correlation. The p- value indicating significance if $p < 0.01$.

3.3.3.3 *HGS and Step-box measures of CRF.*

There was no significant relationship established between the step-box measures of CRF and either the dominant or non-dominant measures of HGS (Table 3.10).

HGS measures:	Fast Step-box time (s)	HR at t 45 seconds (bpm)
Maximum dominant HGS	R^2= 0.024 P= 0.227	R^2= 0.050 P= 0.075
Non-dominant maximal HGS	R^2= 0.011 P= 0.408	R^2= 0.052 P= 0.071
Dominant average HGS	R^2= 0.025 P= 0.220	R^2= 0.053 P= 0.068
Non-dominant average HGS	R^2= 0.006 P= 0.539	R^2= 0.057 P=0.061

Table 3.10: Figure Relationship between the step-box data (the time taken to complete the 20 steps at a fast pace, and the HR, 45 seconds into the recovery period) and HGS. R^2 and p-values presented from Pearson's correlation analysis. Dominancy assigned by each participant.

3.3.4 Muscle (VL) architecture, CPET, HGS and step-box test.

The secondary objective of this study was to explore the relationship between muscle mass as measured using USS and CRF.

No aspect of muscle (VL) architecture ($_{M}T$, $_{p}A$ nor $_{F}L$) was found to correlate with any CPET-derived parameter of CRF (Table 3.11).

	Muscle thickness ($_{M}T$)	Pennation angle ($_{p}A$)	Fascicle length ($_{F}L$)
VO_{2peak} (L/min)	R^2= 0.0.30 P= 0.227	R^2= 0.001 P= 0.862	R^2= 0.066 P= 0.069
AT (L/min)	R^2= 0.015 P= 0.387	R^2= 0.008 P= 0.522	R^2= 0.034 P= 0.196
Wattage at AT	R^2= 0.015 P= 0.410	R^2= 0.005 P= 0.630	R^2= 0.057 P= 0.107
Wattage at VO_{2peak}	R^2= 0.001 P= 0.794	R^2= 0.000 P= 0.999	R^2= 0.050 P= 0.113
RER at VO_{2peak}	R^2= 0.000 P= 0.940	R^2= 0.007 P= 0.578	R^2= 0.030 P= 0.253
VE/VCO_2 at AT	R^2= 0.004 P= 0.681	R^2= 0.014 P= 0.425	R^2= 0.001 P= 0.866
VE/VCO_2 at VO_{2peak}	R^2= 0.014 P= 0.435	R^2= 0.039 P= 0.187	R^2= 0.000 P= 0.930

Table 3.11: Pearson correlation data for the parameters of VL architecture; $_{M}T$, $_{p}A$ and $_{F}L$ determined using USS and the CPET variables. VO_{2peak} and AT are presented in units' L/min as opposed to ml/kg/min for comparison to HGS and VL architecture, both of which were not adjusted for the participants weight. R^2 is the Pearson correlation coefficient, the greater the number, the stronger the correlation. The p- value indicating significance if $p < 0.01$.

Similarly, there was no relationship between any muscle architecture parameter and HGS or step-box test measure (Tables 3.12 and 3.13 respectively).

HGS:	Muscle thickness ($_{M}T$)	Pennation angle ($_{p}A$)	Fascicle length ($_{F}L$)
Dominant maximal HGS	R^2= 0.001 P= 0.833	R^2= 0.008 P= 0.532	R^2= 0.012 P= 0.443
Non-dominant maximal HGS	R^2= 0.002 P= 0.769	R^2= 0.020 P= 0.331	R^2= 0.018 P= 0.359
Dominant average HGS	R^2= 0.000 P= 0.992	R^2= 0.016 P= 0.373	R^2= 0.008 P= 0.542
Non-dominant average HGS	R^2= 0.004 P= 0.689	R^2= 0.015 P= 0.393	R^2= 0.018 P= 0.355

Table 3.12: Pearson correlation data for the parameters of the VL architecture; $_{M}T$, $_{p}A$ and $_{F}L$ determined using USS and HGS. Dominancy assigned by each participant. R^2 is the Pearson correlation coefficient, the greater the number, the stronger the correlation. The p- value indicating significance if $p < 0.01$.

VL architecture:	Fast Step-box time (s)	HR at t 45 seconds (bpm)
$_{M}T$ (cm)	R^2= 0.000 P= 0.942	R^2= 0.000 P= 0.958
$_{p}A$ (degrees)	R^2= 0.015 P= 0.400	R^2= 0.016 P= 0.376
$_{F}L$ (cm)	R^2= 0.005 P= 0.623	R^2= 0.070 P= 0.061

Table 3.13: Pearson correlation data for the parameters of the VL architecture; $_{M}T$, $_{P}A$ and $_{F}L$ determined using USS and the step-box data (the time taken to complete the 20 steps at a fast pace, and the HR, 45 seconds into the recovery period). R^2 is the Pearson correlation coefficient, the greater the number, the stronger the correlation. The p- value indicating significance if $p < 0.01$.

3.3.5 Predicting CPET-derived VO_{2peak} and AT using alternate tests of physical function.

3.3.5.1 *Predicting VO_{2peak}.*

Stepwise backward linear regression revealed that VO_{2peak} can be predicted to some extent from the fast step-box time, gender and BMI (Table 3.14). As resting HR, HR 45 seconds into recovery, dominant hand maximum HGS and age all had a $p>0.1$ in on stepwise backward linear regression (Table 3.15), suggesting no predictive ability, they were not retained in the development of a predictive model.

For: VO_{2peak} (ml/kg/min)	**Coefficient**	**Std. Error.**	**t**	**P> |t|**	**95% CI**
Fast step box time (s)	-0.201	0.062	-3.23	0.002	-0.326 - -0.765
Gender	4.716	1.155	4.08	0.000	2.403 – 7.030
BMI (kg/m^2)	-0.643	0.173	-3.72	0.000	-0.989 - -0.297
Constant	39.09	5.077	7.70	0.000	28.922 – 49.263

Table 3.14: Model data to determine VO_{2peak} based on the variables with predictive ability as determined by the stepwise linear regression of the data.

For: VO_{2peak} (ml/kg/min)	**Stepwise backward linear regression**
Age	P = 0.554
Resting HR	P = 0.933
Dominant maximal HGS	P = 0.151
Fast Hr t 45s recovery	P = 0.797

Table 3.15: Stepwise backward linear regression data for determining the VO_{2peak} using the maximum dominant HGS variable and the variables from the Step-box test including, the fast step-box time and the HR t45 recovery.

Taking the variables with predictive ability, the model for VO_{2peak} (y = a + bx) is as follows:

- **VO_{2peak} (ml/kg/min) = 39.1 + (fast step box time x-0.2) + (gender x 4.7) + (BMI x -0.64)**,
  (Gender scored: 1=female, 2 = male).

with this model achieving an R^2 of 40% (40% of the variability in the VO_{2peak} is explained by these variables).

With a probability of 0.423, (greater than the 0.05 alpha level) the Shapiro Wilk test ascertained the data is normally distributed. The data was also determined not be heteroskedastic (The Breusch-Pagan/Cook-Weisberg test, Probability > chi2 = 0.475).

In addition, although maximum HGS was deemed non-predictive as an independent parameter, in an attempt to present the simplest (by assessment methods) prediction model it was found that dominant HGS can be used to predict VO_{2peak} in conjunction with BMI (Table 3.16); although the R^2 was only 36%:

For: VO_{2peak} (ml/kg/min)	**Coefficient**	**Std. Error.**	**t**	**P> |t|**	**95% CI**
Dominant maximal HGS	0.297	0.678	4.38	0.000	0.161 – 0.433
BMI (kg/m²)	-0.707	0.176	-4.00	0.000	-1.06 - -0.353
Constant	31.648	4.874	6.49	0.000	21.892 – 41.405

Table 3.16: Model data to determine the equation for VO_{2peak} based on the variables with predictive ability as determined by the stepwise linear regression of the data.

- **VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.707)**

The Shapiro Wilk test demonstrated a probability of 0.378, (greater than the 0.05 alpha level) indicating the data is normally distributed. The data was also determined not be heteroskedastic (The Breusch-Pagan/Cook-Weisberg test, Probability > chi2 = 0.936).

Achieving a slightly higher R^2 than that predicted by fast step box-time, gender and BMI, the maximum HGS of the non-dominant hand in conjunction with BMI and the fast step-box time was able to predict VO_{2peak} with an R^2 of 45% (Table 3.17) and as such was our most powerful predictive model for the determination of VO_{2peak} from bed-side-suitable assessments.

For: VO_{2peak} (ml/kg/min)	**Coefficient**	**Std. Error.**	**t**	**P> |t|**	**95% CI**
Non-dominant maximum HGS	0.310	0.065	4.79	0.000	0.180 – 0.440
Step-box fast time (s)	-0.156	0.060	-2.59	0.000	0.277 - -0.035
BMI (kg/m²)	-0.657	0.167	-3.93	0.000	-0.993 - -0.322
Constant	36.064	5.054	7.14	0.000	25.936 – 46.193

Table 3.17: Model data to determine the equation for VO_{2peak} based on the variables with predictive ability as determined by the stepwise linear regression of the data.

- **VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66)**.

The Shapiro Wilk test demonstrated a probability of 0.411, (greater than the 0.05 alpha level) indicating the data is normally distributed. The data was also determined not be heteroskedastic (The Breusch-Pagan/Cook-Weisberg test, Probability > chi2 = 0.805).

Of note, it was not possible to predict the VO_{2peak} using only patient demographic data and non-dominant HGS, suggestive that two forms of physical fitness assessment are required to develop a predictive model of VO_{2peak} when using non-dominant HGS data.

3.3.5.2 *Predicting AT (ml/kg/min).*

It was not possible to derive a significantly reliably model to predict AT from the dominant maximal HGS test or step box-test variables as stepwise backward linear regression revealed that each parameter had a P>0.01 (Table 3.18). On analysis of the non-dominant maximal HGS data, only a weak model (R^2 =19%) between this variable and BMI could be drawn on stepwise backward linear regression (Tables 3.19 and 3.20).

For: AT (ml/kg/min)	**Stepwise backward linear regression**
Age	P = 0.1986
Resting HR	P = 0.36
Dominant maximal HGS	P = 0.7149
Fast step box time	P = 0.4735
Fast Hr t 45s recovery	P = 0.6845
Slow step box time	P = 0.8646

Table 3.18: Model data to determine AT based on the variables with predictive ability as determined by the stepwise linear regression of the data.

For: AT (ml/kg/min)	**Stepwise backward linear regression**
Age	P = 0.1986
Resting HR	P = 0.58
Non-dominant maximal HGS	P = 0.7149
Fast step box time	P = 0.407
Fast Hr t 45s recovery	P = 0.768

Table 3.19: Model data to determine AT based on the variables with predictive ability as determined by the stepwise linear regression of the data.

For: AT (ml/kg/min)	**Coefficient**	**Std. Error.**	**t**	**P> |t|**	**95% CI**
Non-dominant maximum HGS	0.129	0.053	2.43	0.018	0.023 – 0.234
BMI (kg/m^2)	-0.394	0.137	-2.86	0.006	-0.669 - -0.118
Constant	20.33	3.732	5.45	0.000	12.86 – 27.80

Table 3.20: Model data to determine the equation for AT based on the variables with predictive ability as determined by the stepwise linear regression of the data.

- **AT (ml/kg/min) = 20.3 + (Non-dominant maximal HGS x 0.129) + (+ (BMI x -0.394)**.

On further analysis of the data, the Shapiro Wilk test demonstrated a probability of 0.0001, (less than the 0.05 alpha level) indicating the data was not distributed. The data was also determined to be heteroskedastic (The Breusch-Pagan/Cook-Weisberg test, Probability > chi2 = 0.005).

3.3.6 The model incorporating HGS, step-box test and BMI parameters to determine VO_{2peak} and measures of VL architecture.

Using the equation to determine VO_{2peak} as derived above based on the HGS, step-box data and BMI:

VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66).

No relationship was evident between the VO_{2peak} and the parameters of VL architecture (Table 3.21)

	Step-box derived VO_{2peak} (ml/kg/min)
$_{M}T$ (cm)	R^2= 0.026 P= 0.256
$_{P}A$ (degrees)	R^2= 0.028 P= 0.241
$_{F}L$ (cm)	R^2= 0.006 P= 0.598

Table 3.21: Pearson correlation data for the parameters of the VL architecture; $_{M}T$, $_{P}A$ and $_{F}L$ determined using USS and the VO2peak as determined from the model based upon HGS, step-box data and BMI (VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66)). R^2 is the Pearson correlation coefficient, the greater the number, the stronger the correlation. The p- value indicating significance if $p < 0.01$.

3.3.7 Exercise Intervention arm of the study:

3.3.7.1 *Intervention compliance.*

The participants were requested to undertake a total of 12 supervised training sessions (three per week) in a 4-week period, with attendance at 6 sessions or less resulting in exclusion from the study. Of the 14 participants included in final analysis, two completed all 12 training sessions, 4 completed 11 sessions, 1 attended 9 sessions, 2 attended 8 sessions and 2 participants completed 7 sessions. For a number of the participants their attendance at sessions was impacted by a period of very difficult weather with snow preventing their attendance. A number of the participants continued to work or volunteer in some capacity and reported that this affected their ability to attend all sessions.

The training programme required the participants to undertake home-based AET on two days of each week. Adherence to this was to be monitored through use of a diary, however, the participants verbally reported their home-based activities on attendance at training sessions. The participants were all very active and motivated, with a number working as volunteers at Royal Derby Hospital (RDH) and attending gym-based group activities such as aqua-aerobics, two were active members of local bowling clubs which held meetings at least once a week and one was in training for a pilgrimage through northern Spain within 2 months of completing the training programme. All participants therefore reported activities undertaken out with of the training sessions which in the main exceeded the required AET to be completed as part of the training programme.

All participants were physically able to complete the AET at 50% of their maximum wattage as determined from their baseline CPET. With regards to the RET, only one participant had undertaken any form of exercise training using weights in the past and therefore, the majority were quite anxious about using weights and underestimated their ability to do this. When attempting the 1-RM assessment in order to determine their training intensity, a number of participants were reluctant to do this and therefore with gradual familiarity and introduction to RET a modified assessment was used to determine 1-RM using the National Strength and Conditioning Association (NSCA) training load chart(283). Training intensity was then set at 70% of their estimated 1-RM. However, over the course of the RET, participants grew more confident in their abilities and were reassured as to the safety of the exercises. As such, many of the participants pushed themselves to progressively lift heavier weights and undertake more repetitions, consequently the 1-RM was re-evaluated directly, see Table 3.22.

	Leg extension	Leg curl	Leg press	Chest row	Chest press	Chest pull down
1	30Kg	15Kg	35Kg	25Kg	15Kg	25Kg
2	15Kg	10Kg	20Kg	20Kg	10Kg	10Kg
3	60Kg	55Kg	55Kg	25Kg	25Kg	25Kg
4	20Kg	35Kg	30Kg	20Kg	20Kg	10Kg
5	50Kg	40Kg	70Kg	25Kg	10Kg	40Kg
6	10Kg	20Kg	30Kg	10Kg	10Kg	20Kg
7	20Kg	30Kg	50Kg	40Kg	10Kg	35Kg
8	35Kg	35Kg	80Kg	45Kg	50Kg	45Kg
9	30Kg	30Kg	35Kg	30Kg	40Kg	30Kg
10	30Kg	35Kg	55Kg	35Kg	30Kg	30Kg
11	30Kg	30Kg	50Kg	35Kg	15Kg	30Kg
12	25Kg	20Kg	30Kg	25Kg	10Kg	20Kg
13	30Kg	20Kg	30Kg	35Kg	15Kg	20Kg
14	20Kg	10Kg	25Kg	35Kg	10Kg	20Kg

Table 3.22. The 1-RM as determined (direct measurement(281)) for each participant for each weight bearing exercise in the training programme.

3.3.7.2 *Baseline physical function.*

Reference values for CPET data are available. As discussed in section 3.1.1.1.3. it is necessary to understand the demographics of the sample group these values are derived from to ensure where possible these align with those of the study group considered. To account for such differences the consensus clinical guidelines on indications, organisation, conduct and physiological interpretation(239) have made recommendations as detailed in section 3.1.1.1.3. Therefore, the reference values for this study are taken from the Rapp et. al.(240) paper which provides percentile reference values for absolute VO_{2peak} by gender and up to an age of 69 years. Although this age limit falls short on comparison to the age of many of the participants in this study, the other studies commonly used in the clinical setting(237)(238) do not provide reference values by age and are based on samples with a low mean age or broad age range (mean ages of 54 years(237); age range from 15 to 71 years(238)), therefore, where the age of the participant is matched to the normogram where possible, or the value pertaining to the maximum age denoted on the normogram (69 years) is used.

The values for VO_{2peak} (absolute L/min) for each participant measured pre- and post- the 4 week exercise intervention are detailed in Table 3.23 below, alongside the reference percentile value. This reference value denotes the percentage of the reference population which had a VO_{2peak} below that of the participant assessed.

Participant number.	Age (years).	T1 Measured VO2peak (L/min)	Percentile (%)	T2 Measured VO_{2peak} (L/min)	Percentile.(%)
1	68	1.6	74	1.4	59
2	69	1.5	66	1.9	94
3	74	1.1	8	1.0	8
4	71	1.2	20	1.53	66
5	69	1.8	91	2.4	98
6	69	0.9	4	1.3	30
7*	75	1.2	5	1.5	6
8	75	1.2	20	1.4	44
9	69	2.1	96	2.29	98
10	76	1.6	79	1.6	79
11	70	1.1	8	1.2	20
12	75	1.4	44	1.6	79
13*	66	1.5	3	1.6	6
14*	80	1.1	0	1.2	0

Table 3.23. This table depicts the 14 participants, * denotes Male gender, for each participant the absolute VO_{2peak} (L/min) measured pre- exercise (T1) and post (T2), with the respective reference percentile range this value corresponds to based on reference normograms of absolute VO_{2peak} (L/min) by age and gender(240). The percentile figure quoted denotes the percentage of the reference population with a lower VO2peak value than that of the measured value (the participant).

3.3.7.3 *Change in physical function.*

Evidencing intervention efficacy, strength as a composite of assessments across the body (3-upper and 3-lower body exercise) was significantly improved by the exercise training intervention (807 vs 1193 with SEM, 154.4, 197.5 $p<0.002$) (Figure 3.10).

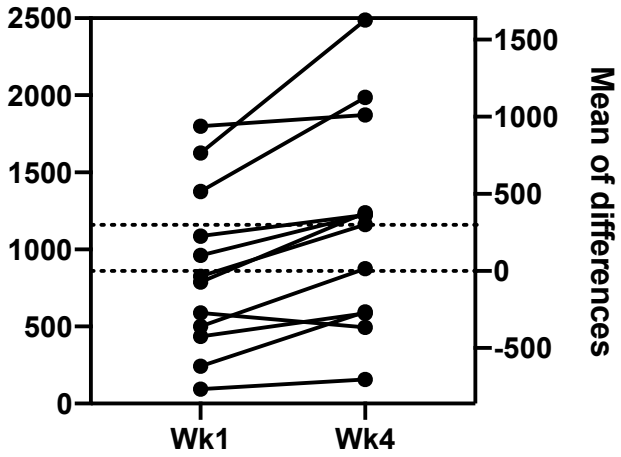


Figure 3.10: This shows the comparison of the composite assessments (mean value for each participant) undertaken on week 1 compared to week 4. Students *t* test R^2 0.585, p < o.o1 denoting significance.

The only other variables which showed a significant change following the exercise training period were those related to CRF as determined by CPET (Figure 3.11.a.-d.). Both VO_{2peak} (1.4 vs 1.6 L/min with SEM 0.09, 0.10, p<0.01) and AT (0.85 vs 1.02 L/min with SEM 0.06, 0.089, p< 0.01) increased with exercise training, and this was true for both absolute (l/min) and relative values (VO_{2peak}: 21.7 vs 24.6 ml/kg/min with SEM, 1.06, 1.4 P<0.01; AT: 13.48 vs 16.15 ml/kg/min with SEM, 0.90, 1.25 p<0.01) (See Figure 3.11.a.-d.). The main increase in absolute VO_{2peak} was 0.17 l/min^{-1} was observed, with an increase in relative VO_{2peak} of 2.9 $ml/kg/min^{-1}$. Similarly, absolute AT increased by 0.17 l/min^{-1}, with an increase in relative AT of 2.7 $ml/kg/min^{-1}$.

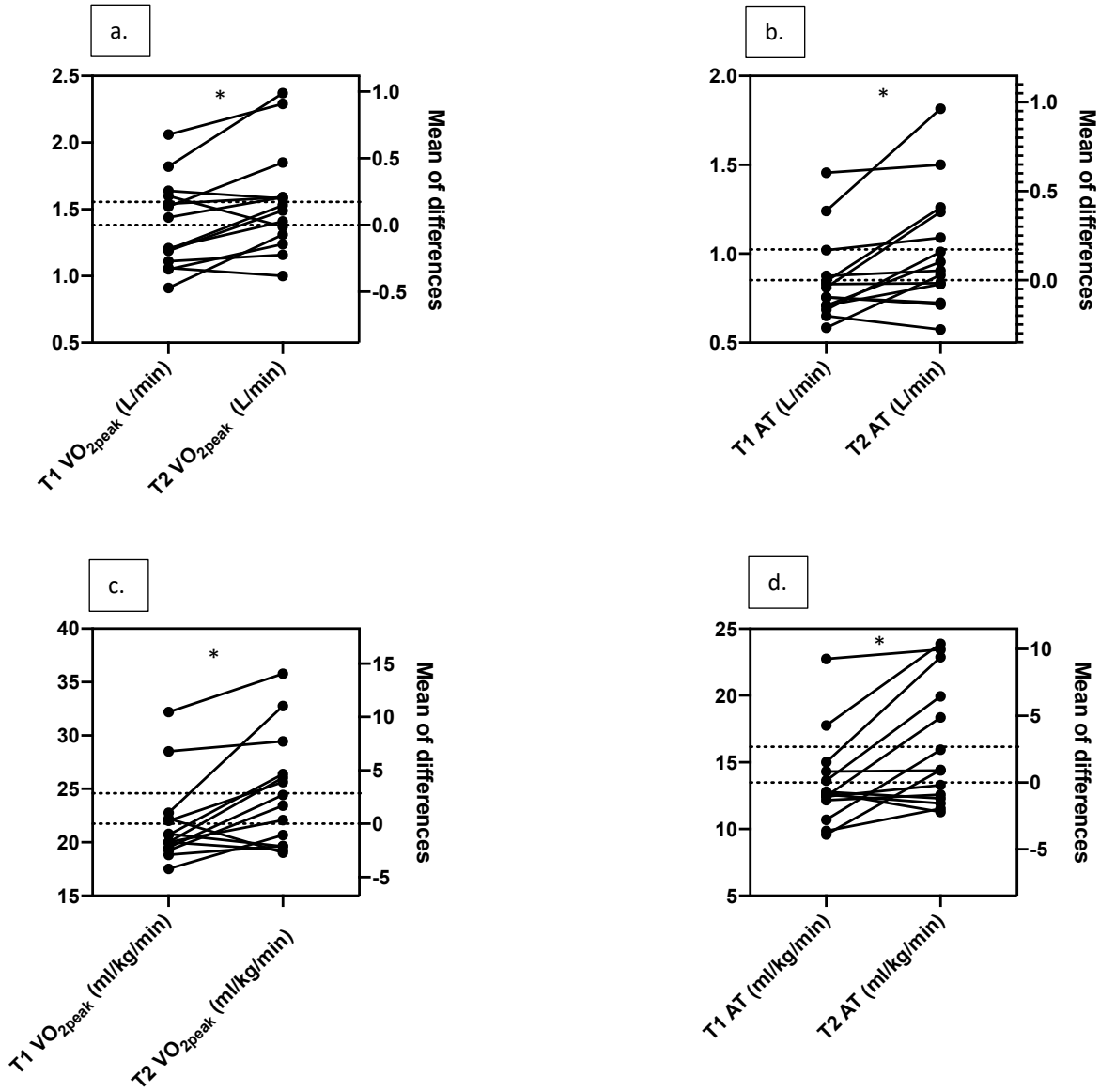


Figure 3.11: CPET variables for the assessment of CRF at baseline (T1) and following the 4-week exercise training intervention T2. Both absolute (L/min) and relative values (ml/kg/min) are compared and presented: a. VO_{2peak} (L/min) and b. AT (L/min), c. VO_{2peak} (ml/kg/min with SEM) and d. AT (ml/kg/min). Analysis via paired Students *t* test. *=p<0.01 between timepoints.

There was no significant change in any aspect of HGS; maximum or average for dominant (maximum: 27.4 vs 27.6 with SEM 1.5, 1.7, p = 0.774; average: 26.2 vs x 25.9 with SEM 1.6,1.7 p = 0.513) or non-dominant hand (maximum: 24.8 vs 24.4 x with SEM,1.7, 1.9 p = 0.608; average: 23.6 vs 23.1 with SEM 1.7,1.8 p = 0.469), following the exercise training programme (Figure 3.12 a.-d.).

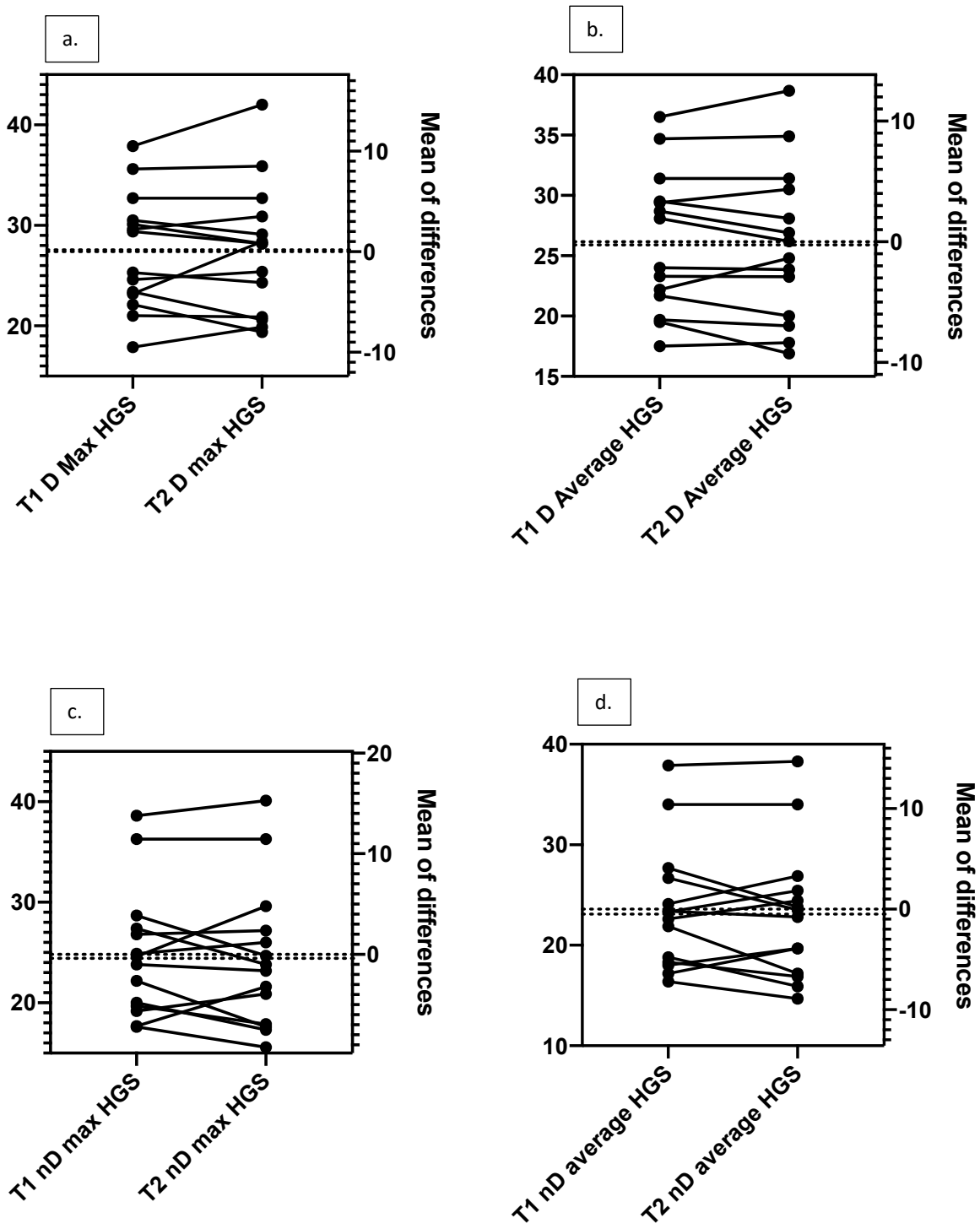


Figure 3.12: Comparison of the HGS variables for the assessment of CRF at baseline (T1) and following the 4-week exercise training intervention T2. D = dominant hand, nD = non-dominant hand, max = maximum, average represents the average of the three tests performed. a. D max HGS b. D average HGS, c. nD max HGS, d. nD average HGS. Analysis via paired Students *t* test. *=p<0.01 between timepoints.

There was no significant change in any aspect of step-box test data; fast time (31.2s vs 30.5s with SEM, 1.8, 1.8 p = 0.167), HR t 45 recovery (93.4bpm vs 91.6bpm with SEM,2.2, 2.6 p = 0.45) after the exercise training programme (figure 3.13 a.-d.).

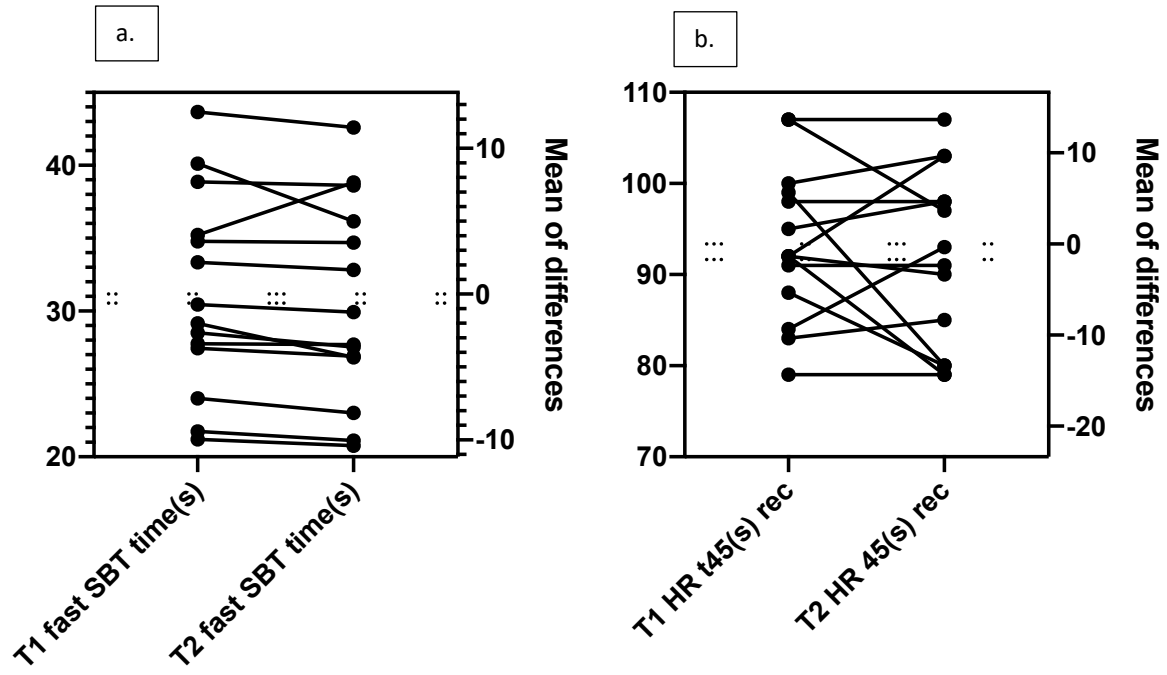


Figure 3.13: SBT variables for the assessment of CRF at baseline (T1) and following the 4-week exercise training intervention T2. A. Fast time refers to the time taken to complete 20 steps at a fast pace as determined by the participant. B. HR t45(s) is the HR recorded at 45 seconds into the recovery period. Analysis via paired Students *t* test. *=p<0.01 between timepoints.

As discussed in the introduction, in chapter 3, 2 equations were derived for predicting VO_{2peak} from the alternative measures of CRF, HGS and the step-box test.

- VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66). (R^2 45%).

- VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.70) (R^2 36%).

No significant difference was found for VO_{2peak} when comparing the baseline data to that following 4 weeks of exercise training using as either of the derived equations above (see figure 3.14.a.-b.).

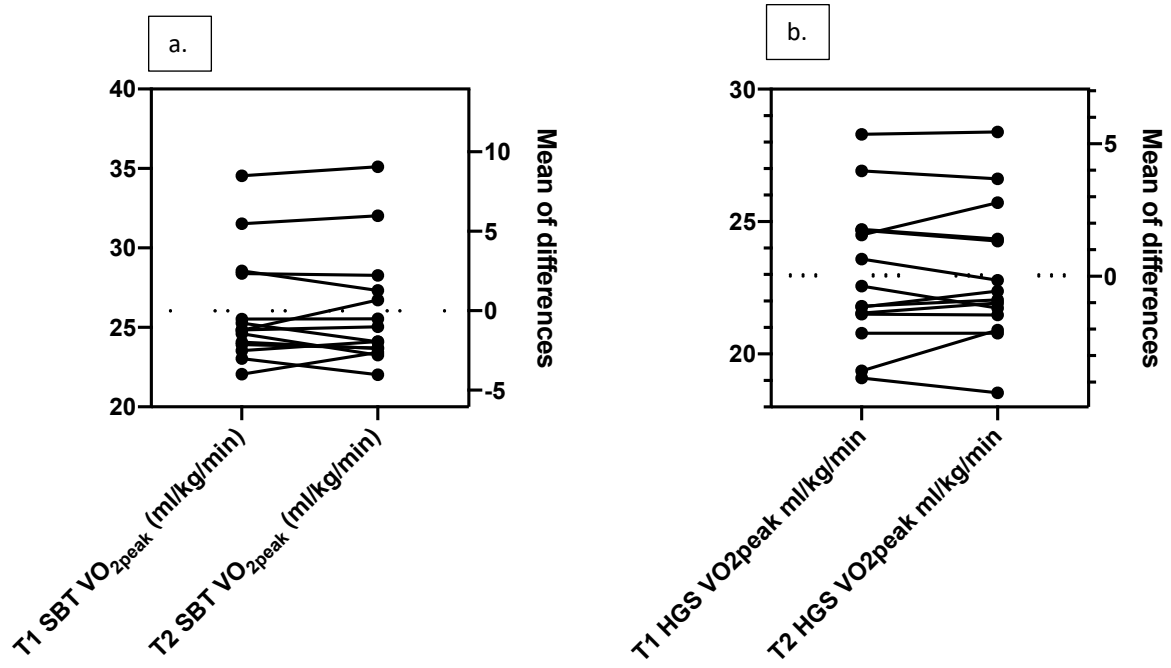


Figure 3.14: VO_{2peak} before (T1) and after 4 weeks of exercise training (T2) as derived from the two equations a. VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66), 26.05 vs 26.02 with SEM, 0.94, 0.98 p = 0.914. and b. VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.70) (R^2 36%) 22.94 vs 22.99 with SEM, 0.94, 0.98 p = 0.774. Analysis via paired Students *t* test. *=p<0.01 between timepoints.

Muscle mass

As with HGS and step-box test parameters, there was no change in any parameter relating to muscle mass/ architecture after the exercise training programme (see Figure 3.15.a.-c.). When assessing the relationship between changes in these muscle architecture parameters and changes in CPET-derived VO_{2peak} (chosen as the CPET parameter to maintain consistency with the equation-predicted outcome) there was no relationship between change in $VO_{2\ peak}$ and change in $_{M}T$ (R^2 0.076, p=0.339), $_{P}A$ (R^2 0.0007, p=0.930) or $_{F}L$ (R^2 0.0215, p=0.617) (Refer to Table 3.24).

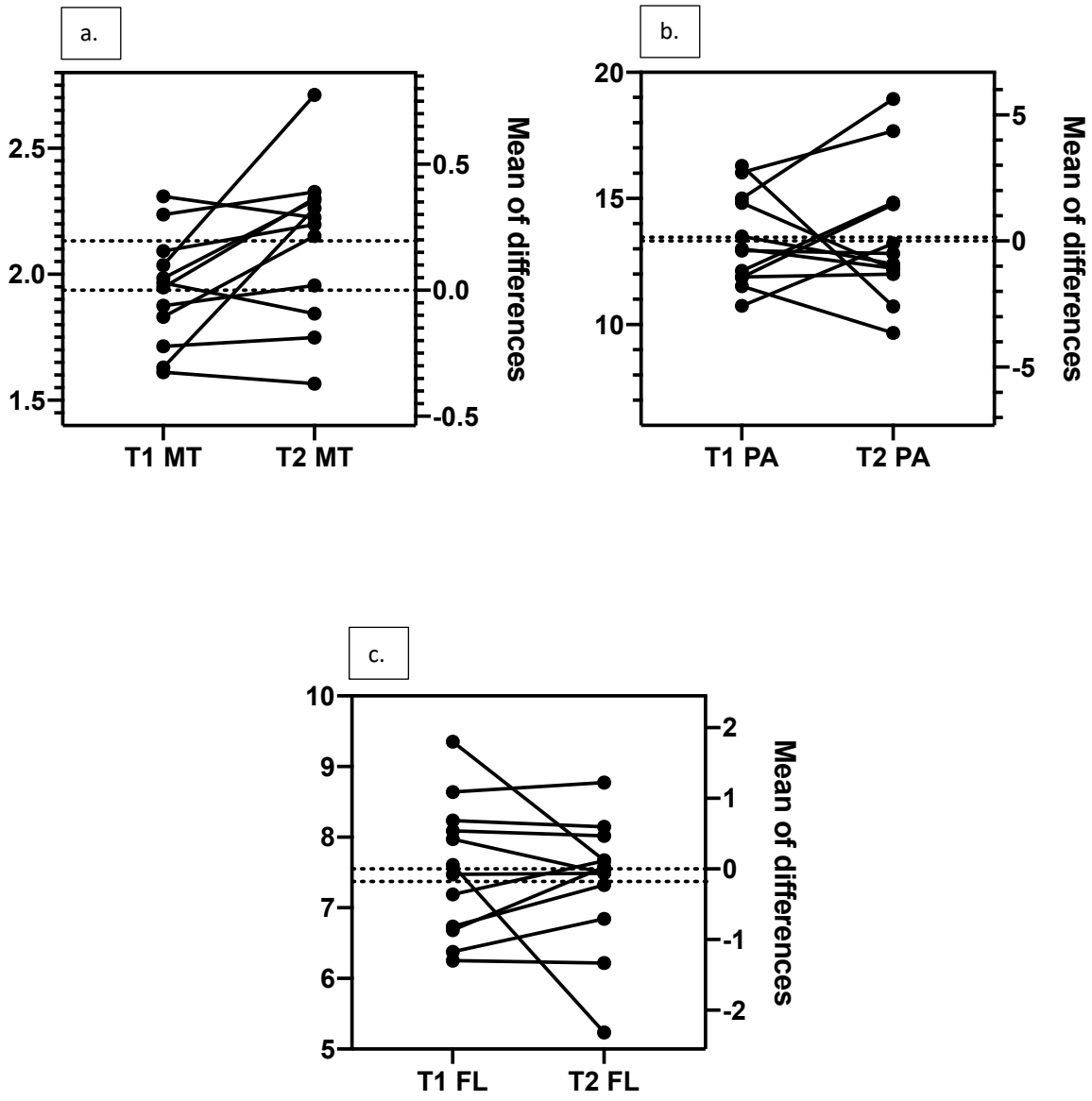


Figure 3.15: Parameters of VL architecture at baseline (T1) compared to at 4 weeks (T2) after completion of the exercise training programme a. $_{M}$T. b. $_{P}$A and c. $_{F}$L. Analysis via paired Students *t* test. *=p<0.01 between timepoints.

3.3.7.4 *CPET and alternative measures of CRF.*

The baseline data collected for this study was included in the data set analysed for chapter 3. On comparative analysis of the data collected following the 4-week exercise intervention programme. There was a significant relationship found between HGS and the CPET VO_{2peak} (L/min) as shown in Figure 3.16 (a.-d.)

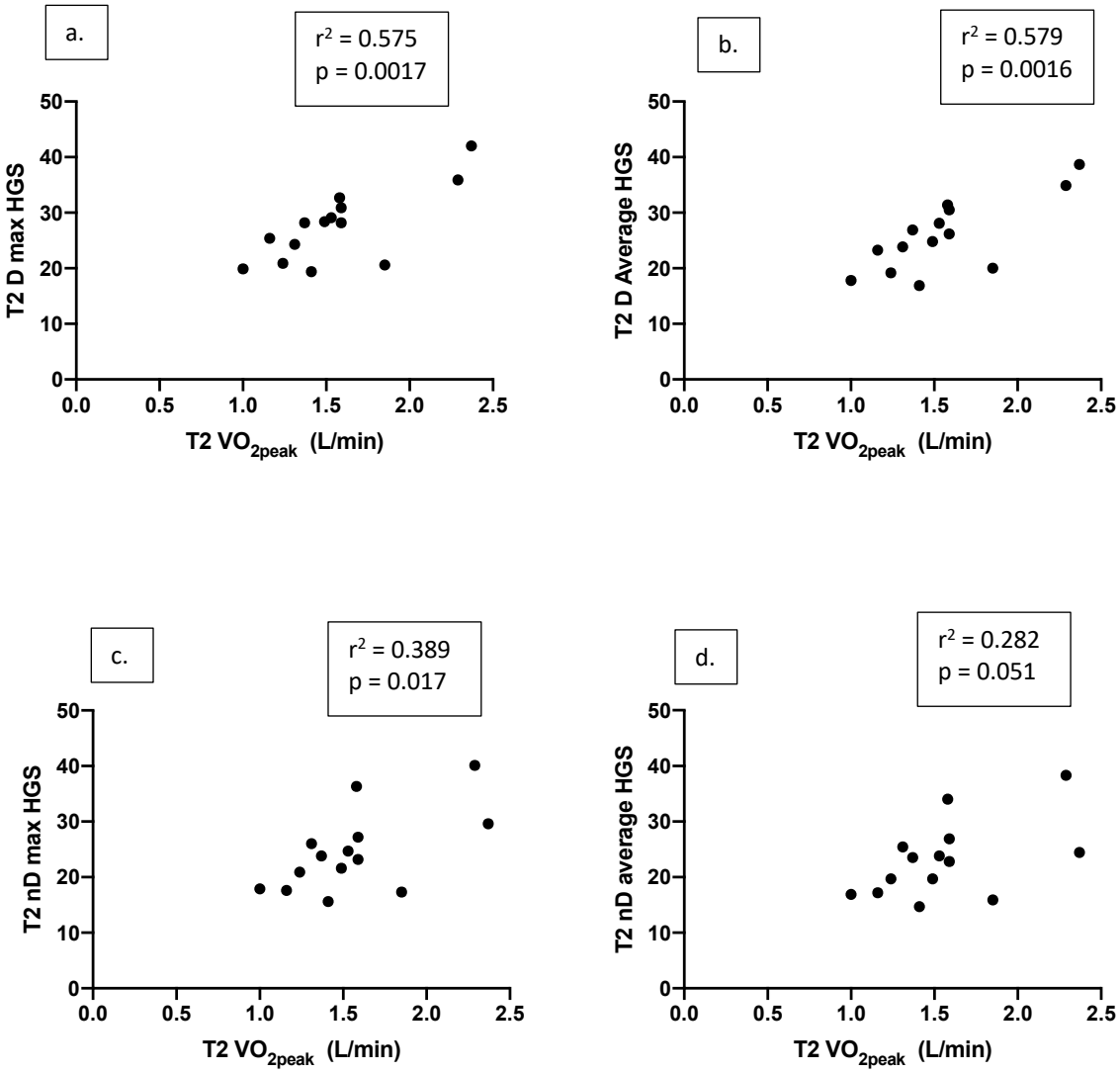


Figure 3.16: Pearson correlation between HGS and CPET VO_{2peak} (L/min). a) maximal dominant HGS and VO_{2peak}, b) dominant average HGS and VO_{2peak} c) non-dominant maximal HGC and VO_{2peak} d) non-dominant average HGS and VO_{2peak}. R^2 denotes the strength of the Pearson correlation and a $p< 0.01$ indicates the relationship is significant. T2 denotes the second testing session following the 4-week training period.

The direct alternative variables of HGS, step-box test and VL architecture, were only compared to the CPET variable of VO_{2peak}, in line with the CPET-derived from the equations based on these alternative measures. No significant relationship was found between any of the step-box test variables of the VL-architecture measures, $_{M}T$, $_{P}A$ and $_{F}L$ conducted following the 4-week period of exercise training and the CPET variable VO_{2peak} (see Table 3.24).

	CPET VO_{2peak} (L/min)
SBT: *Fast SBT time (s)*	R^2= 0.210 P= 0.1
SBT: *HR t45s recovery*	R^2= 0.114 P= 0.238
VL architecture: $_{M}T$	R^2= 0.076 P= 0.339
VL architecture: $_{P}A$	R^2= 0.0007 P= 0.930
VL architecture: $_{F}L$	R^2= 0.0215 P= 0.617

Table 3.24: Pearson correlation data for the step-box data (the time taken to complete the 20 steps at a fast pace, and the HR, 45 seconds into the recovery period) and the VL architecture variables of $_{M}$T, $_{P}$A and $_{F}$L as compared to the CPET variable of VO_{2peak} (L/mins). R^2 is the Pearson correlation coefficient, the greater the number, the stronger the correlation. The p- value indicating significance if $p < 0.01$.

The predictive models of VO_{2peak}:

- VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66).

- VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.70)

were used to derive the VO_{2peak} from the data following the exercise training programme. The derived VO_{2peak} values, for both equations, were found to correlate with the CPET VO_{2peak} results (See figure 3.17.a.-b.).

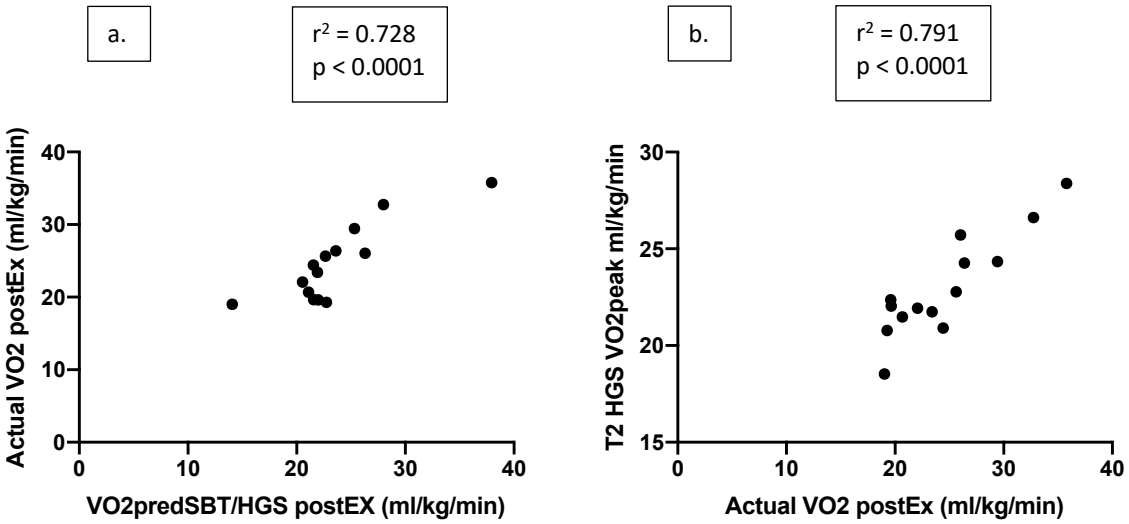


Figure 3.17: CPET variable VO_{2peak} (ml/kg/min) as compared to the derived VO_{2peak} (ml/kg/min) from the predictive equations developed in chapter 3. a. predictive equation: VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66), denoted by SBT/HGS, postEx refers to post exercise training programme. and graph b. predictive equation: VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.70) denoted by HGS. R^2 is the Pearson correlation coefficient, the greater the number, the stronger the correlation. The p- value indicating significance if $p < 0.01$.

3.4 Discussion.

3.4.1 Summary of findings.

The primary aim of this study was to assess if the alternative measures of physical fitness, HGS and the step-box test, were comparable to CPET derived variables and whether these measures could predict change following a 4-week exercise intervention, in the older population. The key findings of this study were that of the alternative measures, the most comparable measure to CPET was HGS, with both dominant and non-dominant HGS found to significantly correlate with both VO_{2peak} and AT. Further, the study was able to derive models of moderative predictive ability for VO_{2peak} based upon HGS and the step-box test in combination with participant demographics, gender and BMI were derived, with one model based on HGS and BMI alone. Although these derived models for VO_{2peak} were unable to measure change in CRF, the predictive model values of VO_{2peak} did correlate with the CPET VO_{2peak} values.

The study demonstrated the ability to improve CRF as measured by CPET following a 4-week exercise intervention based upon National guidelines for the older population(185)(274). However, neither HGS nor the step box test could alone measure this change.

The secondary aim of this study focused on whether parameters of muscle architecture ($_{M}$T, $_{p}$A, $_{F}$L) associated with physical performance correlate with CRF as determined by CPET and whether changes in these parameters measured by USS reflected changes in CRF as measured by CPET following an exercise intervention. It was surprising that this study was unable to demonstrate a relationship between these parameters of muscle architecture and CRF (as measured by CPET) despite a cohort of 64 participants, as there is already supportive evidence linking muscle mass and CRF(244)(245)(246)(247). On review of the cohort of participants, they were predominantly chosen for their age, they were not matched for co-morbidities or for baseline physical activity or fitness levels, which may go some way to explain this result.

3.4.2 Relationships between different assessments of physical function.

Although the evaluation of VO_{2max} through CPET is the gold-standard assessment tool for CRF(95)(96)(97)(98)(99)(100)(101), as discussed in the section 3.1.1.2, it was felt unrealistic to expect the older population to exercise to maximum volition in order to measure this variable. As such VO_{2peak}, an acceptable alternative measure of CRF(230), was used as the primary CPET variable for assessing CRF in this study.

HGS was not shown to correlate with age or BMI (Table 3.3), however, both dominant and non-dominant HGS significantly correlated with the principle CPET measures of CRF, VO_{2peak} and AT (Figures 3.9a-d, 3.10a-d). Supporting the use of HGS as a simple clinical tool to aid in the clinical assessment of patients. Although statistical modelling did not find any of the measures of HGS to be independent predictive tools for VO_{2peak}, in conjunction with BMI, dominant maximum HGS has been successfully modelled to predict VO_{2peak} using the following equation: VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.70). Comparatively, although predictive of $VO_{2peak,}$ the strength of this prediction was less than that of the derived model which incorporated data from the step-box test (R^2 36% vs R^2 45% respectively), VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66). No significantly reliable model using HGS and step-box variables could be derived to predict AT.

Alternatively, a model incorporating step-box data in combination with gender and BMI was developed which could significantly and reliably predict VO_{2peak} (VO_{2peak} (ml/kg/min) = 39.1 + (fast step box time x-0.2) + (gender x 4.7) + (BMI x -0.64)). However, with a R^2 of 40%, this model is not as predictive of VO_{2peak} as compared to the model based upon the dominant maximum HGS with the step-box variable and BMI. Unlike the HGS variables, the main variables of the step-box test; the time taken to complete the 20 steps at a fast pace (as determined by the participant) and the participants HR at 45 seconds in the recovery period, demonstrated no significant relationship with the main CRF variables as measured by CPET, the VO_{2peak} or AT.

Although the step-box test has been used in clinical studies(131)(134), there is no standardised protocol. As discussed in the introduction (section 1.3.2.2.) the methodology for step-box testing falls into two broad categories of either single-stage step test or multi-stage step tests in line with the BTT protocol(130). With the variables assessed inconsistent across the studies, for example HR was recorded during the stepping period(130), 15 seconds into the recovery period(134) and as a HR maximum percentage(136)(137). With HR recovery incorporated into a number of studies(135)(137) based on its use as a prognostic measurement for cardiovascular disease(285) and predictor of mortality(286)(287)(288), with specifically HR at 45 seconds of recovery following step-box testing identified as a predictor of VO_{2peak} (135). Further, the height of the step-box most widely adopted as part of the test (132)(133)(134)(135)(136) was found to be too challenging in the older participant group in preliminary studies, such that a protocol tailored specifically to the older individual(137) was used but the step height was decreased. As such the prior evidence base to support the use of the step-box test as a tool for predicting CRF in the older participant is less robust as compared to HGS, with the protocol used in this study unvalidated. Comparatively, HGS is a simpler test to conduct and has been demonstrated to predict prolonged LoS(138), mortality(138)(140), cognitive decline and HR-QoL(139) and is recommended by the EWGSOP as a tool to predict frailty in older individuals(66). Therefore, although, the best predictive model derived in this study included both HGS data and step-box test data, it is of no surprise that when looking to establish a predictive model for VO_{2peak} using only a single alternative test, either HGS or the step-box test, only a model incorporating HGS was derived which was significantly

predictive. This lack of predictive ability of the step-box test may reflect a low power in the study for this test, and extension of this study may be necessary to determine the validity of the protocol used in this study. However, on consideration of the clinical applicability of both alternative tests, the simplicity and versatility of the HGS dynamometer with its established predictive ability, make the measurement of HGS and the use of the HGS model in combination with a readily measurable BMI to predict VO_{2peak} a more versatile and useful clinical measurement tool.

AT, as described in the introduction (section 1.3.1.), is a useful submaximal measure of CRF and a clinical tool for predicting outcomes in various surgical specialties'(112). However, no significantly reliable tool to predict AT using HGS and or step-box test data with or without other variables such as gender, age or BMI was established. Although week significant predictive ability (R^2 = 19%) was established for the model: AT (ml/kg/min) = 20.3 + (Non-dominant maximal HGS x 0.129) + (+ (BMI x -0.394), analysis revealed the data to be heteroskedastic, undermining the reliability of the statistical significance of this data. This heteroskedasticity can arise for a number of reasons, including the presence of outliers in the data or incorporated skewed data in the model, both of which may be addressed by the increasing the power within the data and by ensuring the cohort of participants are appropriately matched for underlying co-morbidities.

The secondary objective of this study was to explore the relationship between muscle mass as determined from VL architecture and CRF. Supportive evidence linking muscle mass and CRF is available(244)(245)(246)(247), it was therefore anticipated that a relationship between these parameters and CRF in this study would be evident, however, no significant relationship was demonstrated between any of the measures of muscle mass and those of CRF (CPET, HGS or step-box test) in this study. Muscle USS is an established accurate tool for the measurement of muscle size(252)(253)(254)(289) and it's accuracy has previously been demonstrated, in a smaller group (36) of older participants (mean age 68 +/- 5.3 years)(254). The cohort of 64 participants used for this study had a median age of 74 years, they were not matched for co-morbidities or for baseline physical activity or fitness levels. This may have resulted in sufficient variance of the VL architecture and therefore the muscle USS measurements, to prevent any statistical relationships within the data being observed.

3.4.3 Exercise Intervention sub-group study.

This study showed that the NHS guidelines on physical activity for older adults(185)(274) can improve strength and CRF as determined by CPET (VO_{2peak} and AT), with this achievable within a time frame supporting the potential for prehabilitation prior to surgery (e.g., 31-days from decision to treat to surgery for cancer(280)). In section 3.2.6. concerns focused on the specificity of these guidelines for older adults(275), with respect to the apparent lack of consideration for differences in the physical capabilities, comorbidities and other limitations (17)(276)(277) of the older individual. Although the results of this study support the applicability of these guidelines to the older individual, the participants of this study were a highly motivated group with respect to their general health, most were regular members of clubs involved in active pursuits such as bowls and aqua aerobics, and a number of the participants had taken part in previous fitness-based research studies. It became apparent when monitoring the unsupervised activity component of the training programme that a number of the participants within the group were undertaking more than 150 minutes of moderate physical activity per week during the training period. As such, this group were not reflective of the general population, national statistics show that only 40.5% of the population over 75 years of age are physically active (undertaking 150 minutes or more of moderate intensity physical activity a week), as compared to 74.1% of those 16 to 24 years of age(290). Therefore, this affirmation of the NHS guidelines on physical activity for the older individual must be viewed with this in mind.

Although, strength was demonstrated to significantly increase in the group following the 4 weeks of training, a number of the participants struggled with the strength aspect of the exercise programme, they had minimal experience of weight-based training, with a number concerned by the perceived increased risk of injury through the use of weights. The strength training aspect of the programme therefore required a considerable period of familiarisation to overcome reluctance based on fear of injury, which may have slowed down potential strength gains.

3.4.3.1 *Predictive ability of bed-side assessments to determine change in CRF.*

The study detailed in Chapter 3 established models of moderative predictive ability for VO_{2peak} based upon simple alternative measures of CRF, HGS and step-box test in combination with participant demographics, gender and BMI. The study described in this chapter aimed to ascertain if these models were capable of measuring change in CRF. The model with the best predictive ability (VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66). (R^2 45%)) was used along with the simpler derived model based on HGS and BMI alone (VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.70) (R^2 36%)).

The baseline data from this study was part of the data set used to develop the predictive models of VO_{2peak} in Chapter 3, on analysis of the data collected following the 4-week exercise training programme, a significant correlation was evident between the derived VO_{2peak} values using both models and the CPET VO_{2peak} data. However, despite a significant increase in CPET-derived VO_{2peak} following the 4-week exercise training programme, neither of the derived models were capable of measuring this change in VO_{2peak}. Although a significant change was demonstrated in the CPET variable AT with the exercise training programme, the main focus of this study was to determine if the derived models of CRF based on the alternative bed side measures could predict change. The models derived only predicted VO_{2peak}, no reliable positive predictive model for AT was derived in Chapter 3 based on these alternative measures. Therefore, VO_{2peak} was the main CPET comparative variable analysed in this study.

3.4.3.2 *Efficacy of the programme for increasing muscle mass.*

Although there is previous evidence linking muscle mass and CRF(244)(245)(246)(247), despite demonstrating a positively significant affect upon strength as a consequence of this training programme, and a significant improvement in CRF as determined by the increase in the CPET variables AT and VO_{2peak}, no discernible change in the muscle architecture parameters of $_{M}T$, $_{P}A$ and $_{F}L$ were found following the 4-week exercise training programme. This may reflect the limited number of participants recruited to the study. However, no relationship was evident between these muscle parameters ($_{M}T$, $_{P}A$ and $_{F}L$) and CRF (CPET variables VO_{2peak} and AT) in the 64 participants included in the first part of this study. The

participants were not matched for co-morbidities and this may explain the variability impacting the ability to draw any relationships from the data.

A detailed description of the processes underpinning skeletal muscle growth is beyond the scope of this thesis, however, specific detail can be found in the following reviews; Marini & Veicsteinas(291) and Egan & Zierath(292). Skeletal muscle growth is regulated by a number of mechanisms through myogenic regulatory factors (MRFs), which are in turn responsive to RET(281).This growth is also affected by the rate at which muscle protein synthesis occurs, with evidence that this rate is slower in older adults(293)(294). As such, there is evidence to indicate that the processes by which muscle hypertrophy occur differ with age(281)(293)(294)(295). In the older population, the neural adaptations which account for the early strength gains achieved through RET which occur within the first few weeks(281)(295)(296), play a significant role(295). Further, differences are evident between genders in the older population, with the percentage of type II fibres present impacting on the gains in strength achieved, particularly key for women(295). This gender difference is therefore reflected in the outcomes of training programmes, with programmes designed around twice weekly sessions focused on using loads to achieve fast movements positively impacting hypertrophy in women, but with limited hypertrophy observed in men(295). Consequently, these factors should be taken into account when designing training programmes for the older population(281). The training programme designed for this study, did not account for gender differences, yet the cohort was predominantly female, further, at 4-weeks, it was short in duration, during which period the consequent gains in strength from the RET can be attributed to neural changes(295) as compared to actual hypertrophy, without which no change in the parameters of the muscle architecture ($_{M}$T, $_{P}$A and $_{F}$L) would be observed on USS.

3.4.4 Limitations of this study.

Although the median age (74 years) of the participants in this study was appropriate for the aim of the study, the participants were not matched for their underlying co-morbidities and as such this may have resulted in variance and outliers within the data affecting the ability to statistically analyse and draw conclusions.

The primary objective of this study was to document the relationship between simple measures of physical fitness and CRF. The relationship established between HGS and CRF in this study is consistent with the evidence base. However, the relationship between the step-box test data and CRF however is less supportive and consistent with prior work. This may reflect the lack of a standardised step-box test protocol, with various methods and variables used in the statistical analysis in previous work. Also, the protocol used in this study was based on prior validated methods, however, it was adjusted based upon the needs and limitations of the participants and as such was an unvalidated study protocol. Therefore, before determining the use of the step-box test as a simple reliable alternative measure of CRF, standardisation of the methodology and validation of the protocol is required.

As already discussed, the participants in this study were all healthy and highly motivated individuals, and as such may not reflect the general older population and in particular patients who present for surgery. It has been demonstrated for example, that chemotherapy has a significant deleterious impact on CRF(297)(298) and for many cancer management pathways, chemotherapy forms part of the pre-operative management. The development of these predictive models of CRF using bed-side tests such as HGS and the step-box test, is to enable the clinical evaluation of a patients perioperative CRF and to facilitate clinical studies. Therefore, future work developing such measures of CRF needs to involve participants more representative of the general public and patient groups. Further, as mentioned above, the participants recruited should be matched for their co-morbidities.

The RET component of the exercise intervention was not specifically tailored to the age and gender requirements of the older population as discussed above in section 3.4.3.2., and to elicit hypertrophy and therefore measurable changes in muscle architecture, was likely to short in duration. Further, the familiarisation period with the various weights was to short, such that initial 1-RM values were an underestimation impacting on initial training targets, progression and thereby strength gains and achievable muscle hypertrophy.

3.4.5 In summary.

This study established models of moderative predictive ability for VO_{2peak} based upon simple alternative measures of CRF, HGS and step-box test in combination with participant demographics, gender and BMI. Further one simple model based on HGS and BMI alone was also derived. As such these models provide a simple and cost-efficient clinical assessment tool for the assessment of CRF. However, the ability of these assessments, and indeed the predictive models, to determine change in CRF has not been explored. This has clinical application in relation to determining the effectiveness of both pre- and rehabilitation regimes, and for assessing losses of CRF over time.

The NHS guidelines on physical activity for the older individual can elicit change in CRF following 4-weeks of training, in line with previous evidence(278)(279) and supportive of prehabilitation as a pre-operative tool to improve patient outcomes even in a limited time frame of 4-weeks/31 days.

Overall, none of the bed-side assessments of physical fitness, or muscle mass as assessed in this study appear to be useful independent tools in the prediction of CRF. In addition, when measures of these assessments were used in models shown to be predictive of CRF, they were still unable to predict positive change as elicited by the exercise-training programme.

4 Chapter Four:

Consensus opinion on the recovery needs of the older patient following major abdominal surgery.

4.1 Introduction.

The growing focus of attention on the geriatric syndrome of frailty(3) and the potential interventions to improve patient perioperative outcomes is discussed in Chapter one. Although the argument for such interventions is clear, the clinical perspective often is focused solely on clinical outcomes such as morbidity, mortality, and LoS, outcomes which are clearly measurable and comparable across services locally, regionally, nationally, and even internationally, enabling service evaluation, providing clear targets for service development and influencing funding streams. Although, such outcomes are relevant to patients on a personal level, such clinically focused outcome measures overlook those outcomes more pertinent to the patient, specifically QoL. As such Patient-reported outcome measures (PROMs) have developed, with their aim to measure health, focusing on the patients symptoms, functional ability and QoL(299). However, these measures have in the main been used to assess patient satisfaction, a surrogate marker for measuring the quality of the health care system(300) and as such are often used to improve service provision, for example by attempting to assess performance, and drivers for quality improvement(301). However, understanding a patient's satisfaction with a system does not equate to knowing what their needs are and whether these have been met. The Cambridge dictionary described the word "need" as a verb meaning to "have to have something" or dependent on the context of its use it would it could confer the individuals will "get an advantage from having it"(302) and in clinical context it has been defined as "in the sense of subjective desire and a lack of something necessary"(303). A patients' needs therefore can be very broad, ranging from a desire to have a good surgical outcome, access to good transport facilities when attending hospital visits, to be pain free, to retain the ability to complete the cross word, to still be physically able to look after themselves and their loved ones, to return to their own home on discharge from hospital; important "things/factors to have" as determined by themselves for their QoL. Consequently, these needs are more personal as compared to the clinical outcomes of morbidity, mortality and LoS, which are more distinct and quantifiable. It is therefore harder to measure the quality-of-service provision, to direct service improvement, and to link these to funding structures, if the focus primarily is upon meeting patient needs, however, it does not make them any less pertinent.

Ultimately, to ensure good quality health care is delivered, both clinical and patient orientated outcomes addressing their needs must be met, reflecting this, perioperative medicine is an evolving area with its aim as stated by the RCoA "to deliver the best possible care for patients before, during and after major surgery"(27). Within this aim, the necessity to meet the patients' needs from the point of referral to surgery extending throughout their recovery period is addressed, with the focus on a multi-disciplinary approach, linking primary and secondary care to enable this(27).

It is therefore clear, that even when there are demonstrable clinical outcome improvements achievable with respect to morbidity, mortality and LoS, when considering service development, including researching potential clinical interventions, such as the use of exercise training following surgery, that a patient need is also evident. In doing so, this will help to frame the service, intervention, around the patient at its centre.

The focus of this thesis is on frailty and the ability to address this in the perioperative period of the older patient through the use of a post-operative exercise training programme. Chapter 2 reviewed the evidence base for post-operative exercise training programmes and older surgical patients, whilst Chapters 3 focused on the assessment of CRF. Chapter 5 describes a RCT with the primary aim of assessing the feasibility of a post-operative training programme following major non-cardiac surgery in the older population, with a secondary aim of assessing the impact of such a training programme on CRF. This Chapter, however, moves away from a focus on clinical measurable outcomes, to focus on the patient perspective through an attempt to assess the needs of older patients undergoing major non-cardiac surgery by surveying the patients, along with the primary care and secondary care teams. With the knowledge of these needs, it is then possible to ascertain if an exercise programme could address these, if an exercise programme is even something these patients desire to undertake.

4.1.1 The patient and the caregiver's perspectives of recovery needs.

As stated above, the RCoA describe a multi-disciplinary approach in the assessment of patients' needs(27). The aim of this study was therefore to ascertain not only the recovery needs of the patients but also what the anticipated needs were from the various caregivers

involved in the patients care pathway. This therefore included the primary care team, both the general practioners (GPs) and the practice nurses, plus the various members involved in the secondary care journey such as the surgeons, anaesthetists, nursing and physiotherapy staff. The aim was to build a comprehensive multi-disciplinary understanding of the patients' needs during their post-operative recovery period.

Due to the difficulty accessing patient information from across multiple hospitals and Trusts, only patients who had undergone surgery at the RDH were approached to take part in this study. However, the survey was distributed to primary and secondary care teams from across the East Midlands region.

4.1.2 Surveys.

Very broadly surveys are tools used to collect data, and therefore it is a frequently used tool in politics, science, education, and more recently social media. In turn, survery instruments take various forms, they can be paper based, online, or conducted through interviews in person or by telephone. As such they are a familiar tool to the general public. Within the NHS, surveys are commonly used to assess patient and staff satisfaction(304) and are used therefore to aid service development.

When looking to source data from individuals, depending upon the nature of the data required (in this case assessing information of patient needs), direct interviews can provide the most in-depth information as they provide both objective and subjective information. However, they are costly to both the interviewer and interviewee in time and potentially financially depending upon where and how the interview will be conducted, i.e., will it be a face-to-face interview or a telephone or online video call. Therefore, when aiming to source information from a large group of individuals/a population, interviews are generally not a feasible tool to use, and surveys are more appropriate. Surveys can be easily distributed at low cost by mail or online and can be completed at the interviewee's leisure. However, there are a number of limitations to collecting data through the use of surveys, the subjective componenet of the information, such as a behavioural response to a question, can be lost and often the questions are simplified to ensure the survey is kept to a minimum length, maintaining the interviewees attention increasing the response rate. Ultimately,

there is no guarantee the survey will be completed and returned; therefore, information can be lost and as such many more surveys are often distributed to ensure a minimum response rate is achieved.

Surveys were chosen as the main tool for data collection due to the size of the target populations. On occasion the patient surveys were completed in the format of an interview, in these circumstances the questions and the formatted answers i.e., the multiple choice answers, were read directly from the survey. Otherwise for the patients, a paper-based survey was distributed. Paper-based surveys were also used for the primary care team, this format was used instead of the online format to facilitate reaching all members of each primary care practise. All paper-based surveys were distributed with a stamped addressed return envelope to ensure no cost was conferred to the interviewee and to improve the response rate. In secondary care, initially the survey was distributed via email to the various departments, however, the response rate was very poor across all of the disciplines. Consequently, the paper-based survey was distributed within the local hospital.

4.1.2.1 *Survey Design.*

A web-based survey tool was used to develop the surveys for this study. Such web-based tools facilitate the survey design and distribution to large target groups, whilst also storing and analysing the data. As the surveys are then web-based they can easily be distributed through sharing website links, however, the surveys can also be downloaded and therefore shared in a paper-based format, enabling a multi-modal approach to survey distribution which has been shown to increase response rates(305). The web-based survey tool, Bristol Online Surveys (University of Bristol, https://www.onlinesurveys.ac.uk/, endorsed by the University of Nottingham) was therefore used to develop the surveys, each survey was then available to both be distributed electronically or in paper-based format. Various styles were adopted for the question format throughout the survey to ensure continued engagement with the survey by the participant, these styles included yes/no answers, multiple choice questions, Likert 5-point scale questions (answer options: not at all likely, slightly likely, moderately likely, very likely, extremely likely) and free text.

4.1.3 Study aims.

The aim of this study was to build a comprehensive multi-disciplinary understanding of the patients' needs during their post-operative recovery period and ascertain whether these needs are currently being met.

4.1.4 Study objectives.

The objective of this study was to ascertain the recovery needs of older patients undergoing major abdominal surgery and to establish the anticipated recovery needs of these patients as judged by the caregivers involved in the patients care pathway. These carer givers included the primary care team, GPs and the practice nurses, plus the various members involved in the secondary care journey such as the surgeons, anaesthetists, nursing and physiotherapy staff.

4.2 Materials and Methods.

4.2.1 The Survey formats.

All the surveys used in this study were developed using the web-based survey tool (Bristol Online Surveys, University of Bristol, https://www.onlinesurveys.ac.uk/) as described in section 4.1.2.1. The surveys were then all available to be distributed electronically or downloadable and used in paper-format.

4.2.2 Patient survey.

4.2.2.1 *Participants:*

The patients were only recruited from the RDH (Derby, UK). As the definition of major surgery includes any operation within or upon a major body cavity(306)(307), within the surgical specialties' that are hosted at RDH which include general surgery, colorectal, hepatobiliary, upper gastrointestinal, urology, gynaecology and vascular, the definition of major surgery encompasses a broad range of surgical procedures, such as laparoscopic cholecystectomy and open aortic aneurysm repair.

The implementation of Enhanced recovery after surgery (ERAS) programmes, designed to optimise the perioperative provision of care in elective surgery has led to the improvement in patient outcomes across many surgical specialties' with demonstrable cost savings for the

hospitals(308)(309). ERAS programmes initially were developed for elective surgery, and although there is evidence to support the use of ERAS programmes for emergency surgery(310), such care pathways are not commonplace in the emergency setting. Therefore, the patient who has undergone care through an ERAS programme would be anticipated to have had a better experience and potentially better outcomes as compared to a patient who has not had such a tailored multi-disciplinary care service. This is in addition to the greater morbidity and mortality risk associated with emergency surgery(311) impacting post-operative recovery as compared to elective surgery. Although the aim of this study initially was to target patients who had undergone elective major abdominal surgery, this became confused as many patients had initially attended for elective surgery but also underwent emergency surgery, some were unclear as to whether it was elective or emergency surgery, consequently the survey was opened up to include patients undergoing elective or emergency major abdominal surgery.

At the time of this study, patients who had undergone major surgery at the RDH were requested to attend for follow-up with their surgical team in the outpatient surgical clinic 6-months after surgery. The clinic lists were reviewed weekly over a 1-year period and eligible patients identified. At the clinic the patient was approached to take part in the survey, and they were provided with the option of completing the survey in an interview manner, completing the survey alone in the clinic or completing the survey at home with the provision of a stamped addressed envelope to return the completed survey. This helped to ensure all patients, irrespective of potential difficulties such as poor eyesight or reading difficulties could complete the survey should they wish too. If patients did not attend their clinic appointment the survey was posted to them directly with a stamped addressed envelope for the return of the survey.

4.2.2.2 *Survey Design*

The survey was divided up into the following sections:

- Details on the surgery undertaken, including the date of the surgery, whether it was planned or an emergency.
- How long the patient was in the hospital for prior to and following the surgery.

- Did the patient require admission to the Intensive Care unit or the Step-Down Unit (Level 1 unit at the RDH) and if so, how many days where they admitted to these units for.
- Regarding physical tasks, they were asked how long it took for them to return to these physical tasks following surgery.
- They were asked if they felt they were as physically active as they had been prior to the surgery and how long it took them to reach their baseline activity. If they felt they were not as active, they were asked to describe how things had changed.
- They were asked about the effect of the operation on their cognition, if they were able to clearly read, follow information and instruction, and if this had been affected for how long.
- The patient was asked if they felt they had been discharged from the hospital at the right time.
- With regards to the first 6-weeks of their recovery period they were asked how many times they had visited their GP or seen the practise nurse.
- They were questioned about fatigue, if they had or where experiencing this and how it impacted on their QoL and normal daily activities and hobbies.
- Pain management on discharge and once at home was discussed.
- They were asked if they felt “their needs” had been met, and if not in what way have they not been in met and how could this be rectified.
- For those patients with a stoma there were questions focused on their ability to physically manage their stoma, if help was required who provided this, did they feel they were coping with their stoma and was it preventing them from returning to their daily activities and hobbies. Their thoughts on stoma care service in place were sought.
- One section focused on communication between the patient and their GP and hospital and also on their perception of the communication between the GP and the hospital directly.
- There was a section devoted to what support and help the patient had required if any prior to the surgery as compared to afterwards.
- Patient demographic details were collected.

- Finally, the patient was asked if this opportunity to provide feedback was helpful to them.
-

4.2.3 General Practioner survey.

4.2.3.1 *Participants:*

A database of all general practices across the East Midlands region was developed and the GP survey was distributed by post to each named GP at the medical practise with further copies to be distributed to the practice nursing staff. A stamped addressed return envelope was provided.

4.2.3.2 *Survey Design:*

The survey was structured into the following sections:

- They were asked if they felt that the patients' needs are met by the current follow up and recovery services, and if they felt they were not met they were asked to expand on this to explain their thoughts.
- They were asked if they felt the patients suffer from persistent fatigue.
- Whether they felt patients were likely to experience chronic pain.
- They were asked about the impact of surgery on cognition.
- They were asked regarding those patients with a stoma if they felt the management of this was a persistent problem for the patient and if they thought the current service provision was meeting their needs.
- They were asked if they believed patients were being discharged from hospital at the right time.
- They were asked how many times they perceive a patient to access primary care services by booking visits to seem themselves, the practise or district nursing teams.
- They were asked if they felt a support service aimed at improving post-operative physical function would be of benefit to the patient.
- They were asked if they felt communication between themselves and the hospital was sufficient or could be improved.
- They were also asked to anticipate roughly the expected recovery times following both major laparoscopic and major open surgery for the specialties': Upper Gastro-

Intestinal, Lower Gastro-Intestinal, Hepatobiliary, Gynaecological, Renal, Urological and Vascular surgery, with examples of an operation for each.

-

4.2.4 Surgical team surveys.

The aim was to the survey the surgical view of the patients anticipated recovery and their experience of recovery and their needs. Surgeons across the East Midlands were contacted either directly or through their secretaries, and the surveys were distributed electronically. A number of surgeons were spoken to directly in order to discuss the completion of the survey within their department and clarify the best method by which to distribute the survey, all requested an online link to the survey be emailed to them directly.
The surgical specialties contacted represented the specialties' operating at the RDH such that their responses could be directly compared to those of the RDH patients surveyed. Therefore, the surgical specialties approached included; general surgery, colorectal, hepatobiliary, upper gastrointestinal, urology, gynaecology and vascular surgery. Surveys specific to each of these specialties were designed and distributed.

4.2.4.1 *Survey Design.*

As described below, a number of adapted versions of the survey were developed to accommodate the feedback provided by the surgical team. Despite the version of the survey, they were all divided up into the following general sections:

- They were asked if they felt that the patients' needs are met by the current follow up and recovery services, and if they felt they were not met they were asked to expand on this to explain their thoughts.
- They were asked if they felt the patients suffer from persistent fatigue.
- Whether they felt patients were likely to experience chronic pain.
- They were asked about the impact of surgery on cognition.
- They were asked regarding those patients with a stoma if they felt the management of this was a persistent problem for the patient and if they thought the current service provision was meeting their needs.
- They were asked if they believed patients were being discharged from hospital at the right time.

- They were asked how many times they perceive a patient to access primary care services by booking visits to seem themselves, the practise or district nursing teams.
- They were asked if they felt a support service aimed at improving post-operative physical function would be of benefit to the patient.
- They were asked if they felt communication between themselves and the GP was sufficient or could be improved.
- They were also asked to anticipate roughly the expected recovery times following both major laparoscopic and major open surgery for various surgical procedures typical within their speciality.

4.2.5 Anaesthetic team surveys.

Anaesthetists are a part of the multi-disciplinary team driving the development of perioperative care(27). As such, the aim was to survey the anaesthetists to establish their understanding of the patients anticipated recovery and their experience of recovery and their needs. Anaesthetists across the East Midlands were contacted either directly or through their departments, and the surveys were distributed electronically. As with the surgeons, a number of anaesthetists were spoken to directly in order to discuss the completion of the survey within their department and clarify the best method by which to distribute the survey, all requested an online link to the survey be emailed to them directly. Although many anaesthetists specialise within the field of anaesthesia, for example as Obstetric anaesthetists, paediatric anaesthetists, it is understood within the East Midlands region, that despite this most anaesthetists will have some experience of the recovery process, through out-of-hour commitments or varied job descriptions, with the associated surgical specialties' focused on in this survey; general surgery, colorectal, hepatobiliary, upper gastrointestinal, urology, gynaecology and vascular surgery. Therefore, generic surveys in line with those distributed to the GPs were designed for completion by the anaesthetists, as with the surveys designed for the surgeons, the design was amended based upon feedback received.

4.2.5.1 *Survey Design.*

The survey was divided up into the following sections:

- They were asked if they felt that the patients' needs are met by the current follow up and recovery services, and if they felt they were not met they were asked to expand on this to explain their thoughts.
- They were asked if they felt the patients suffer from persistent fatigue.
- Whether they felt patients were likely to experience chronic pain.
- They were asked about the impact of surgery on cognition.
- They were asked regarding those patients with a stoma if they felt the management of this was a persistent problem for the patient and if they thought the current service provision was meeting their needs.
- They were asked if they believed patients were being discharged from hospital at the right time.
- They were asked how many times they perceive a patient to access primary care services by booking visits to seem themselves, the practise or district nursing teams.
- They were asked if they felt a support service aimed at improving post-operative physical function would be of benefit to the patient.
- They were not asked if they felt communication between the hospital and the GP was sufficient or could be improved as following feedback, this is a part of the patients care anaesthetists are not a part of and therefore many felt they were not in a position to comment upon this.
- They were asked to anticipate roughly the expected recovery times following both major laparoscopic and major open surgery for various surgical specialties and procedures.

4.2.6 Nursing team surveys.

4.2.6.1 *Survey Design.*

The survey was divided up into the following sections:

- They were asked if they felt that the patients' needs are met by the current follow up and recovery services, and if they felt they were not met they were asked to expand on this to explain their thoughts.
- They were asked if they felt the patients suffer from persistent fatigue.

- Whether they felt patients were likely to experience chronic pain.
- They were asked about the impact of surgery on cognition.
- They were asked regarding those patients with a stoma if they felt the management of this was a persistent problem for the patient and if they thought the current service provision was meeting their needs.
- They were asked if they believed patients were being discharged from hospital at the right time.
- They were asked how many times they perceive a patient to access primary care services by booking visits to seem themselves, the practise or district nursing teams.
- They were asked if they felt a support service aimed at improving post-operative physical function would be of benefit to the patient.
- They were asked if they felt communication between the hospital and the GP was sufficient or could be improved.
- They were also asked to anticipate roughly the expected recovery times following both major laparoscopic and major open surgery for various surgical specialties and procedures.

The design of the survey was amended based on feedback received from the nurses, the initial versions required specific knowledge, however, the nursing staff stated that they did not have specific knowledge in certain areas and therefore felt unqualified to comment. Also, the surveys had to be completed in their own time and therefore most aimed to complete the survey on their break periods, however, the feedback indicated to enable this and improve the response rate the surveys need to be shortened.

4.2.7 Statistical analysis.

Where possible the data retrieved from the surveys was statistically analysed using Stat Version 16 (TIBCO Data Science).

The free text was transcribed into Microsoft Excel (Microsoft Excel version 16.43) and scrutinised for common themes, with frequent words or phrases collated to determine these themes.

4.3 Results.

4.3.1 Patient survey results.

In total 84 patient surveys were completed with a gender split of 46.9% Males and 53.1% females, the majority (70.4%) of the patients were between 65 and 80 years of age, with 14.8% between 80 and 84 years of age and only 4 respondents between 90 and 94 years of age.

4.3.1.1 *Survey response rate.*

No response rate was calculable as there was no set attendance of patients at the surgical outpatient's clinic, patients were identified one week in advance of their attendance at the clinic, although the research and outpatient nursing team endeavoured to ensure all potential participants were approached to take part, some participants were missed due to the nature of the flow through clinic and the limited time resource of the research.

4.3.1.2 *Survey answers.*

The results of the survey are provided in tabulated form in Table 4.1.

Question Category:	Answers:
Home support:	• 86.3% of the patients had not required any form of pre-operative support with their ADLs. • 53.6% had a partner living with them. • 36.3% stated they were alone without a partner or children for support.
Elective or Emergency surgery:	• 32.9% had elective surgery. • 67.1% had emergency surgery.
Level of post-operative care required:	• 64.1% were admitted to ICU post-operatively. • A number stated they did not know how long they had been in hospital for.
LoS:	• 67.5% were admitted for 14 days. • A small number said they were unable to recall which ward they were on post-operatively.
Discharge home:	• 90% believe that they were discharged at the right time. • 8.8% felt that they had been discharged too soon. • 1.2% felt they were discharged too late.
Pain management on discharge:	• 85.3% stated they were pain free on discharge. • 66.2% denied any ongoing problems with pain at 6 months.
Physical function post-surgery:	• 51.3% felt that they were able to do the same physical tasks as they had done pre-operatively and for 41.7% of these patients it had taken them 6 months to reach this point. • For the remaining 48.7% the response was highly varied.
Experience of fatigue post-surgery”	• 50.7% suffered ongoing fatigue, affecting their daily activities and hobbies
Effect on cognition post-surgery:	• 71.6% did not feel that their cognition had been negatively impacted by their surgery • Of those that had stated it was affected, 45.5% stated the impact was felt for the first 6-weeks alone.
Stoma care: 54.4% had a stoma as a consequence of their operation.	• 86.7% are managing their stoma well. • 72% receive help from the stoma nurse. • 53.3% do not feel it impacts on their physical ability. • 83.3% feel they are coping with their stoma. • 82.8% feel the stoma service meets their needs.
Communication: Between GP & patient: Between hospital & patient: Between hospital & GP:	Reported as: • Poor: 8.8%, sufficient: 24.1%, good 41.8%, excellent: 17.7%, unknown: 1.3% • Poor: 7.6%, sufficient: 21.5%, good: 41.8% excellent: 25.3%, unknown: 3.8% • Poor: 7.6%, sufficient: 25.6%, good: 43.7%, excellent: 11.4%, unknown: 7.6%
Patient needs:	• 88.2% felt their needs had been met.

Table 4.1: The results of the patient survey broken down into question categories and results presented as percentages. Italics denote quo

4.3.1.3 *Survey themes.*

Many of the patients used the free test sections of the survey to provide feedback and a number provided supplemental feedback in the form of attached letters or comments at the end of the survey. Table 4.2 depicts some of the comments and the running themes in each of the categories of questions.

Question Category:	Comments & themes.
Home support:	• Partners provided the most support, although many live alone. • Many relied on family to help with shopping and general ADLs, a number felt guilty about this. • A number commented on the poor health of their partners who they then relied on for post-operative support. One patient lost their long-term partner and 4 members of their family during their recovery period.
Discharge home:	• "*They knew when*" • "*Too soon, didn't want to go into rest bite*" • "*At the right time, had requested to stay in hospital longer*" • "*I felt ready to go home*"
Pain management on discharge:	• 85.3% stated they were pain free on discharge. • 66.2% denied any ongoing problems with pain at 6 months.
Physical function post-surgery:	• "*unsure of myself*" – lacking confidence was a common theme. • "*not as much energy*" • A number of comments focused on their persistent lack of strength with respect to shopping and ADLs.
Experience of fatigue post-surgery"	• "*tire quickly*" • Many out this down to problems with returning to their normal diet following surgery. • Many put this down to their increasing age.
Effect on cognition post-surgery:	• "*friends noted I was talking rubbish*" • "*I remain a little slower*" • "*tired, very slow, I cannot think, my husband helped me fill this in"* • "*I can't multi-task anymore*" • "*took a while for me to be able to read a book again*" • "*felt low in mood for 2 weeks*" • "*lack of interest in activities*" • "*forgetful*", "*impatient*", "*short-tempered*" • "*I think the surgery has accelerated my short-term memory loss*"
Patient needs:	*"I just need to understand myself and my progress. I should like to understand what went wrong with me and to feel sure that I should recognise when help may be needed in the future"* *"I have felt rather left in the dark with not enough information about my recovery (I realise everyone is different) More explanation would have been helpful."*

Table 4.2: The results of the patient survey broken down into question categories with the running themes and comments provided in the free text and additional feedback. Italics denote quotes.

4.3.2 GP survey results.

4.3.2.1 *Response rate.*

1700 surveys were distributed to GPs across the East Midlands region, 121 surveys were returned equating to a response rate of 7%.

4.3.2.2 *Survey answers.*

The results of the survey are provided in tabulated form in Table 4.3.

Question Category:	Answers:
Discharge home:	• At the right time: 55.4% • Too soon: 42.1%
Chronic pain:	• Agreement that laparoscopic surgery is associated with less chronic pain than open surgery.
Exercise as part of a recovery programme:	• 86.8% felt this would be helpful to improve recovery.
Fatigue post-surgery:	• Yes: 70.2% • No: 27.3%
Effect on cognition post-surgery:	• Irrespective of whether the operation was laparoscopic or open, the majority of the GPs agreed that cognition was affected acutely (93.4%, 86.8% respectively). • There was no consistent agreement on the length of time cognition may be affected for.
Stoma care:	• 84.3% of patients manage their stoma well. • 65% feel the stoma services meet the patients' needs.
Accessing the primary care team: • The practise and district nursing teams: • The GPs:	• Although the question focused on anticipated additional appointments to those required as part of their perioperative care, no consensus opinion was possible on how many times a patient may request to see a practise nurse or district nurse. • 64.5% believed on average patients would request between 1 to 2 appointments to see them following surgery for reasons other than a visit planned as part of their perioperative care.
Communication with hospital:	Main themes: • Details in the discharge summaries need improving – more comprehensive & expectations of recovery. • Discharge summaries need to reach GPs quicker. • Surgical team contact details on discharge summaries for follow-up or further information.
Patient needs:	• Yes: 46.3% • No: 47.9% • Other answers included: *"Extremely variable", "not sure", "not consistent", "don't know", "sometimes".*

Table 4.3: This table provides some of the results of the GP survey.

4.3.2.2.1 GP opinions on the patients' needs.

47.9% of the GPs stated that they did not feel that the patients' needs were met during their recovery period. The explanations provided all focused around the access patients have to specialised information once they have been discharged from hospital. Many patients suffer an "expectation mismatch" such that they do not feel they are recovering as well as they had anticipated, consequently they present to their GP for guidance and possible investigation to address if there are any problems/post-operative complications. A number of patients simply want detailed information on what happened during their hospital stay, they may not recall details provided by the surgeon whilst in hospital. There is the perception that patients are informed on discharge from the secondary care that should they have any further problems, issues or questions to "go and see your GP". However, the GPs nearly unanimously stated the discharge letters provided minimal information to help them to address any of the patients queries or concerns and in turn there was no secondary care point of contact for either the GP or the patient, that could be easily reached to help with this. The GP's themselves stated they often lack the specialist knowledge and cannot be expected to keep abreast of all the latest updates in the various surgical fields. The reason therefore that there is a perceived failure to meet the patients' needs, is that with a noticeable reduction in follow-up surgical appointments and minimal information resources to hand, GPs feel that the patients' needs with respect to communication and understanding of their surgery and recovery process are not met.

4.3.2.2.2 Anticipated recovery times and the impact of surgery on pain and cognition.

This survey was attempting to gauge the perception of the primary care team on the general recovery process of the older surgical patient. However, this lack of specificity with regards to the surgical speciality, procedure and patient population prohibited a detailed analysis of the views on anticipated recovery times and post-operative experiences of pain, fatigue and cognition. These topics could only be explored very broadly by the survey and the general findings are described in Table 4.3. With respect to the anticipated recovery times, there was too much variation in the responses to draw any conclusions, a number of the GPs explained that they have very limited experience across the variety of the surgical specialties' and procedures to be able to predict anticipated recovery times.

4.3.3 Surgeon survey results.

4.3.3.1 *Response rate.*

The response rate was negligible for these surveys. Surgeons were contacted and asked to provide feedback on the survey design to see if this could be altered to improve their engagement with the survey. The initial feedback stated that the surveys were too broad, in line with the GP surveys and to try to keep a general overview, the surveys covered broad topics such as laparoscopic compared to open surgery, however, the surgeons felt this was too generalised and therefore were unable to comment. Revised surveys were then completed and re-distributed, however the response rate remained negligible. The surgeons were again approached, and the feedback provided verbally and received by return email in response to the distributed survey stated again, they felt the surveys remained too general, with anticipated recovery expectations and patients needs too specific to the patient, the exact details of their surgical procedure, the nature of their underlying co-morbidities and social circumstances, and therefore they remained uninclined to generalise these points.

Part of the feedback on the surveys touched on the specialism of the consultant surgeon's within the surgical specialties', such that not all procedures are undertaken by all surgeons, therefore restricting their ability to complete the survey. Consequently, it was decided to expand the survey to the senior surgical registrar's who through the nature of their training programmes and general surgical out-of-hours commitments, would be anticipated to have a wider variety of surgical experience within their chosen speciality, and with their seniority, experience and understanding of the patients recovery process. However, the response rate was also negligible for this group, despite offering online and paper-based versions of the survey to complete.

4.3.4 Anaesthetic team survey results.

4.3.4.1 *Response rate.*

No surveys were completed by anaesthetists from outside of RDH and no feedback was provided despite "reminder" emails with the link to the survey with multiple points of contact for the research team provided along with a request for feedback or concerns to help improve the survey design should this be appropriate. Paper-based surveys were

therefore distributed locally to the anaesthetists of the RDH, this achieved a response rate of 25% (17 surveys returned out of a potential of 68).

4.3.4.2 *Survey answers.*

The results of the survey are provided in tabulated form in Table 4.4.

Question Category:	Answers:
Discharge home:	• At the right time: 58.8% • Too soon: 23.5% • Too late: 11.8%
Chronic pain: • Open surgery: • Laparoscopic surgery:	Anticipated likelihood as a percentage: • 70.6% moderately likely, 17.6% slightly likely to experience chronic pain. • 29.4% moderately likely, 70.6% slightly likely to experience chronic pain.
Exercise as part of a recovery programme:	• 82.3% felt this would be helpful to improve recovery.
Fatigue post-surgery: • Open surgery: • Laparoscopic surgery:	Anticipated occurrence as a percentage: • 94% believe fatigue is experienced. • 64.7% believe fatigue is experienced, 11.8% unsure and 11.8% do not believe this will occur.
Effect on cognition post-surgery: • Open surgery: • Laparoscopic surgery:	For both open and laparoscopic surgery there was a majority consensus that cognition would be affected acutely (100% & 94.1% respectively). However, there was significant variation in the anticipated duration of this affect. • Mainly reported as based upon: *Patient feedback, personal experience, anecdotal evidence, conferences and personal learning.*
Stoma care:	• 82.4% of patients manage their stoma well. • The majority felt unable to answer if the stoma service is meeting patient needs due to lack of experience/knowledge.
Accessing the primary care team: • The practise and district nursing teams: • The GPs:	• 76.5% believed the patients would request between 1 and 2 appointments for reasons other than a visit planned as part of their perioperative care • 41.2% believed on average patients would request between 1 to 2 appointments to see their GP following surgery for reasons other than a visit planned as part of their perioperative care. Whilst 53% felt the patients would attend more often than this.
Anticipated recovery times for the various surgical specialties' and procedures:	No consensus was evident in the survey data, many fed back that this was too generalised as recovery depends upon numerous factors specific to the individual patient and their surgery.
Patient needs:	• Yes: 29.4% • No: 23.5% • Unsure/unknown: 29.4%

Table 4.4: This table provides some of the results of the Anaesthetists survey

4.3.5 Nursing team survey results.

4.3.5.1 *Response rate.*

The aim of the study had been to survey the multi-disciplinary members involved in the patients surgical journey, with respect to the nursing profession this includes, the outpatient clinic nurses, the ward-based nursing teams, specialist surgical nursing teams such as the stoma nurses, primary care nursing practioners and district nurses. Locally there is considerable flux in the nursing staff, particularly on the surgical wards, with many of the nurses working on the wards not employed by the Trust, this is not unique to RDH. As such it was not possible to quantify exactly how many nurses fall into this group locally or regionally. Further, this this led to a multi-modal approach to the distribution of the surveys, with some sent out electronically but many distributed in paper-based format. As part of the distribution of the surveys to the GPs copies of the nursing survey were included, and on the wards and in clinic multiple copies of the survey were left on the ward with the ward secretary or in the nurse's coffee room with posters used to advertise the study and encourage participation. Consequently, the number of surveys distributed bore no relation to the number of nurses expected to have the experience to be able to take part in the survey. For these reasons, it was not possible to calculate a response rate for these surveys.

No surveys were returned from primary care and it was very difficult to distribute surveys to other hospitals and Trust within the region, and as such no surveys were returned from outside of the RDH.

Within the RDH 30 surveys were returned, the role of the nurses who took part in the study is presented below in Table 4.5.

Nursing Role	Number participated in survey
Senior Sister.	3 (one based surgical outpatients).
Sister and stoma care specialist.	3
Staff Nurse.	22
ICU nurse.	1
Health Care Assistant (HCA)	1

Table 4.5: This table details the various roles and the number in those roles that completed the survey.

4.3.5.2 *Survey answers.*

The results of the survey are provided in tabulated form in Table 4.6.

Question Category:	Answers:
Discharge home:	• At the right time: 37% • Too soon: 40% • Too late: 7% • Did not know: 16%
Chronic pain: • Open surgery: • Laparoscopic surgery:	Anticipated likelihood as a percentage: • 11% extremely likely, 22% very likely, 33% moderately likely, 33% slightly likely to experience chronic pain. • 22% very likely, 22.2% moderately likely, 38.9% slightly likely and 5% not at all likely, to experience chronic pain with 5% unsure.
Exercise as part of a recovery programme:	• 83.3% felt this would be helpful to improve recovery.
Fatigue post-surgery: • Open surgery: • Laparoscopic surgery:	Anticipated occurrence as a percentage: • 78% believe fatigue is experienced, 11% unsure and 11% do not believe this will occur. • 50% believe fatigue is experienced, 5% unsure and 44.4% do not believe this will occur.
Effect on cognition post-surgery: • Open surgery: • Laparoscopic surgery:	For both open and laparoscopic surgery there was a majority consensus that cognition would be affected acutely (78.7% & 66.7% respectively). However, there was significant variation in the anticipated duration of this affect. • Mainly reported as based upon: *Patient feedback and personal experience.*
Stoma care:	• 83.3% of patients manage their stoma well. • 72.2% stated they felt the stoma service is meeting patient needs, 11.1% felt it does not meet their needs and 11% were unsure.
Accessing the primary care team:	This section was removed as the feedback stated they felt they did not have the knowledge of the system to answer this question.
Anticipated recovery times for the various surgical specialties' and procedures:	Despite amending the survey based on feedback to generalise this question as much as appropriate, many declined to answer this section based on a lack of knowledge of the answers provided there was no consistency in the data.
Patient needs:	• Yes: 61.1% • No: 22.2% • Unsure 16.7%

Table 4.6: This table provides some of the results of the nursing staff survey.

4.3.5.3 *Survey themes.*

Limited written feedback was provided, however, with respect to the question looking at whether patient's recovery needs are met, these comments were noted:

"*patients are sent home too early, to rely on elderly partners to care for them"*

"more follow up in the community is needed"

"follow up services, rehabilitation care, depleted"

"not meeting psychological needs" – "no psychological support when waiting for results"

"stoma nurses are not carers"

"no counselling services",

"patient support differs across the areas of the East Midlands. Increased population areas deserve increased medical teams".

4.4 Discussion.

4.4.1 Survey engagement.

A way to quantify participant engagement with a survey is through evaluation of the response rate, which is generally viewed as a measures of a surveys ability to represent the views of a target population as a whole(312). With a low response rate impacting on the validity of the study due to non-response bias as a consequence of the potential anticipated difference between the responders and the non-responders(313). However, response rates are in general declining(312)(314)(315), negatively impacting the perceived reliability of surveys and through attempts to improve these rates, driving up survey costs(312). The three main general reasons for lack of engagement in surveys include; a lack of interest in the subject matter of the survey, the potential participants are too busy and the survey itself is too time consuming(314). However, there is evidence suggesting that there may be too much significance attached to the response rate alone(312)(314)(316), with the direct relationship between response rates and nonresponse bias questioned(312). Consequently, alternative strategies to survey populations are suggested, for example, one option is to randomly sample target populations(314). Such a method also confers the benefit of potentially minimising survey fatigue in the target population, an important consideration when for example the target population are GPs(317) (318), such as in this study. Similarly,

the Delphi method(319), which focuses on the opinions of a structured group, with multiple rounds of surveys, shared analysis and feedback, can ultimately lead to a consensus opinion of the group representative of the target population. This method also combats survey fatigue, however, through its iterative process it can address group issues, and this may have been very useful when attempting in particular, to survey the surgeons opinion, in this study.

4.4.1.1 *Patients:*

As discussed above, a response rate was not evaluated for the patient surveys due to the nature of the study design, with the surveys conducted over the period of a year, and with patients identified through outpatient clinic attendance, a pre-determined target number of patients was not established. A multi-modal approach (interviews and paper-based surveys) was used which helped to address any potential difficulties faced by potential responders for example due to difficulties with reading (the paper-based survey was printed in a large font to help with reading) and as response rates are in general declining(312)(315), to minimise the potential for a low response rate if the survey had been solely distributed by post. Anecdotally, the patients who were approached at the outpatient clinic reported they appreciated being provided with a choice as to how they wished to complete the survey, and as observed previously(305), this in itself may have helped improve the response rate.

4.4.1.2 *Health care professional engagement with surveys:*

The significant lack of engagement with the surveys by the surgeons and by the anaesthetists from across the East Midlands region was very disappointing and although the response rate for doctors completing surveys has declined over recent years(320), this remained somewhat surprising. However, although the poor response rate for the GP survey was also disappointing this was not so unexpected, with the evidence supporting low survey response rates amongst GPs, in particular, common(318).

Although surveys are commonly used to source information, the postal survey has been superseded by web-based surveys shared through email and social media(321). For the health care professionals (Anaesthetists, Surgeons, specialist nursing staff) across the East Midlands region, initially web-based surveys were distributed by email to department

secretaries and leads for local distribution. This was partly necessitated by the dynamic nature of these departments and restricted shared information on contact details, prohibiting the postal distribution of paper-based surveys. However, as postal surveys have been demonstrated to be more effective than either email or telephone surveys when eliciting information from GPs(318), paper-based surveys were distributed by post to the GPs across the target region. The use of postal surveys enabled the research team to address the GPs personally, which was felt to be more professional and courteous than emailing the GP practice and requesting the email be distributed by the administrative staff, this may be a factor in the different response rate as compared to that of the other health care professionals. Further, distributing the web-based survey electronically risked resulting in spam emails (emails distributed without the knowledge of the consent of the receiver). Although such emails would not be illegal under the Privacy and Electronic Communication Regulations (PECR) (2003), the anti-spam law at the time restricted unsolicited marketing emails and not emails relevant to the receivers work, such emails can be perceived to be a nuisance and are often automatically redirected by email systems into spam folders and therefore not viewed by the intended recipient (Since the completion of this study the General Data Protection Regulation law (GDPR) (2018) has come into effect). This risk was avoided by the postal distribution of the surveys to the GPs and again may be a further factor in the improved response rate for the GP survey.

Incentives were considered to improve the response rates(312), however, postal paper-based surveys alone are costly(305) and therefore financially this was not possible. Reaching out to the various health care professionals directly by telephone proved to be very difficult due to the busy working schedule of the individuals and the research team, this is in line with evidence indicating that response rates to telephone surveys are also diminishing(314). One consideration was to conduct interviews as undertaken with the patients. However, for the GPs there is evidence indicating the impact of this on their time and practise management is prohibitory(317) and it was felt that this would also be the case for the surgeons, a view verified on discussion with a number of surgeons locally at RDH. For the anaesthetists and the nurses, many were directly approached, however, all requested they complete the survey at their own leisure. Following this approach locally there was observed an increase in the survey responses from the anaesthetists, however, this may

have also been attributable to the fact that the member of the research team who approached the anaesthetists was an immediate colleague. With this in mind, although opinions from each discipline were sought to aid in the survey development, the study design may have benefited from more active involvement of representatives from each of the disciplines of anaesthetics, general practice, surgery and nursing to aid with engagement.

A common complaint raised with regards to the surveys from the anaesthetists and the surgeons was the generalisability of the questions. Initially specific surveys pertaining to each of the surgical specialities were designed, however, despite this, for both specialties' it was felt that with respect to questions focused on anticipated patient recovery times and patients needs, these were too dependent upon specific patient personal and surgical factors and consequently, it is likely this will have impacted on their engagement with the survey and the response rate.

From the feedback gained from the nurses, the main reasons for lack of engagement with the surveys were a lack of time to complete the survey, ideally, they did not want to complete the survey in their own personal time, and also, they felt the survey was too long and therefore time consuming. Although this was addressed and the survey was shortened, the second main reason for lack of engagement hinged on the nurse’s belief that they did not possess the knowledge or understanding of the systems in place to feel free to comment on some of the questions. Although the nurses were encouraged that knowledge per se was not required, we were simply seeking their thoughts and opinions, this failed to improve the response rate, and is an example of where a nursing representative on the research team would have been well placed to address these concerns. Ultimately, these concerns lead to the removal of the questions centred on communication and patient access to primary care resources.

Reasons for the low response rates are ultimately many fold; in addition to those already discussed above, due to their common use survey fatigue can occur(318) plus there are also personal reasons such as a lack of interest pertaining to the subject of the survey, and also a lack of interest or engagement in research in general(322).

4.4.2 Impact of surgery on pain, fatigue and physical function.

The patients did not report issues with pain management on discharge or throughout their recovery period, the survey was adapted to ask about pain without linking it to the form of surgery undertaken i.e. open or laparoscopic surgery, as many of the patients were unable to describe in any detail what surgery they had undergone, and this included whether the surgery was laparoscopic or open, therefore resulting in unclear answers to the question. Understanding the patients experience of pain is relevant to their needs and also their post-operative physical function. There is sufficient evidence to support the general view, that in the main laparoscopic surgery is associated with less post-operative pain as compared to open surgery(323)(324)(325)(326)(327) and this was reflected in the survey responses of the various health care professionals.

Post-operative fatigue is a recognised condition negatively impacting physical function and QoL(328). Therefore, it is something that should be anticipated by patients, and this is reflected in the health care professional surveys, where the majority believed patients would suffer from fatigue post-operatively. However, of the 50.7% of the patients who reported fatigue, the majority in the feedback attributed this to either their diet or their advancing age, it was not evidently apparent that this was something they anticipated as a consequence of the surgery, which supports the GP comments pertaining to patients suffering an “expectation mismatch” and the need for improved patient education and information on their anticipated recovery journey.

With 50.7% of the patients stating they were suffering from ongoing fatigue, and with fatigue defined as “*a feeling of debilitating tiredness, loss of energy, or malaise*”(328) it is of no surprise that in the patient comments describing their ability to return to baseline physical function, that for those that struggled to achieve this, they described a lack of energy and strength. As detailed in Table 4.2, the majority struggled with their physical function post-operatively, some of this will have been attributable directly to the physical consequences of surgery, however, this was not addressed in the patients feedback. This impact on physical function is clearly apparent to the health care professionals, with 86.8%

of the GPs, 82.3% of the anaesthetists and 83.3% of the nursing staff all agreed that some sort of exercise training intervention would be beneficial to the patients recovery.

4.4.3 Impact of surgery on cognition.

In line with the evidence base which links surgery and post-operative cognitive decline(329)(330)(331), across the health care professionals, GPs, anaesthetists and nursing staff, it was felt that the majority of the patients would suffer a negative impact on their cognition secondary to their surgery. However, although of those patients who had suffered from some cognitive impairment following their surgery (28%), 45.5% stated it was only for the first 6 weeks, in line with the majority health care view that cognition was negatively affected acutely. Overall, 71.6% of the patients denied any impact on their cognition at all.

The patient survey provided examples to illustrate the question on cognition (questions focused on the ability to think clearly, read or follow information or instruction as POCD is associated with difficulty in concentration and memory loss(332)), rather than using the term directly as it was felt that few may understand the term "cognition" and it may also be associated with negative connotations around significant mental health complications. This is reflected in some of the comments fed-back from the patients "*I remain a little slower*", "*tired, very slow, I cannot think, my husband helped me fill this in*". Despite this, as POCD can be mild(330), and potentially therefore unnoticed by the patient, the results of this question should ideally trigger further focused questioning on this topic to truly understand the patients perceived impact of surgery on their cognition, alongside definitive assessment.

4.4.4 The understanding of patients' needs.

The majority of the patients felt that they had been discharged from hospital at the right time, with only 8.8% believing it was too soon. This is in direct contrast to the view of the GPs, with 42.1% believing they are discharged too soon. This disparity is mirrored in the results regarding the patients' needs, as despite 88.2% of the patients believing their recovery needs were met, only 46.3% of the GPs agreed with this. From the feedback provided by the GPs, this belief that the system is failing to meet the patients' needs is centred on a lack of understanding of the patients anticipated recovery, both by the patient and by themselves (what constitutes an expected recovery symptom as compared to

something that is unexpected and therefore warrants investigation), and the lack of a clear pathway to ascertain this information. As such the patients need to understand their recovery, what is to be expected and what is not, is not being catered for, and this is reflected in the two comments provided by patients on why their needs were not met….

> *"I just need to understand myself and my progress. I should like to understand what went wrong with me and to feel sure that I should recognise when help may be needed in the future"*

> *"I have felt rather left in the dark with not enough information about my recovery (I realise everyone is different) More explanation would have been helpful."*

Although the majority of the nurses did feel the patients' needs were met, 22.2% disagreed and the theme in the feedback provided to justify this centred around follow up and support services, in line with those voiced by the GPs. Also of relevance, considering the survey highlighted that 36.3% of the patients surveyed were alone with no family for support.

4.4.5 Limitations of the study.

Even if it is assumed that less emphasis should be placed on the response rates, those achieved for the surveys conducted as part of this study, in particular the surveys targeting the secondary care health professionals, are inadequate to ensure the risk of nonresponse bias is low and that the results are representative of the target population. Therefore, no reliably meaningful conclusions can be drawn from this data. However, the data does highlight differences in perceptions of post-operative recovery between the patients and health care professionals that would warrant further investigation.

As discussed in section 4.4.1. achieving adequate response rates for surveys in general is fraught with multiple issues, and this needs to be accounted for early in the study design process, ensuring adequate resources; time, personnel and finances, are available to facilitate this. Also, it is key to ensure the surveys are written with the nature of the target population in mind.

The study design is the major limitation of this study. The overall aim was to develop a consensus opinion on the recovery experience of older patients who had undergone major non-cardiac surgery. This is a very broad aim, chosen in line with the overarching focus of this thesis on the post-operative recovery of the older surgical patient, and the broad aims of the various studies contained within this thesis assessing physical function and exercise interventions following major non-cardiac surgery. The belief underpinning these studies and this thesis, is that despite the specific complexities of the individuals as patients and their surgery, a certain amount of what may be experienced and suffered by the patient is generalisable, and certainly the need of the patient as identified by the GPs in this study, their need to understand their recovery, is irrespective of the individual or the surgery undertaken. However, such a broad approach is in stark contrast to the usual targeted approach within the surgical arena, where the surgeons have become super-specialised within their field(333). The design of this study attempted to ensure the surveys were directly comparable and therefore used the same or similar questions across the various speciality surveys. Looking forward, a better approach for future work in this area may be to employ the Delphi method(319) as described above, or at least in-line with the multi-disciplinary nature of the study reflect this with more active multi-disciplinary representation in the research team.

4.4.6 In summary.

This study aimed to understand the recovery experience of older patients undergoing major non-cardiac surgery and compare this with the perceived experience of their recovery by the health care professionals involved in the patient's perioperative pathway. The general approach to this determination of experience and need undermined the study design and this, along with the difficulties as noted in ascertaining reliable data through surveys, needs to be accounted for in any future study design.

Despite the limitations of the study, the disparity in the experiences as reported by the patients and as anticipated by the health care professionals, particualry with respect to the impact of surgery on cognition and fatigue, show work is required to address this "expectation mismatch" as highlighted by the GPs. This further demonstrates how though

improved partnership between the primary and secondary care sectors, identification and understanding of the patients needs can be more readily addressed to improve patient care.

5 Chapter Five:

Determining the feasibility of bed-side tests to measure physical function in the post-operative period for the older surgical patient.

5.1 Introduction.

The aim of Perioperative medicine is to improve the patients care pathway through surgery to facilitate recovery(27). Frailty, an independent risk factor for morbidity, mortality and increased LoS(4)(5), which correlates with post-operative complications(38) (described in section 1.2), is a multi-factorial, dynamic process(51). A key component of frailty is sarcopenia(7), which describes the loss of skeletal muscle mass and strength(83) (refer to section 1.2.) and is itself linked to major post-operative complications and increased LoS(84). With exercise demonstrated to improve overall physical function, CRF, sarcopenia and cognition in the older frail population(334), as an intervention, exercise programmes in the perioperative period may improve physiological and QoL outcomes, by addressing modifiable factors such as frailty, sarcopenia. This thesis therefore centred around the premis, that by incorporating exercise training programmes in the post-operative care pathway of the older surgical patient, facilitating recovery, clinical and patient focused outcomes could be improved.

To assess the evidence base for post-operative exercise programmes to address physical function in the older population following surgery, Chapter 2 detailed a systematic review of the evidence for physical exercise programs following major non-cardiac surgery in the older patient. Although the review is limited by the paucity of evidence available, such that only five studies were included, with significant clinical heterogeneity and lack of consistency between these studies. The statistical analysis of the evidence supported the use of post-operative exercise programmes as a means to improve physical fitness, however, it was clear from this review that further studies in this area are required.

With the potential benefit to clinical outcomes through the use of exercise as a post-operative intervention in the recovery process of older patients supported by the systematic review. With the emphasis of perioperative medicine focused on patients needs to ensure “the best possible care” (27) is delivered, Chapter 4 explored the patient’s perspective and evaluation of their needs, along with the perspectives of the various stakeholders involved in the patient care pathway, such as GP’s surgeons and anaesthetitsts, on recovery following major abdominal surgery. The results of the survey’s conducted and the GP views on the

patient recovery experience, indicated that some form of exercise programme to address physical function recovery could be seen by patients and GPs as beneficial.

With the results of both Chapters 2 and 4 supporting the need for further work assessing the impact of exercise training programmes in the post-operative period for older patients on clinical and patient outcomes. This study aimed to implement an exercise programme in the post-operative period for those older patients undergoing major non-cardiac surgery. To enable this study, Chapter 3 focused on determining the suitability of bed-side assessments to measure CRF in older adults, with predictive models for VO_{2peak} derived using the alternative measures of CRF, HGS and step-box testing along side participant demographics, gender and BMI.

Although the survey results in Chapter 4 implied there would be support for such an initiative amongst patients and in the Primary care environment, as evidenced by the systematic review in Chapter 2, there is limited evidence to support the feasibility of such interventions. Therefore, the primary aim of the study was to determine the feasibility of such an exercise intervention post-operatively in the older population.

5.1.1 Study population.

As discussed in section 1.1. the NHS faces increasing challenges as the proportion of individuals undergoing surgery who are over the age of 75 years is increasing(2), and with this older population comes an increase in comorbidities such as COPD, diabetes and IHD(17) alongside common geriatric syndromes such as frailty(3). Consequently, the proportion of older patients undergoing surgery, who fall into the high-risk(2) group, which accounts for 80% of all post-operative deaths(24), is in turn increasing. Notwithstanding the impact of this upon clinical and patient outcomes, post-operative complications contribute significantly to the financial cost(25) of the NHS and therefore targeting interventions through perioperative medicine to address these outcomes, will in turn potentially lead to financial benefits in a difficult economic climate.

Those older patients undergoing major cavity non-cardiac surgery were included in this study. Cardiac surgery was excluded for the same reasons it was not included in the systematic review in Chapter 2, as a specialised surgical discipline, the complex surgery, the consequent impact of this physiologically on the patient, in addition to the underlying cardiac pathology, ensures these patients are not representative of the general surgical population. Further, this study was to be undertaken at RDH which as discussed below in section 5.2.3. does not host the surgical disciplines of cardiac, thoracic and neurosurgery. Major cavity surgery at RDH therefore includes the surgical specialties' of general, colorectal, hepatobiliary, upper gastrointestinal, urology, gynaecology and vascular surgery. All of which encompass surgical procedures which would trigger a surgical stress response which could negatively impact on Frailty(37).

5.1.2 Exercise Programme Design.

Although there is a growing body of work focused on the impact of perioperative exercise programmes on outcomes including physical fitness, frailty and wellbeing. As discussed in the systematic review in Chapter 2 looking at the use of exercise training programmes in the post-operative period, there is no consistency in the exercise programmes implemented, with programmes varying in their design; from supervised to non-supervised, with variations in exercise intensity, goals and duration. Therefore, with this lack of consistency, the evidence to support the choice of exercise programme, to achieve improved outcomes, is limited.

5.1.2.1 *Supervised vs Non-supervised intervention.*

The systematic review in Chapter 2 included studies with a mixture of supervised and non-supervised exercise interventions. None of the studies in the review addressed the feasibility of the post-operative exercise programmes implemented, therefore no comparison between the supervised and non-supervised exercise sessions could be drawn. Three of the studies(214)(335)(336) did report high dropout rates attributable to patient specific factors such as illness and changes in personal circumstances, however, two(215)(336), one with supervised training(336) and the other with home-based training(215), documented good exercise adherence rates. The Cochrane review assessing the effectiveness of supervised, centre-based exercise programmes compared to home-

based programmes in the older population(337) found that the exercise adherence rates were better for the home-based programmes, although this was based mainly on the results of one study, and although the physiological outcomes were better for the centre-based exercise programmes these may have been attributable to the exercise itself which differed between the centre and home based studies with the centre-based studies incorporating training on a treadmill. However, with a considerable body of evidence available assessing cardiac rehabilitation, the systematic review looking at exercise based cardiac rehabilitation(338) found that the improved outcomes of cardiovascular mortality and hospital admission with exercise intervention were consistent irrespective of whether the rehabilitation programme was delivered in a supervised manner or at home in a non-supervised form.

In choosing the exercise programme to use in this study, key factors considered included not just the form of exercise most likely to improve physical fitness and QoL, but also the design of the programme most likely to be desirable to the participant, most achievable and cost effective. As there was no clear evidence to support a supervised as compared to a non-supervised exercise training programme, a home-based non-supervised programme was chosen. The cost savings of a home-based exercise programme as compared to a supervised centre-based programme in terms of time, personnel, facilities and equipment are evident. From the participants perspective, a home-based design would reduce the impact of the training programme on the participants time, a centre-based supervised programme would involve transport time and impose restrictions on the timing of the training sessions, although such factors could be ameliorated through the use of study funding to provide taxi's or cover transport costs with ample training session opportunities available to maximise connivence to the participants. Further, considering the cost savings and the perspective of the participant, a home-based exercise programme could potentially prove to be more achievable to implement long term if established to be feasible and effective.

5.1.2.2 *Exercises.*

High intensity interval training (HIIT) arose as a means by which athletes could improve their endurance performance(339). It involves bursts of cardiovascular exercise at a high intensity with periods of rest or low effort exercise in between(340) The exact nature of the exercise, intensity, number of intervals and nature of the rest periods varies across programmes(341). However, the goal remains the same, with the participants spending some proportion of the training period exercising at an intensity which metabolically is at a level of performance requiring at least 90% of the VO_{2max} (340). Despite the variability in HIIT programmes, it is established to be an effective means to improve physical fitness as demonstrated though improvement in VO_{2max} and thereby cardiovascular capacity in non-athletes, sedentary individuals(342) and those with chronic diseases such as obesity, metabolic syndrome, hypertension, heart failure and CAD(343).

HIIT has recently gained much more attention in the arena of exercise-for-health(344). In relation to health parameters, HIIT has been shown to produce a greater improvement in VO_{2max} when compared to endurance training in healthy non-athletic adults(345), with numerous short-term HIIT programmes (less than 12 weeks in duration) showing improvements in VO_{2max}, diastolic BP and fasting glucose levels, and longer-term programmes also improving resting HR, systolic BP, and percentage body fat levels(346). To date, although the majority of the evidence for HIIT has not been focussed on older adults, recent work has shown that in older adults HIIT is similarly beneficial(279). With exercise in general shown to improve both physical and cognitive function in older adults(347), HIIT has specifically been shown to increase CRF(348)(349)(350), decrease the falls risk(351), improve glycaemic control in type 2 diabetics(352), and lead to improved memory performance(353) in the older population. However, despite these benefits, the anticipated effectiveness of HIIT programmes to improve public health is debated, due to the complex theories underlying public psychology and philosophy towards exercise(354).

HIIT normally (similar to endurance exercise training) takes the form of running or cycling. However, the population of interest for this study was the older population undergoing major cavity surgery (see section 5.1.1.). The exercise programme therefore had to be appropriate for the age group and also achievable physically following this type of surgery,

without risk to organ and wound healing, as such for this reason training programmes incorporating running or cycling were deemed inappropriate. Instead, the focus of the exercise training programme was to improve physical function by targeting functional gains in the post-operative period.

One alternative exercise strategy, with some format similarities to HIIT, that has been shown to be safe in older adults, and that I believed would be suitable for the patient population in this study is HIFE(355). With the **HIFE** acronym representing **high intensity functional exercise**, this type of exercise training involves primarily body-weight based strength training of the lower limbs, and has been shown to be safe, not only in a healthy older adult cohort, but also in an older population with some degree of cognitive(356)(357) and physical impairment(356).

The HIFE program was used in the Swedish study; The Frail Older People – Activity and Nutrition study in Umea (the FOPANU study)(357). The FOPANU study was a RCT conducted across nine residential care facilities involving 191 older people with a mean age of 85 years. The participants were dependent in ADLs and a proportion had physical and cognitive impairment. The study utilised the HIFE program which is a functional weight bearing exercise programme tailored to the participant's functional ability. The exercises include everyday tasks such as getting up from a chair and therefore are easy to follow, easily reproducible and require no specialist exercise trainers or facilities. The study showed that 3-months after completing the HIFE program there remained positive effects on gait, balance and strength as compared to the sedentary control group(186). Regarding the safety of the HIFE program, 179 adverse events were reported to have occurred during 1906 exercise sessions, with an adverse event defined as discomfort during the exercise that manifested itself or became worse because of the exercise, examples included muscle pain, dizziness, shortness of breath(357).

The catalogue of exercises aimed to improve lower limb strength, balance and mobility included are described in Appendix IV. These exercises are also designed to be adaptable to the various functional abilities of an older population, including individuals independent of support and those requiring assistance with their mobility needs, and modifiable to facilitate

training progression. The exercises in the HIFE programme use functional weight bearing positions, such as squats and lunges plus balance exercises to challenge the individual's postural stability. The HIFE programme does however only target lower limb function and therefore in order to develop a global body exercise regimen, upper body exercises from an exercise programme developed to prevent falls by the Help the Aged(13) were added to the HIFE programme to form the exercise training programme used in this study (see Appendix III). The preventing falls exercise programme(13) was developed by the Help the Aged in collaboration with the Wandsworth Primary Care Trust and Camden Active Health Team in London. This programme was written by a trainer in exercise for older people and a member of the department for primary care and population sciences at the Royal Free and University College London Medical School. In line with the criteria used to develop the HIFE programme, the exercises included do not require any specialist equipment or trainers and the exercises are adaptable to the individuals needs can be tailored to meet fitness progression targets.

5.1.3 Assessment of Physical Function.

5.1.3.1 *Bed-side measures of CRF.*

5.1.3.1.1 HGS.

HGS is recommended for the assessment of frailty in older individuals(66), it is a simple low-cost assessment tool which is predictive of all-cause mortality(138), cardiovascular and non-cardiovascular mortality(140), cognitive decline(139), prolonged LoS in hospital(139) and impaired QoL(139). As an assessment tool it is discussed in section 1.3.2.3. and Chapters 3 where it was demonstrated to correlate with the CPET measures of CRF, VO_{2peak} and AT. Although as described in the study undertaken in Chapter 3, it was not found to be an independent predictor of CRF, HGS does form part of two derived models to predict VO_{2peak} (see below), providing an alternative measure of CRF as compared to CPET.

- VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.707)

- VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66).

5.1.3.1.2 The Step-box test.

The Step-Box Test as an alternative method of assessing CRF is discussed in section 1.3.2.2. and Chapters 3. Various methods and protocols have been described(129) (130)(131) (132) for the use of the step-box test, the studies in this thesis all used a adapted version of the method developed by Petrella et al.,(137) which had been specifically designed for the older individual(137). Although the step-box test method used in the Chapter 3 study was not found to independently predict CRF, with HGS it is part of a model derived which can predict VO_{2peak} (see above).

The ability of these derived models to measure change in CRF following a 4-week exercise programme was described in Chapter 3. This study showed that a 4-week exercise programme based upon the NHS guidelines on physical activity for older adults(185) could elicit improvements in strength and CRF as measured by CPET (VO_{2peak} and AT). However, neither of the derived models (shown above) were able to measure this change in CRF. The primary objective of this study was to determine the feasibility of the exercise intervention post-operatively, however, the secondary objective was to ascertain whether the exercise programme could elicit change in the patients CRF. Despite the results of Chapter 3 as described, taking into consideration the limitations of the study as described in 3.4.4. alongside the positive relationship evident between both of the derived models and the CPET VO_{2peak} following the exercise programme (refer to 3.4.3.1.), these alternative measures of CRF, HGS and the step-box test and their derived models to predict VO_{2peak} were to be used to assess this secondary objective.

As described in below in section 5.2.3.1. it became apparent once the study had commenced that recruitment was significantly limited by the exclusion of patients taking beta-blocker medication. This exclusion criteria were necessitated by the step-box test which measures HR and this is explained in section 5.2.3.1. below. Consequently, following an amendment to the study protocol to include the TUGT (section 5.1.3.1.3.below), the exclusion criteria for beta-blocker medication was removed, and any patient who consented to the study, but took beta-blocker medication, completed the TUGT instead of the step box test.

5.1.3.1.3 The TUGT.

The TUGT is a simple test requiring only a chair and 3 metres of space(63). It is validated for use in the older population and is a recognised test for frailty(62)(78), such that it is incorporated into the EFS(37).

5.1.3.1.4 Sarcopenia and muscle mass.

As discussed in section 1.2.5., sarcopenia, the age-associated loss of muscle mass and function(78) is linked with frailty(7), increased length of hospital stay and major post-operative complications(84). A relationship between CRF and muscle mass has been shown across the life-course(244)(245)(246), with some evidence of this in pre-operative patient cohorts also(247). Of the various techniques used to assess the muscle mass component of sarcopenia, there is evidence to support the use of radiological assessment as a pre-operative prognostic tool(84), the various imaging techniques for the assessment of muscle mass, including the use of USS as used in this study, are discussed in section 1.2.5.1.

5.1.3.2 *Gold-standard assessment of CRF; CPET.*

Physical fitness as measured using CPET (described in detail in section 1.3.1) was judged to be inappropriate as this would require the patient to exercise on a cycle ergometer, their ability to manage this would be limited by their surgery and potentially could impact on wound recovery. Alternative forms of CPET include the use of a treadmill or hand crank. Although the treadmill CPET generates a higher VO_{2peak} due to greater muscle involvement through action against gravity, and is less daunting for participants as walking is familiar to all as compared to cycling, as a test there is more noise interference and work rate cannot be measured, it is also more physically challenging due to gravity and weight bearing and as such it is not deemed appropriate for patients(358)(359)(360). The hand crank CPET would negate the impact of abdominal surgery on the ability to perform the test and is used when an individual is unable to cycle(96), however, the metabolic stress generated is limited affecting the validity of the test(358).

5.1.4 Assessment of Frailty.

The various assessments of frailty are discussed in detail in section 1.2.2 with the EFS and its amended version REFS, chosen for use in this study, described in section 1.2.2.4. The EFS can be easily implemented in the clinical setting and is validated for use by non-geriatricians(4)(37)(61). Therefore, the EFS was chosen as the frailty assessment tool for this study, however, it was felt that it would be logistically difficult to reliably perform at the patient's bed-side, the TUGT component of the EFS, therefore, the amended version, the REFS(64).

5.1.5 Assessment of Cognition.

Cognition and mental health factors are key components of frailty and feature in the Cumulative Deficit model of frailty(50), plus the CGA(39), EFS[7][21], PRISMA-7(12), the GFI(67) and the TFI(70) assessments (refer to section 1.2.2.). With exercise shown to positively impact cognition(334) and mental health in the older individual(361). Assessment of the effect of the exercise programme on cognition and mental health was therefore included in this study and undertaken by using the validated questionnaires; The MOCA(362), the EQ-5D-5L(363)(364) and the GDS(365) (described in section 5.2.9.2.).

5.1.6 Study Aims:

5.1.6.1 *The Primary Outcome measure:*

The primary outcome of the study was the feasibility of an 8-week post-operative home-based exercise training programme following major cavity surgery in the older population.

5.1.6.2 *The Secondary Outcome measures:*

- The impact of an 8-week post-operative home-based exercise training (HIIT) on physical fitness (as measured using HGS and the step box test) following major cavity surgery in the older population.
- The impact of an 8-week post-operative home-based exercise training (HIIT) on frailty and cognition following major cavity surgery in the older population.

5.2 Materials and Methods.

5.2.1 Study overview.

Older Patients undergoing major body non-cardiac surgery were recruited to participate in this RCT. The intervention arm required the participants to undertake a 6-month home based exercise training programme, commencing immediately on discharge following surgery. Due to difficulties with participant recruitment to the study, the duration of the exercise intervention was decreased from 6-months to 3-months and the lower age limit of participants was decreased from 70 to 60 years of age part way (after 2 months of recruitment) through the study recruitment period. The primary outcome of the study was the feasibility of a post-operative home-based exercise training programme. The secondary outcome measures included participant physical and cognitive function which were assessed pre-operatively and then at set intervals post-operatively.

5.2.2 Ethical approval.

Ethical approval was granted through the Integrated Research Application System (IRAS) (REC reference: 16/EE/0137) with Health Research Authority (HRA) approval. Amendments were submitted and granted as required. The study was registered with ClinicalTrials.Gov (ID NCT03064308).

5.2.3 Identification of potential participants.

Patients over the age of 60 years undergoing major body non-cardiac surgery were eligible to be recruited to the study. Major surgery is defined as surgery with potential risk of life to the patient with body cavity surgery involving an organ located within the cranium, thoracic cavity, abdomen or pelvis(366). Therefore, participants could be recruited from a wide range of surgical specialties, including general surgery, colorectal, hepatobiliary, upper gastrointestinal, urology, gynaecology and vascular. As the study was undertaken at the RDH (Derby, UK), the surgical disciplines of neurosurgery, cardiac and thoracic surgery were not included in the study as they are not provided at the hospital. The definition of major surgery has been refined very little since an early description in 1917(306), whereby it includes any operation within or upon a major body cavity(306)(307) , such that within the surgical specialties outlined above, the definition of major surgery encompasses a broad range of surgical procedures, for example laparoscopic cholecystectomy and open aortic aneurysm repair could both be included. When potential patients were identified to take

part in the study the intended operation was reviewed by a member of the general surgical team independent of the study to ensure it complied with the surgical definition of major body cavity surgery. Within the vascular speciality, endovascular procedures involving interventional radiology were not included as the surgical stress impact was deemed to be minimal. Consequently, the participants recruited to the study could cover a broad range of surgical disciplines and procedures, with this potentially bringing a wide variety of co-morbidities that may affect their ability to undertake an exercise training programme. However, as the primary aim of the study was to determine the feasibility of a post-operative home-based exercise intervention programme, and the impact on physical and cognitive function (as secondary outcomes), it was felt that this was acceptable to assist with adequate recruitment to the study and enhanced the pragmatic potential of this research.

Potential participants were identified from local multi-disciplinary team (MDT) meetings held by each surgical speciality. The surgical specialties also identified potential participants at the surgical outpatient clinic when patients were listed for surgery. After identification, potential participants would be assessed against the eligibility criteria as outlined below.

5.2.3.1 *Eligibility Criteria.*

The eligibility criteria are listed in Table 5.1

INCLUSION CRITERIA
• **Male and female participants over 60 years undergoing major non-cardiac body cavity surgery.**
• **Sufficient capacity to consent for the trial**
EXCLUSION CRITERIA
• **Participants under the age of 60 years**
• **Significant past medical history, including:**
○ **Recent myocardial infarction (within last 6 months)**
○ **Unstable angina**
○ **Heart failure (New York Heart Association class III/IV)**
○ **Uncontrolled hypertension (BP>160/100)**
○ **Taking beta-blocker medication***
○ **Severe respiratory disease, including: known pulmonary hypertension (>25 mmHg), forced expiratory volume in 1 second (FEV1) <1.5 litres, brittle asthma, exercise induced asthma**
○ **Known cerebral aneurysm or abdominal aortic aneurysm**
○ **Previous stroke**
• **Metabolic disease including untreated hypo- and hyperthyroidism, hypo- or hyperparathyroidism, Cushing's disease and type I or II Diabetes**
• **Musculoskeletal, rheumatoid or neurological disorders, limiting the participants ability to undertake exercise training or study fitness assessments**
• **Body weight greater than 160kg (due to equipment limitations) and/or BMI >35kg/m^2**
• **Cognitive impairment which may reduce an individuals' ability to provide informed consent**

Table 5.1: Study inclusion and exclusion criteria. **As one method of physical function assessment of used in this study was the step-box test which relies on measures of heart rate responses to exercise, taking beta-blocker medication which affects HR variability and responses to exercise was deemed an exclusion criteria. This was amended when the TUGT was included in the study as described below.*

Older participants were the target population for this study; therefore, the lower age limit was set at 70 years of age with no upper age limit. Defining age by chronological years lived as compared to function within society, the UN defines old age as greater than 65 years(255). In developed countries old age has been linked to retirement age which traditionally was 60 to 65 years of age, although recently this has changed with life expectancy increasing(255) and the retirement age altering(257). Age sub-groups such as young old (60-69years), middle old (70-80 years) and very old (80+ years)(258), provide a more realistic reflection of the aging process in society. Therefore, by setting the lower age limit to 70 years with no upper limit this would include all individuals defined as middle old and very old and fall in line with recent changes in retirement age. However, as the study progressed and recruitment was limited, following an amendment to the ethical approval, the lower age limit was reduced to 60 years of age, thereby including the "young old" individuals and those likely to still be in employment. This age reduction was chosen as, on review of the local surgical data, it was apparent that there was a high proportion of patients undergoing major abdominal surgery in the age range of 60 to 70 years and to include them could improve study recruitment.

The step-box test was part of the study methodology to assess the secondary outcome measure, physical function (see section 2.8.1.2 below). This test measures HR response to the exercise and therefore, as beta-blocker medication affects HR variability and response to exercise, the use of beta-blocker medication by a potential participant was initially an exclusion criteria. As the study progressed recruitment was difficult and a significant contributing factor to this was the exclusion of patients on beta-blocker medication, therefore, on review an alternative form of physical assessment (the TUGT) was added to the study protocol with ethical approval such that patients on beta-blocker medication could be recruited to the study and would not undertake the Step-box test. Therefore, beta-blocker medication was removed from the exclusion criteria.

5.2.4 Sample size and justification.

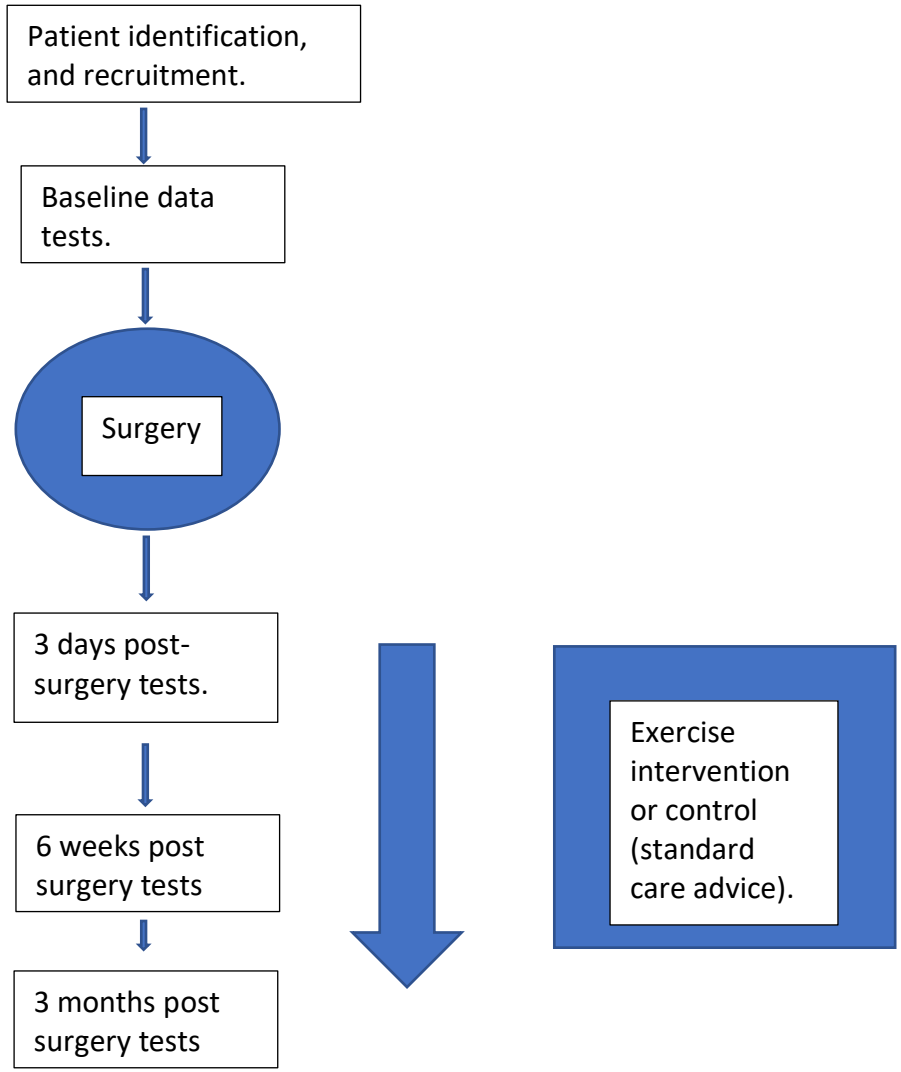
As a feasibility study, there was no data available to provide a statistical power calculation for this study. As patients were to be recruited from the RDH, based on the number of anticipated elective surgical procedures in the older patient group to be undertaken within the study period, it was estimated that a recruitment target of 30 patients would be realistically achievable.

5.2.5 Randomisation and blinding.

When participants had completed the informed consent process, they were then randomised via sequential numerical codes to either the control or intervention arm of the study. The randomisation was conducted using 30 sealed envelopes, 15 of each. There was no outwardly apparent discriminatory factor to determine which group the envelope belonged to and the envelope was of sufficient thickness to ensure that the information contained within could not be read through the paper. The envelopes were prepared by a member of the research department independent of the team running the study. The envelopes were labelled with a number and a computer randomisation programme (www.sealedenvelope.com. A randomisation and online database for clinical trials) allocated the envelope numbers to participant study identification (ID) codes.

5.2.6 Study regimen.

All participants were screened with standard NHS blood tests (full blood count and inflammatory marker), ECG, clinical examination (cardiorespiratory examination, height and weight, BP and resting HR, part of standard NHS care and as per National Institute for Health and Care Excellence (NICE) guidance) and a medical questionnaire (part of standard NHS care). With the exception of the health questionnaire, all aspects of the screening process were part of the standard NHS pre-operative assessment which the participant was required to complete as part of their surgical care.



Baseline data tests:

- Written consent shall be obtained.
- Participant shall be randomised to either the control or intervention arm of the study.
- Assessment & Questionaires: DASI, MoCA, IPAC (short form), EQ5D, GDS, REFS.
- Tests: ECG, Bloods (FBC & Inflammatory markers).
- Physical function tests: HGS, Step-box test, TUGT, Muscle USS

3 days post surgery tests:

- Physical tests: HGS and muscle USS.
- Tests: Bloods (FBC & Inflammatory markers)

6 weeks post surgery tests:

- To occur at planned surgical follow up appointment
- Assessments & Questionnaire: DASI, MoCA, IPAC (short form), EQ5D, REFS, GDS, compliance with exercise.
- Tests: Bloods (FBC & Inflammatory markers).
- Physical tests: HGS, Step-box test, TUGT, Muscle USS
- If in the exercise group: Compliance with exercise programme assessed and exercises reviewed.

3 months post surgery tests:

- To occur at planned surgical follow up appointment
- Assessments & Questionaires: DASI, MoCA,, IPAC (short form), EQ5D, REFS, GDS, compliance with exercise.
- Tests: Bloods (FBC & Inflammatory markers).
- Physical tests: HGS, Step-box test, TUGT, Muscle USS
- If in the exercise group: Compliance with exercise programme assessed and exercises reviewed.

Figure 5.1: This figure illustrates the study design. Initially assessments were to be completed at 6 months but as described below this was amended due to difficulties with recruitment

The study design is illustrated in figure 5.1. The study assessments took place pre-operatively and at 3-days, 6-weeks, and 3-months. Once discharged from hospital the assessments were timed to coincide, whenever possible, with the participants planned attendance at the hospital for standard NHS post-surgery follow-up. The participants completed the assessments at the Clinical, Metabolic and Molecular Physiology research unit in the University of Nottingham, School of Medicine, RDH. The assessment sessions were all supervised by medically qualified research staff trained in ALS.

For the participants enrolled in the intervention arm of the study, the exercise training programme was explained to the participant whilst they were in hospital and the exercises reviewed by the ward physiotherapist. The participant was provided with a paper copy of the exercise training programme instructions plus contact details for members of the research team should they require any assistance or need to notify the team of any problems (see appendix I).

5.2.7 Exercise training programme.

The choice of exercise training programme implemented in this study is discussed in detail in section 5.1.1. with the training programme provided in Appendix III. In brief, the training programme required the participant to exercise three times per week in their own home. It was anticipated that each session would vary in length depending upon the individual's fitness and physical function. Participants were asked to complete a training diary recording when they completed the exercises and which exercises were performed. The exercise training programme is illustrated in Figure 5.2.

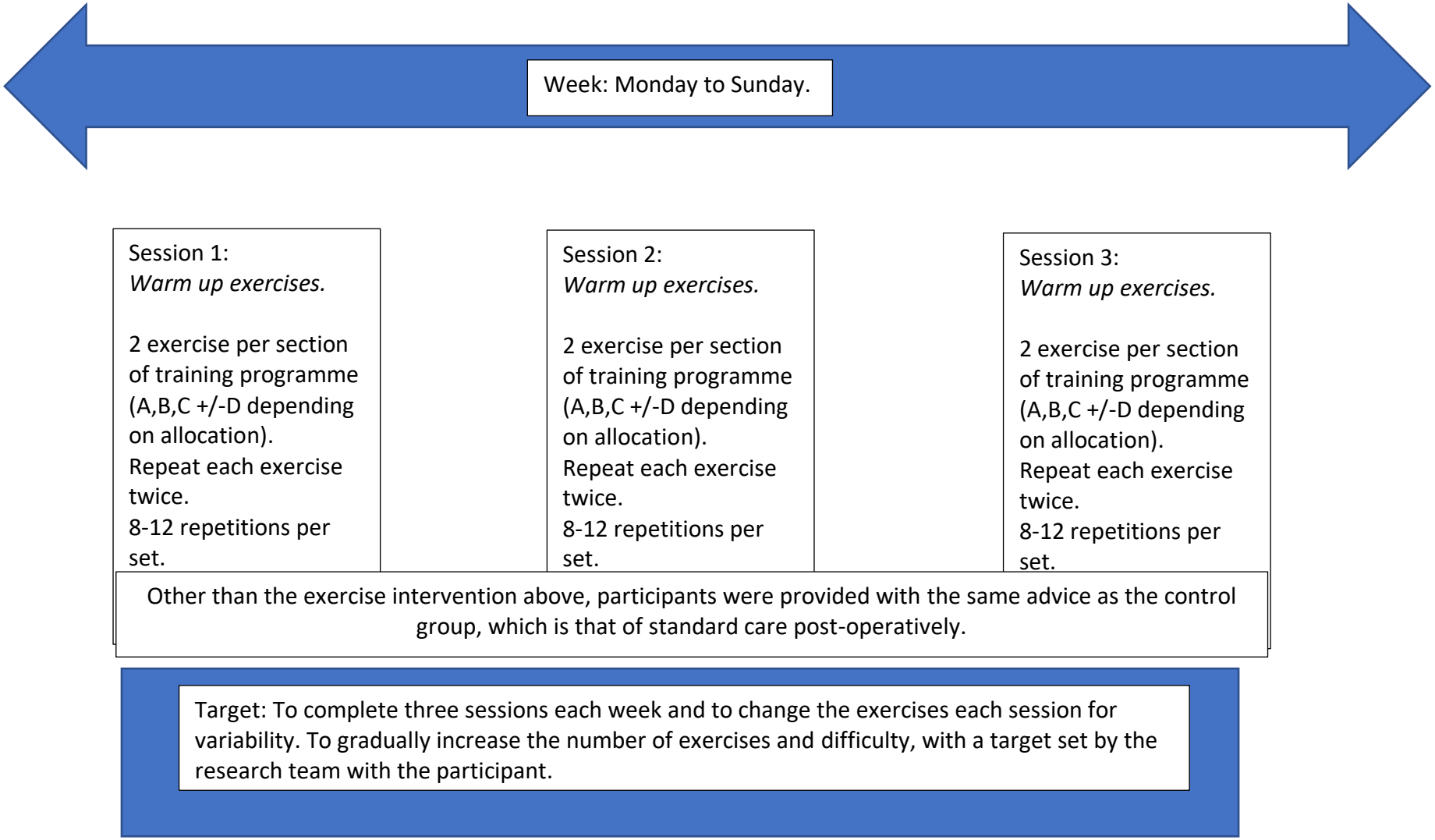


Figure 5.2. This figure provides a schematic overview of the exercise training programme.

The exercises were divided into sections covering the following categories (Table 5.2):

A.	Static and dynamic balance exercises in combination with lower-limb strength exercises. This included 9 exercises.
B.	Dynamic balance exercises in walking. This included 7 exercises.
C.	Static and dynamic balance exercises in standing. This included 12 exercises.
D.	Upper limb strength exercises. This included 3 exercises.

Table 5.2: The categories covered by the HIFE exercise programme.

Following surgery, on assessment at day 3 or on discharge the exercises which the participant would complete as part of the exercise programme were reviewed and selected on their ability to walk a short distance of approximately 10-metres unaided. The participants were allocated into one of two physical function groups depending upon whether they were able to walk with or without any physical support or supervision. For those not requiring support or supervision, they would complete sections A, B and D as described above and for those requiring supervision or support an extra set of exercises, section C, was incorporated into the training programme. The ward-based physiotherapists involved in the participants care were also consulted with regards to the suitability of the selection of exercises chosen.

Each exercise session involved warm-up (Figure 5.3) and recovery exercises (repetition of certain exercises used in the warm up session) taken from the Help the Aged Preventing falls exercise programme(13). At the start of the training programme, for the main exercises, the participant chose two exercises out of each section (A, B and D, or A, B, C and D) and completed two sets (8-12 repetitions per set) of each exercise. The participant was required to complete three exercise sessions per week, and we recommended that for each session in a week, they completed different exercises per section to improve variability. The aim was for the participants to gradually increase the number of exercises they completed each session, the target number of exercises would be reviewed on an individual basis when the research team contacted the participant. The written instructions that accompanied the

programme explained how the participant could increase the difficulty of the exercises as they began to feel more comfortable with each exercise and wished to challenge themselves further. The participant would be encouraged to keep increasing the number and difficulty of exercises completed per session until the end of the training period which was 6-months (initially, then revised to 3-months) post-surgery.

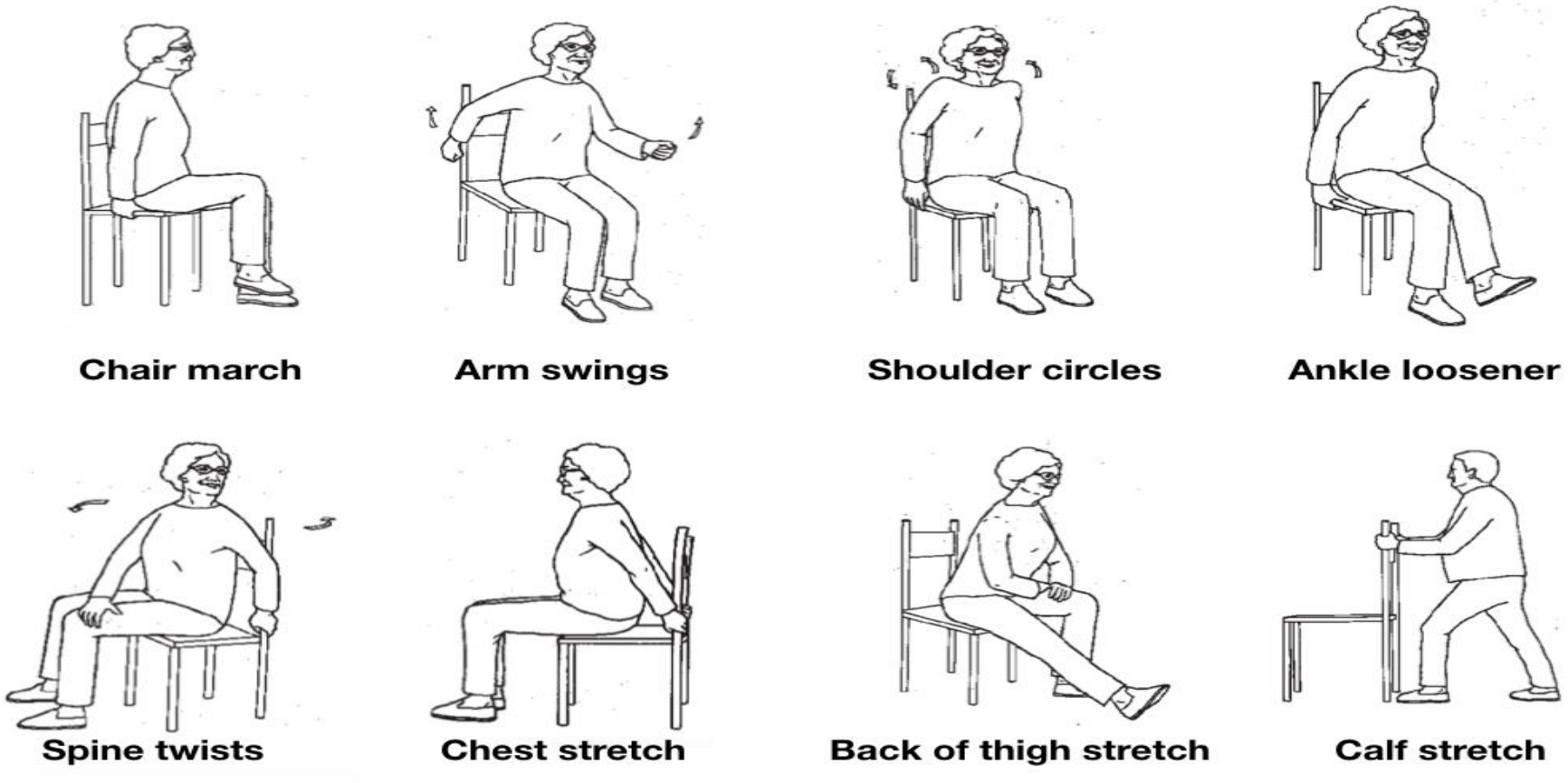


Figure 5.3: The warm-up exercises taken from the Help the Aged Preventing falls exercise programme (13) (Pictures reproduced from the by Help the Aged Preventing falls exercise programme (13)).

5.2.8 Assessment of the primary outcome.

The primary outcome of the study was the feasibility of the post-operative home-based exercise training programme. To measure this, compliance with the exercise training programme was assessed, and participant feedback on the exercise training programme was collected at the end of the intervention period. Participants were requested to complete an exercise training-log and this was reviewed at the 6-week, 3-month and 6-month assessment visits to assess compliance. In addition, the participants (if consent provided) were also contacted by telephone at 2, 4, 8, 10 and 15-weeks to have an unstructured discussion with regards to how they were progressing with the training programme. Feedback on the training programme was collected in the format of a questionnaire the participants completed at the end of the study.

5.2.9 Assessment of secondary outcome measures.

5.2.9.1 *Assessment of physical function.*

5.2.9.1.1.1 HGS assessment.

HGS was assessed using a handgrip dynamometer (Takei A 5401 hand grip dynamometer (GRIP-D, measuring range 0 – 500kg, produced by Takei, made in Japan, see Figure 3.6.). The method for this assessment is discussed in detail in section 3.2.5.3.

5.2.9.1.1.2 Step-box test assessment.

The methodology of the step-box test included in the battery of tests to assess physical fitness is described in section 3.2.5.2. A example of the step-box usedin shown in figure 3.5.

5.2.9.1.1.3 Models for the prediction of VO2peak using HGS and the step-box test variables.

As described in the introduction (5.1.3.) two models were derived in Chapter 3 to predict VO_{2peak} using HGS and step-box test data:

- VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.707)
- VO_{2peak} (ml/kg/min) = 36.1 + (Non-dominant maximal HGS x 0.310) + (fast step box time x-0.156) + (BMI x -0.66).

Both of these models will be used to analyse the study data for the assessment of the secondary outcome.

5.2.9.1.1.4 TUGT assessment.

The TUGT assessment is validated for use in older adults as a recognised test for the assessment of physical function(63) and frailty(62)(78), and as such is incorporated into the clinically utilised EFS system(3). The test requires minimal equipment as the participant is required to rise unaided from a standard chair, walk forward 3 metres at their normal walking pace, turn and then return to the chair and sit down(63). The time taken to complete this task is recorded, with a time of longer than 10 seconds a diagnostic component for frailty with high specificity and sensitivity(66).

As outlined above, this test was not initially included in the study design, however, the study protocol was amended to include the TUGT to improve study recruitment by enabling the recruitment of participants on beta-blocker medication. Participants on beta-blocker medication undertook the TUGT instead of the step-box test to provide a measure of global physical fitness.

5.2.9.1.2 Muscle architecture assessment.

The muscle architecture of the VL of each participants' (self-nominated) dominant leg was assessed using USS. This has been described in detail in section 3.2.5.1. Figure 3.3. shows the USS machine (Mylab 70, Esaote Biomedica) used in this assessment and Figure 3.4 provides an example of the USS images obtained and measurements collected.

5.2.9.2 *Assessment of frailty and cognition.*

5.2.9.2.1 Edmonton Frailty Scale.

The Reported Edmonton Frailty Scale(64) was used, this is a validated modified form of the EFS whereby the TUGT of physical function is replaced by patients self-reported physical activity. The is a clinical tool which is relatively quick to undertake, it covers the domains of cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance. Each domain scores 0 to 2 points with a total achievable of 17, the scoring is then divided such that 0 to 5 points indicate no frailty, 6 to 7, vulnerability, 8 to 9 mildly frail, 10 to 11 moderately frail and 12 to 17 severely frail.

5.2.9.2.2 Cognitive Assessment.

The Montreal Cognitive Assessment (MoCA) questionnaire is a validated cognitive screening tool designed to screen for mild to moderate cognitive impairment(362). It is scored on a 30-point scale and involves a clock drawing and trail test (connecting the dots). There are three versions of the MoCA, all of which were used in this study. One version was used twice due to the number of assessments in this study, the repeated versions were completed at the start and at the end of the study to reduce the risk of participant learning.

The original study plan aimed to use the computerised cognitive tests, the Simon test and the Symbol Substitution test. The Simon test assesses cognition by testing three stages of processing: stimulus identification, response selection and response execution, based on colour identification(367)(368) The Symbol Substitution test involves timed number and symbol matching in test grids to assess implicit learning and memory, with low scores for this test associated with increased risk of mortality(369),(370) These tests were removed from the study plan when the technological difficulties in running the tests arose and threatened to impact completion of the study.

5.2.9.3 *Duke Activity Status Index (DASI).*

The DASI is a validated questionnaire assessing activities of daily living. There are 12 questions in total, each weighted, and a summed total is derived between 0 and 58.2, which can then be used to predict peak VO_2 (ml/Kg/min)(371)(372).

5.2.9.4 *International Physical Activity Questionnaire short form (IPAQ-SF).*

The IPAQ-SF is a validated questionnaire for assessing physical activity levels(373)(374). The short form version which has been specifically designed and validated for older population (IPAQ-E) (375) was used for this study.

5.2.9.5 *EQ-5D-5L.*

The EQ5D is a questionnaire first introduced in the 1990's by the EuroQol group as a standardised method to assess generic health status(363). The questionnaire has undergone a number of changes to improve validity and reliability with the EQ-5D-5L(364) recommended for use in the older population. The questionnaire is a preference-based

measure which provides a single index score for the participant's health status after assessment in the dimensions of:

1) mobility,
2) self-care,
3) usual activities,
4) pain/discomfort and
5) anxiety/depression

5.2.9.6 *Geriatric Depression Scale (GDS).*

The GDS is a screening tool for mild to moderate depressive symptoms. The short form version of this tool consisting of 15 questions was used for this study(365) (376) It is recognised that depression is largely undiagnosed in the older population(377) and therefore could be a potentially confounding factor in this study as depression has been shown to effect engagement with exercise training programmes(378)(379) and, of course, general well-being (380)(381).

5.2.10 Statistical Analysis.

Statistical analyses were performed using Prism version 9.0.2 (Graph Pad Prism 9.0.2. (134), Graph Pad Software, LLC.), with all data reported as median ± the standard error of the mean (SEM), with significance set at $p<0.05$. Two-tailed Student's *t* tests were used to compare before and after training values.

5.2.10.1 *Assessment of the VL architecture.*

Section 3.2.8.2. details the methology for the statistical anlysis of the USS images using Image J (Image K 1.51s Wayne Rasband, National Institute of Health, USA, software in the public domain).

5.3 Results.

5.3.1 Participant Recruitment.

54 patients were screened to participate in the study, of these 11 consented to take part and 3 completed the study. Of those screened, 25 were male and 29 female, of the 11 which consented to take part in the study; 5 were male and 6 female with a mean age of 74 years (SEM 2.144). For the three patients which completed the study in its entirety, these consisted of one male and two females with a mean age of 70 years (SEM 2.028).

Of those patients screened there were various reasons why the potential participants were either excluded or themselves declined to take part in the study. 10 potential participants were excluded due to their beta-blocker medication, this prompted a review of the study protocol and amendment as described above in section 5.2.3.1. Participants on beta-blocker medication were excluded as this medication prohibited accurate analysis of the step-box test due to its effects on HR variability. The protocol amendment introduced the TUGT to replace the step-box test in those participants on beta-blocker medication, enabling such patients to be recruited to the study. 6 participants were excluded due to cardiovascular co-morbidities including atrial fibrillation and severe angina, 1 participant suffered a stroke at the time of the pre-operative assessment and one participant was excluded due to a severe respiratory condition limiting their physical function. Limited mobility and sight prevented a further 3 participants from undergoing recruitment. 4 participants had holiday arrangements which would have prevented them from fully committing to the study. A lack of transport into the hospital to undertake the testing prevented 5 participants from agreeing to take part. Two participants screened had already consented to take part in a similar study and for the remaining participants the reasons for not taking part included the consequent time pressure commitment to the exercise programme would cause.

Of the 11 patients who consented to take part in the study, the reasons for patient withdrawals are listed in Figure 5.7.

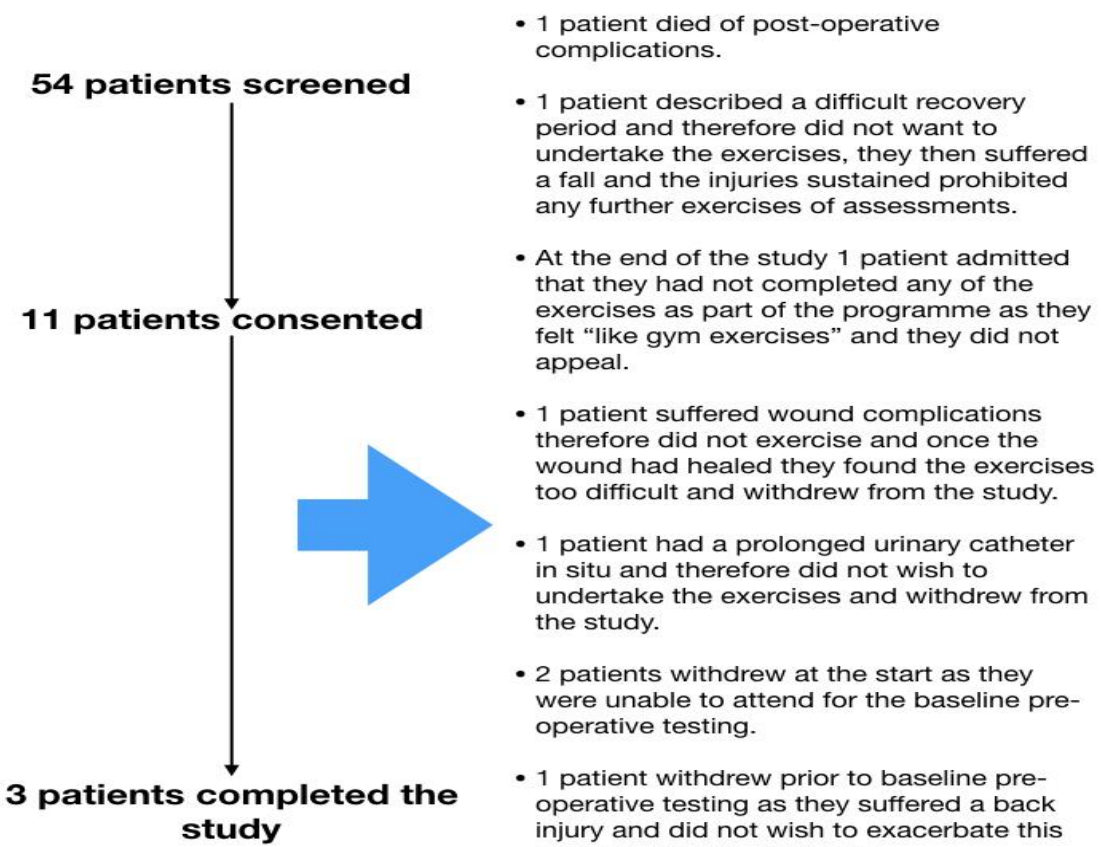


Figure 5.7: This figure details the reasons patients withdrew from the study.

5.3.1.1 *Participant Randomisation.*

The 11 participants consented to take part in the study underwent randomisation as described above in section 5.2.5. 5 were allocated to the control arm and 6 to the intervention (exercise programme) arm. Of the three participants who fully completed the study, all were in the control arm.

5.3.2 Compliance with the Exercise Programme.

One participant in the randomisation arm, did complete the study in that they were compliant with all aspects of the study except the exercise programme. The participant throughout the study, at meetings and when contacted by telephone, had admitted they struggled to motivate themselves to undertake the exercises but "were giving it a go", however, at the very end of the study they admitted they had not completed any of the exercises and explained that they had not admitted this sooner as they did not want to upset the research team and had not wanted to let the study down, a friend had convinced them to come clean at the final meeting.

Comments from the participants who attempted to undertake the exercise programme but failed to complete it, included a fear of doing harm to themselves by undertaking the exercises, one participant complained that the exercises were like going to the gym and they did not like going to the gym, and the partner of one participant stated, "you need to be in the SAS to do this".

5.3.3 Data Analysis.

The median age of the three participants who completed the study as directed per protocol (control group) was 70 (SEM 2.03) years, 2 were female and 1 male. The participant who was recruited to the intervention arm, but ultimately did not complete any of the exercise programme was 71 years of age (female). The median age of all those participants that consented to the study (both those that completed and those that withdrew / were withdrawn from the study) was 74 (SEM 2.1) years.

Of the four participants who completed the study testing, the three controls and the participant in the intervention arm but who failed to undertake the intervention, the data was not analysed as no meaningful data and conclusion pertaining to the primary or secondary outcomes of the study could be drawn from these results.

5.4 Discussion.

The UN publication on World Population Ageing in 2017(15) highlighted the change in global population dynamics, with the expected number of individuals over the age of 60 years to double by 2050 to approximately 2.1 billion, with the number of those over 80 years of age expected to increase from approximately 137 million to 425 million. This alongside the reduction in fertility accounts for the change in population dynamics such that the proportion of the population over 60 years of age is increasing(15). Despite these changes in population demographics, in research older participants are generally under-represented(382). This failure to incorporate older participants into studies compromises research outcomes as it impacts on the generalisability of the findings to the population, limiting the external validity of the research. The significance of this is recognised and as such there is a drive to improve the involvement of older individuals in research and this is exemplified by the European charter for older people in clinical trials (PREDICT) which advocates the rights of older individuals to be involved in clinical trials(383)

5.4.1 Participant recruitment.

Although it is easy to address the exclusion of older participants from trials by changing factors in trial design, such as removing or increasing the upper age limit for the target recruitment group, and for this study there was no upper age limit. The actual recruitment and retention of older participants in research is challenging, for example recruitment of participants over 65 years of age to the SUSTAIN programme which incorporated a home based physical activity intervention, saw 124 patients screened with only 4 consenting to participate(384). Such a low recruitment rate is not uncommon in research focused on addressing physical function in the older participant, a 11% recruitment rate was quoted for one study looking at exercise programmes in the at risk of physical disability, older population(385). In the papers included in the systematic review in chapter 2 looking at

physical exercise programmes following major non-cardiac surgery in the older patient, the Latham et al(215) study had a recruitment rate of 15%, whilst for the Porserund et al(386) study it was 20%, however, a recruitment rate of 55% was achieved by Park et al(387). The recruitment rate of 20% (11 participants consented to take part out of 54 screened) for this study therefore is not out with the common experience for this type of research.

Few studies attempting to recruit older participants have specifically looked at the recruitment issues faced and compared these to the recruitment strategies employed(388). However, a unwillingness to travel is a repeated barrier to recruitment for many studies(384)(389) and other common recruitment barriers include the additional demands of the study(390), a distrust in research(388) and a lack of benefit along with health difficulties(388).

For this study, the exercise intervention itself had a negative impact on recruitment and retention. Although no potential participant approached stated that the thought of exercising itself was a negative, the impact of undertaking an exercise programme on their time was a negative factor. Further a number of participants were excluded based on their physical co-morbidities impacting on their ability and risk with regards to undertaking the exercise intervention. A number of participants who were excluded or declined to participate due to personal circumstances had stated that they would have liked to undertake the challenge of the exercise intervention as they could understand the potential benefit this may offer them. Although it has been shown that frailty and intervention intensity does not predict recruitment outcomes(391), this work did not involve participants undergoing surgery, and the intensity of the exercises required of them in the recovery period, in this study was a reason for one participant to withdraw from the study.

The anticipated difficulty in recruiting older patients to a study involving exercise following major abdominal surgery had impacted the design of the study. Factors in the protocol design to minimise the impact of the exercise programme and the testing sessions included, wherever possible, matching the meetings with the patient to undertake consent and physical function assessment to the timings of meetings the patient had with their surgical team. The exercise programme itself was chosen as it was felt a home-based programme

would have less of a negative impact on the patient's time as compared to a supervised exercise programme which would need to be undertaken in the University and therefore have a restricted time frame for completion and also a need for transport. One of the reasons a number of participants declined to participate in the study was due to the need for transport into the hospital to undertake the physical function assessment sessions. Therefore, a supervised exercise programme in the hospital would for this reason potentially have further negatively impacted recruitment. In contrast, Chapter 4 used a supervised exercise training programme as part of its study protocol. The supervised nature of the training programme did not prohibit those screened from taking part, however, a number of participants did not complete the study and no feedback was obtained specifically addressing this point, therefore it may have not been reported. Further, the manner in which the participants were recruited was different such that they responded to advertisements, however, for this clinical study potential participants were approached. As such it is of no surprise that he participants in the Chapter 3 study were not reflective of the general population (see section 3.4), or those undergoing major cavity surgery, as this group, in the main was formed of highly motivated healthy individuals, with an interest in their physical fitness.

Although as stated above, intensity has not been shown to predict recruitment outcome(391) as this study involved undertaking exercises following major cavity surgery, the intensity of the exercises was deliberately kept low with the option to increase the difficulty of the exercises on an individual participant basis. It was hoped this would help with retention of the participants in the study, however, as already stated, one patient withdrew due to the perceived difficulty of the exercises, and one participant was fearful that the exercise would cause them harm despite reassurances to the contrary.

5.4.1.1 *Psychological Factors impacting recruitment.*

Engagement of the older population in physical activity(392)(393) and with physical activity programmes is limited(392). Barriers to physical activity include a lack of time and fear over their ability to undertake the exercises or the possible risks and complications of the exercises(393), with such barriers arising as recruitment and retention issues in this study.

A deliberate design feature of the exercise programme was that it should be home based to reduce the impact of the programme on the participant's time. Consequently, the participant undertook the exercises alone, albeit potentially with family or friends close by. The participant recruited to the intervention arm but who did not complete any of the exercise programme despite otherwise complying with the study, stated that they would have preferred group exercises as it would have helped to provide the motivation, they needed to get on with the exercise programme. There is evidence to support the positive influence of group exercises on participation and adherence to exercise programmes(361)(393) and the study described in Chapter 3 demonstrated this. Although the study design in Chapter 3 did not explicitly involve group exercise sessions, as the study progressed a number of the participants intentionally chose times to undergo their supervised training sessions when other participants would be present, and the support and encouragement this company provided was clearly apparent during the sessions, such that a number of the participants stated they would miss the sociable aspect of the training programme once it was completed. Although, group training sessions may not suit all individuals, the option of such sessions or a training programme mixed with supervised and non-supervised sessions would potentially address these issues and improve recruitment and retention to future training programmes.

5.4.1.2 *When to recruit?*

It is apparent from the findings of the surveys in Chapter 4 that for many older patients undergoing surgery, there is possibly an un-realistic expectation of their recovery process. Therefore, recruiting patients pre-operatively to a post-operative exercise intervention programme, is liable to suffer retention issues as the patients no longer are willing or feel able to undertake the exercises as their recovery process begins. Recruiting patients in the immediate post-operative period would pose its own logistical challenges but would potentially enable the feasibility of the post-operative exercise programme to be truly determined, the primary outcome of this study. It would not have enabled the secondary outcomes of impact on cognition and physical function to be measured as baseline assessment pre-operatively would be essential.

5.4.1.3 *Patient and public involvement (PPI) and recruitment.*

Patient and public involvement (PPI) improves study design and thereby recruitment by ensuring the study is relevant to the target population and the information provided on this and the study design is appropriate(394). PPI was not a part of the study development process, and it is possible that it may have highlighted some of the recruitment and retention issues i.e. the concerns over transport, the impact on participant time and the design of the exercise programme, enabling a more participant focused study design to be developed at the beginning. Also PPI incorporated into the actual recruitment process itself can be of benefit(394) and this was demonstrated in the exercise intervention study in chapter 4 when one participant enjoyed the study so much that they actively recruited to the study.

5.4.1.4 *Study design and recruitment.*

Although for many studies, strict eligibility criteria often precludes the recruitment of the older participant(395), after removing the use of beta-blocker medication as an exclusion criteria by adapting the study protocol to account for this, the eligibility criteria of this study was not a major limiting factor in recruitment.

Other than the factors already discussed above, recruitment may be facilitated through the use of services such as private transport services. Taxi services minimise the cost, both financially and psychologically (removes anxiety for example associated with hospital parking) to the participant. In this study it was possible to ensure there would be no parking costs, but options such as a free taxi service may have helped recruitment and retention and it is recommended that budgeting for such a service is included in study finances to facilitate this(394). Other factors contributing to facilitating recruitment, such as an appropriately adjusted typeface to improve the legibility of the PIS for those with diminished sight were implemented as recommended(394).

5.4.1.5 *The research team.*

This study was undertaken by a small research team, involving research staff with clinical commitments and as such recruitment was at times limited by the availability of the team, a factor that is recognised as a common problem in RCTs(390).

5.4.2 In summary.

It is imperative that studies are conducted involving older participants representative of the general population(395). Although this study design attempted to address the needs of the target population, a closer inspection of these needs would likely be achieved through the involvement of PPI, ensuring the study protocol is as "user friendly" to the participants as possible and thereby potentially improving recruitment and retention. Further, the study design and protocol should take into account other factors limiting recruitment such as financial constraints limiting the provision of services such as taxi's and also the time and resources of the research team.

Many of the participants had been positive and motivated by the study pre-operatively when they consented to take part, however, the reality of the recovery process changed their minds. To therefore fairly consent the individual to the study, should recruitment occur post-surgery in the recovery period, when they can truly understand what is being asked of them and reason their ability to undertake this. If so, this impacts not just on the study design but also on the objectives of the study, the secondary objectives in this case.

6 Discussion.

With the title of this thesis; determining the need for, effectiveness and feasibility of bed-side measures to determine physical fitness in the older surgical patient, the aims as outlined in section 1.4. where to evaluate the evidence underpinning the use of exercise-based therapies in the post-operative period, for older surgical patients, through systematic review as presented in Chapter 2. With the need for further work in this area clarified by the outcome of this review, Chapter 3 aimed to explore the utility of bed-side assessments of physical fitness in the older adult, at both a single time point and as a tool to track change. As previously discussed in Chapter 1, it is important to ensure the patient is at the center of their care, as such Chapter 4 aimed to ascertain the view of patients and the associated clinical teams to develop a better understanding of patient recovery needs. With Chapter 5 pulling these strands together to determine the feasibility of an 8-week home-based exercise programme following major abdominal surgery in the older population.

As stated in Chapter one, we are an aging population, life expectancy has increased since the establishment of the NHS in 1948(14), with in particular those over 85 years of age increasing at the fastest rate(1). However, with an aging population comes an increase in comorbidities such as COPD, diabetes and IHD(17) alongside common geriatric syndromes such as frailty(3) and as the proportion of individuals undergoing surgery who are over the age of 75 years is increasing(2), this poses increasing challenges to the NHS to meet the needs of these patients. As discussed in section 1.1., these needs such as access to good acute services, rehabilitation, and person-centred care, require this shift to a multi-disciplinary approach and a review of public health strategies, necessary to ensure inequalities in life expectancy and premature mortality are addressed(19).

Perioperative medicine aims to improve the patients care pathway through surgery to facilitate recovery, it does this by taking a multi-disciplinary long view of the care pathway; from initial presentation to the GP through to discharge and recovery(27). This along with the success of enhanced recovery programmes to improve LoS and reduce complication rates across surgical specialties'(396), show how a more global approach to patient care has been fostered. Specifically for the older patients, and in light of the dynamic nature of the geriatric syndrome frailty(51), an over-arching multi-disciplinary approach is warranted and

exemplified by the CGA(39). Consequently, around surgery there has been an increasing focus on the multi-disciplinary perioperative management of the older patient(397)(398).

As such, with frailty an independent risk factor for morbidity, mortality and increased LoS(4)(5) with links to post-operative complications(38), this global, multifactorial syndrome as described in section 1.2. is the focus of attention for this thesis. As a dynamic process(51), by addressing modifiable factors leading to frailty, there is the potential to improve patient outcomes and QoL. With physical function included in all the various frailty assessments(6)(7)(8)(9)(10), and sarcopenia (the loss of skeletal muscle mass and strength and described in section 1.2.5.) strongly linked with frailty and adverse outcomes(7)(8), these modifiable factors offer the potential to address frailty through the implementation of perioperative exercise training programmes.

Although prehabilitation has been shown to improve patient surgical outcomes and QoL across various surgical specialities(197)(198)(199)(200)(201), the main body of work looking at exercise interventions post-operatively has been through rehabilitation programmes implemented after cardiac surgery (see section 2.1.). However, as described in section 2.1. this surgical population is not representative of the general surgical population. The systematic review in Chapter 2 therefore aimed to evaluate the evidence base for post-surgery exercise interventions to improve physical function and QoL in the older non-cardiac surgical population. The review showed post-operative exercise interventions, in particular multi-modal exercise programmes (resistance and aerobic), could benefit physical fitness as demonstrated by an increase in the walking distance during a 6MWT of 33m which was consistent with previously reported MID values (section 2.4). However, no improvement in mental health as measured using the SF-36 questionnaire was established. Unfortunatley, this review was limited by the significant clinical heterogeneity and lack of intervention consistency across the five studies included. Consequently, this review highlighted the need for further research to establish the benefit of post-operative exercise programmes. It also highlighted the need to establish the feasibility of post-operative exercise programmes. Such feasibility was not addressed by any of the studies included in the review, and although adherence rates were reported as good, suggesting the exercise was well tolerated by the patients in two of the studies(215)(217), three studies(214)(216)(217) suffered from

high drop-out rates, with one study(214) reporting that a reasonable proportion of the withdrawals occurred during the exercise training period.

With the attention of the thesis focused on the modifiable factor of physical fitness in the post-operative period, appropriate bed-side measures of CRF, valid for the older population and appropriate following surgery were compared to the gold-standard test for CRF, CPET(95)(96)(97)(98)(100) in Chapter 3. These alternative measures included HGS and the step-box test which are discussed in detail in section 1.3.2. The use of HGS as a simple clinical tool to aid in the clinical assessment of patients was supported by the study findings. The results revealed both dominant and non-dominant HGS correlated significantly with the principle CPET measures of CRF, VO_{2peak} and AT (Section 3.3.3.1, Figures 3.8a-d, 3.9a-d) and although statistical modelling did not find any measures of HGS to be independent predictive tools for VO_{2peak}, in conjunction with BMI, dominant maximum HGS was successfully modelled to predict VO_{2peak} using the following equation: VO_{2peak} (ml/kg/min) = 31.648 + (dominant maximum HGS x 0.297) + (BMI x -0.70).

A model incorporating step-box data in combination with gender and BMI was developed which could significantly and reliably predict VO_{2peak} (VO_{2peak} (ml/kg/min) = 39.1 + (fast step box time x-0.2) + (gender x 4.7) + (BMI x -0.64)). However, the main variables of the step-box test demonstrated no significant relationship with the main CRF variables as measured by CPET, the VO_{2peak} or AT (refer to section 3.3.3.2). Further, a model incorporating both HGS, the step-box test and BMI was also devised which could predict VO_{2peak} (refer to section 3.3.5). However, for simplicity in the clinical environment, a single alternative option for measuring CRF is required, either HGS or the step-box test, and based on the data from the Chapter 3 study this would support HGS. HGS itself is methodologically a simpler tool to use as compared to the step-box test, which is discussed in section 3.4 and its use clinically is well supported in the literature(66).

With the aim of the thesis to look at the implementation of a post-operative exercise training programme. The sub-section of the study in Chapter 3 focused on the ability of these bed-side tests and predictive models to measure change in CRF following an exercise intervention. 4 weeks of exercise training based upon the NHS guidelines on physical activity

for older adults(185)(274) was demonstrated to improve physical fitness in older healthy volunteers as assessed using CPET (see section 3.3.7.). However, the derived models were unable to predict this positive change. Only 14 participants completed the study and with a significant relationship demonstrated between HGS and the CPET VO_{2peak} (L/min) data following the exercise intervention (refer to Figure 3.11a.-d.), this could suggest that there was insufficient power in the study to measure change in CRF using the derived models.

In addition to assessing the relationship between the bed-side measures of physical fitness and CRF, the relationship between muscle mass (using muscle USS(252)(253)(254)(289)) and CRF was also explored. Despite prior evidence supporting a relationship between CRF and muscle mass irrespective of age(244)(245)(246), no significant relationship was evident between any of the measures of muscle mass and those of CRF (CPET, HGS or step-box test) in the studies conducted in Chapter 3. There is no clear explanation for this, other than the participants were not matched for co-morbidities or for baseline physical activity or fitness levels, which may have resulted in sufficient variance in the VL architecture and therefore the muscle USS measurements, to prevent any statistical relationships within the data being observed.

Although the engagement by the secondary care health care professionals with the surveys assessing their anticipated expectation of a patient's recovery experience following major non-cardiac surgery, as described in Chapter 4, ensured that no reliable conclusions could be drawn. The information provided was mainly positive with regards to the potential value of post-operative exercise programmes to target physical fitness.

Drawing on this support for post-operative exercise interventions during recovery, the bed-side measures as described above where used in the protocol for the study in Chapter 5, whereby one of the secondary aims of the study was to assess the impact of an exercise programme in the post-operative period on physical fitness in older patients. However, as described in Chapter 5, the study failed to implement a post-operative exercise programme that was accepted by the patients, therefore it was not possible to determine whether these bed-side tests and models could feasibly be used to measure post-operative physical fitness and outcomes following an exercise intervention.

The ultimate conclusion of the RCT in Chapter 5 is that it was not feasible to implement a post-operative training programme for older surgical patients undergoing major non-cardiac surgery. The findings of the RCT were in contrast to those established in the systematic review conducted in Chapter 2, although feasibility had not been measured by any of the studies reviewed, patients had completed the studies, unlike the patients in the Chapter 5 RCT. However, it is probably more accurate to attribute the lack of demonstrated feasibility to the study design (see section 5.4.1.4.). The patient and health care professional surveys focused on the patients post-operative recovery experience and needs (see Chapter 4), highlighted the patients "expectation mismatch" and this was evident in the result of the Chapter 5 RCT. Patients had been willing, and in some cases were very engaged, committed, to undertaking the exercise programme following their surgery. However, once in the recovery period this engagement ceased and from feedback provided this could in part be attributed to this expectation mismatch.

The attempt to form a consensus opinion on the recovery needs of the older patient following major abdominal surgery, as presented in Chapter 4, proved to be enlightening work on a personal level. Although the study design was limited, the information garnered, and lessons learnt were invaluable. This study demonstrated the importance of direct engagement with patients, not just when conducting research but on a day-to-day basis, to ensure their needs, what is important to them, remain the primary focus of health care delivery. The "expectation mismatch" as highlighted by the GPs, seems obvious in hindsight, however, only through engagement with the patients and the primary care sector, is this the case. It is therefore evident, that to fully understand the patients journey along their care pathway, to ensure health care provision is patient centred, requires improved communication links and partnerships between the primary and secondary care sectors and patients.

Ultimately this is the ethos of perioperative medicine and the global approach to patient care. Focusing back on clinical research study design, this body of work highlights the need for a broader perspective in our approach. A multi-disciplinary approach, with active involvement by the various stakeholders in the patient's perioperative journey would

facilitate a thorough understanding of the clinical challenges and patient's needs. In particular, going forward, it is clear that prior to implementing change to the recovery pathway, the patient's expectations must be understood, to inform the study design, such that for example, with respect to a post-operative exercise intervention, valid consent may only be achievable post-surgery and successful engagement may depend in part on patient education focused on their expectations, before true feasibility can be determined. Ultimately, if the patients are not at the centre of the study design process, then is the risk that the outcome of the study may prove meaningless to those very patients it aims to improve health care for.

6.1 The next step.

Although this thesis has demonstrated further work is required to explore the feasibility of exercise interventions in the recovery period following surgery for the older patient, and from this to establish the impact of targeting physical fitness on patient outcomes. Prior to undertaking this, the first step would be to clarify the outcomes which matter to the patient, ensuring their needs are met, placing them at the centre of this work and from that then evaluating pertinent clinical outcomes such as morbidity, mortality and LoS. The opinions of the various stakeholders involved in the patient's care remain pertinent, as discussed, the information gleaned from the results of the GP survey helped to clarify an understanding of the patients recovery expectations. However, the aim of the study in Chapter 4, to try and ascertain all of these views was bold, under-estimating the enormity of that task, and thereby failing to achieve the desired results. Therefore, the next step would be to go back to the patients, and as discussed in section 4.4.5. the use of the Delphi method(319) would enable a consensus opinion on their needs to be achieved. This knowledge, along with the involvement of representative patients throughout the design process and conduct, can ensure future studies provide answers to the questions that matter to the patients directly and to the health care system to enable meaningful change.

6.2 In conclusion.

As a body of work this has demonstrated the need for, and potential value of addressing physical function through the use of exercise interventions in the post-operative period for older patients. With alternative tests of physical fitness, such as the HGS useful clinical tools. However, as detailed in each Chapter discussion, the studies have suffered from a number of limitations and as such further work is required in this field. This thesis has highlighted the need for greater collaboration between health care disciplines in order to understand patients' needs along-side clinical outcomes, improving study design, facilitating patient and health care engagement in research, thus ensuring future work leads to meaningful and better outcomes.

Appendix I

Chapter 6 Exercise training programme.

The HIFE Programme

The High-Intensity Functional Exercise Programme

Second Edition

Developed at Umea University, Sweden.

With Exercises and information provided incorporated from the Help the Aged Preventing Falls programme.

CONTACT INFORMATION:

Principal Research Investigator: Dr Laura Carrick

Mobile: 07429377430

Tel: 01332 724601 ext. 24731

Email: msxlc2@nottingham.ac.uk

Research Investigators and Contributors to exercise programme:

Dr John Williams, Clinical Associate Professor and Consultant Anaesthetist.

Mr Jon Lund, Clinical Associate Professor and Consultant Colorectal Surgeon.

Dr Beth Philips, Assistant Professor.

The exercise training programme is a combination of the HIFE programme developed by Umea University, Sweden and the Preventing Falls: Strength and balance exercises for health ageing training programme developed and published by The Help the Aged.

The exercises cover the following categories:

A. Static and dynamic balance exercises in combination with lower-limb strength exercises.
B. Dynamic balance exercises in walking.
C. Static and dynamic balance exercises in standing.
D. Upper limb strength exercises.

We will assess the level of physical support you will require on day three after your surgery, depending upon this we will select the exercise programme best suited for you.

Physical Function Group	Categories for selection of exercises
Walking without any physical support or supervision.	A. Static and dynamic balance exercises in combination with lower-limb strength exercises. B. Dynamic balance exercises in walking. D. Upper limb strength exercises.
Walking with supervision or minor physical support from one person.	A. Static and dynamic balance exercises in combination with lower-limb strength exercises. B. Dynamic balance exercises in walking. C. Static and dynamic balance exercises in standing. D. Upper limb strength exercises.

Safety Instructions:

Wear Comfortable clothes and supportive footwear.

Prepare a space in which to do the exercises free of obstacles.

While exercising, if you experience chest pain, dizziness or severe shortness of breath, stop immediately. If the symptoms do not improve contact your GP or attend A&E. If they do improve contact your GP and a member of the research team before doing any further exercise.

If you experience any pain in your joints or muscles, stop, check your position and try again. If the pain persists contact a member of the research team.

Exercise Sessions:

We ask that you complete three exercise sessions each week, starting slowly with a few exercises chosen from each section and building up each week until you can complete all of the exercises. The programme also explains how you can increase the difficulty of the exercises if you want to.

Each exercise session has a set of warm up and cool down exercises.

For the main exercises we ask that you do a set of 8 to 12 repetitions of each exercise and complete two sets.

At the start, for each session we ask you to choose two exercises from each section and complete two sets, over the week you will complete three sessions and we suggest you change the exercises for each session. With time you build up the number of exercises you do each session.

WARM UP EXERCISES

The Chair march:

- Sit tall.
- Hold the sides of the chair
- Alternately lift your feet and place them down with control.
- Build to a rhythm that is comfortable for you.
- Continue for 30 seconds.

Arm swings:

- Place your feet flat on the floor below your knees.
- Bend your elbows and swing your arms from the shoulder.
- Build to a rhythm that is comfortable for you.

- Continue for 30 seconds.

Shoulder circles:

- Sit tall with your arms at your sides.
- Lift both shoulders up to your ears, draw them back, then press them down.
- Repeat slowly 5 times.

Ankle loosener:

- Sit tall away from the chair back.
- Hold the sides of the chair.
- Place the heel of one foot on the floor, then lift it and put the toes down on the same spot.
- Repeat 5 times on each leg.

Spine twists:

- Sit tall with your feet flat on the floor.
- Place your right hand on your left knee and your left hand behind you on the chair back or side of the chair.

- Sit very tall, then, with control, turn your upper body and head towards your left arm.
- Repeat on the opposite side.
- Repeat 5 times.

Chest stretch:

- Sit tall away from the chair back.
- Reach behind with both arms and hold the chair back.
- Press your chest forwards and upwards until you feel the stretch across your chest.
- Hold for 8 seconds.

Back of thigh stretch:

- Move your bottom to the front of the chair.
- Place your right foot flat on the floor, then straighten your left leg out in front of you with your heel on the floor.
- Place both hands on the right thigh, then sit tall.
- Lean forwards and upwards until you feel the stretch in the back of your left thigh.
- Hold for 8 seconds.
- Repeat on your other leg.

Calf stretch:

- Stand behind the chair holding the chair back.

- Step back with one leg checking that both feet are pointing forward.
- Now press the heel of the back foot into the floor until you feel the stretch in your calf.
- Hold for 8 seconds.
- Repeat on your other leg.

SECTION A: Static and dynamic balance exercises in combination with lower limb strength exercises.

A1: Squats in a parallel stance.

- Stand with feet parallel to one another, shoulder width apart.
- Bend then straighten the knees and hips.

The difficulty can be increased by:

- Making deeper squats.
- Reducing the base of support.

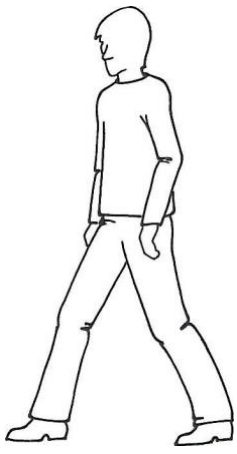
A2: Squats in walking stance.

- Stand with one foot in front of the other, shoulder width apart.
- Bend then straighten the knees and hips.

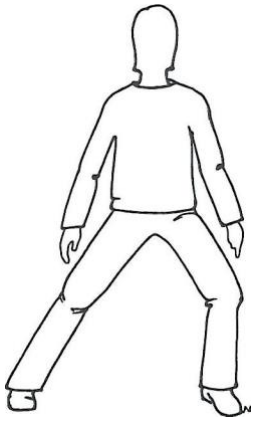
The difficulty can be increased by:

- Making deeper squats.
- Reducing the base of the support.

A3: Body weight transfer in parallel.



- Stand with feet parallel, slightly wider apart than shoulder width.
- Transfer body weight back and forth to each leg on a bent knee.

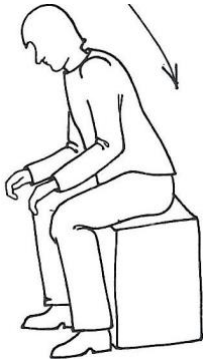


A4: Standing up from sitting in a parallel stance.

- Stand up and sit down on a chair with feet parallel.
- You can use hands on the chair for support if needed but the aim is to progress to no hands over time.

  The difficulty can be increased by:

  - Reducing the height of the chair.
  - Reducing the base of support.



A5: Standing up from sitting in a walking stance.

- Stand up and sit down on a chair with one foot in front of the other.
- You can use hands on the chair for support if needed but the aim is to progress to no hands over time.

The difficulty can be increased by:

- Reducing the height of the chair.
- Reducing the base of support.

A6: Forward Lunges.

- Stand with feet shoulder width apart.
- Take steps forward and back.
- Alternate your feet, bending the forward knee,
- Then shoot back to the start position.

The difficulty can be increased by

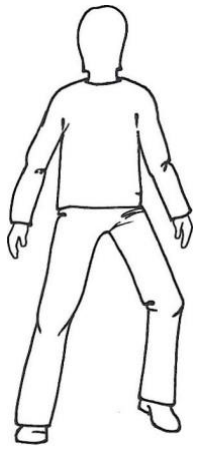
- Making deeper squats.
- Lunging further forward.
- Increasing the speed of the movements and the change of feet.

A7: Side Lunges.

- Stand with feet shoulder width apart.
- Take steps to the side and back
- Bend the knee that steps out.
- Then shoot back to the start position.

The difficulty can be increased by

- Making deeper squats
- Lunging further to the side
- Increasing the speed of the movements and change of feet.



A8: Walk up and down stairs.

Walk up and down stairs.

A9: Heel raises.

- Standing tall.
- Hold a sturdy table or chair
- Raise your heels taking your weight over the big toe and second toe.
- Hold for a second
- Then lower your heels to the floor with control.

The difficulty can be increased by

- Performing with one leg at a time.

- Reducing the base of support.

SECTION B: Dynamic balance exercises in walking.

B1 Walking forward on a flat surface.

Walk forward on a flat surface.

The difficulty can be increased by:

- Increasing or varying the walking speed.
- Walking with a narrower base of support, for example on a line.

B2 Walking in various directions.

Walk forwards, backwards or sideways.

The difficulty can be increased by:

- Increasing or varying the walking speed.
- Varying the speed more often.

B3 Walking with numerous turns.

Walk forward and frequently change direction by 180 degrees.

The difficulty can be increased by:

- Increasing the speed of the changes in direction
- Changing the direction more often.

B4 Walking over obstacles.

Walk forward or sideways, stepping over obstacles, for example sticks or step boards.

The difficulty can be increased by:

- Stepping over higher or longer obstacles.
- Varying the directions more often.

B6 Walking on a soft surface.

Walk on a soft surface forwards, backwards and sideways. Use a rug or quilt but be careful not to trip.

The difficulty can be increased by:

- Walking on a thicker surface.
- Increasing or varying the walking speed.
- Varying the direction.

B7 Walk in a circle on the spot.

Walk in a circle on the spot and then change direction.

The difficulty can be increased by:

- Increasing the speed.

SECTION C: Static and Dynamic balance exercises in standing position.

C1 Maintaining stance with feet parallel or in a walking position.

Stand with feet shoulder width apart parallel or in a walking position.

The difficult can be increased:

- Reducing the base of support.
- Transferring body weight in various directions within the foxed base of support.
- Close your eyes.

C2 Turning the head in various directions sideways, up and down.

- Stand with feet shoulder width apart.
- Turn your head to the right, to the left, look up to the ceiling, and down to the floor.

  The difficulty can be increased by:

  - Reducing the base of support.
  - Increasing the degree of the turn.

- Increasing the speed of movements.

C3 Reaching for an object in various directions.

- Stand with feet shoulder width apart.
- Reach for and grasp objects.
- Move the objects in various directions.
- The objects may be placed on for example a table.

The difficulty can be increased by:

- Reducing the base of support.
- Increasing the distance to the object.
- Increasing the variation in direction.
- Increasing the weight of the object.

C4 Trunk Rotation.

- Stand with feet shoulder width apart.
- Rotate your trunk and head to the right and then to the left.

The difficulty can be increased by

- Reducing the base of support.
- Increasing the degree of rotation.
- Increasing the speed of rotation.

C9 Throwing and catching a ball.

Catch and throw a ball.

The difficult can be increased by:

- Throwing the ball faster to various points.

C10 Side step and return.

- Starting with feet shoulder width apart.
- Take one step to the side and then return to the starting position.
- Weight should be on a bent knee of the leg that is moved before it is returned to the starting position.

The difficulty can be increased by:

- Reducing the base of support at the start.
- Increasing the distance the leg is moved to the side.
- Increasing the speed of the changeover from leg to leg.

C11 Forward step and return.

- Stand with feet shoulder width apart.
- Take one step forward, then return to the starting position.
- Weight would be on a bent knee of the leg that is moved before it is returned to the starting position.

The difficulty is increased by:

- Reducing the base of the support at the start.
- Increasing the distance the leg is moved forward.
- Increasing the speed of the changeover from leg to leg.

C12 Stop and kick a ball.

Stop a ball with your feet and kick it back.

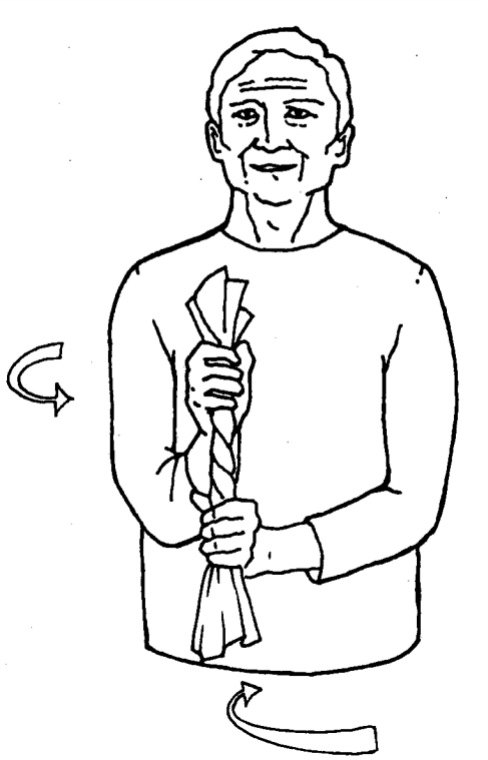
The difficult can be increased by:

- Kicking the ball faster or in different directions.

SECTION D: Upper Limb Strength Exercises.

D1 Wrist Strengthener.

- Fold or roll a band (towel or tights).
- Holding it with both hands, squeeze hard.
- Then twist by bringing your elbows close to your body
- Hold for a slow count of 5 (count out loud so you do not hold your breath).



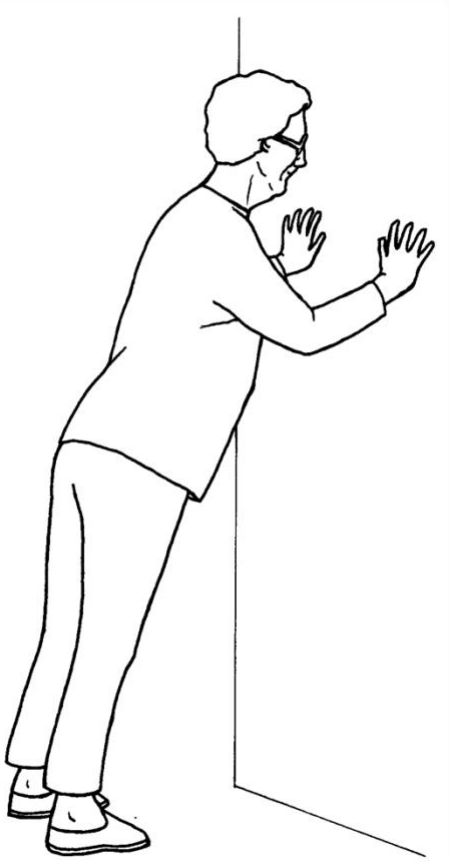
D2 Upper Back Strengthener.

- Hold the band (towel or tights) with your palms facing up and wrists firm and straight.
- Pull your hands apart, then draw the band towards your hips.
- Squeeze your shoulder blades together.
- Hold for a slow count of 5 (count out loud so you do not hold your breath).
- Then release.

D3 Wall Press-up.

- Stand at arms length from the wall.
- Place your hands on the wall at chest height, fingers upwards.

- Keeping your back straight and tummy tight, bend your elbows lowering your body with control towards the wall.
- Press back to the start position.



COOL DOWN EXERCISES.

March at a relaxed pace for 1 to 2 minutes, then repeat the last three exercises from the warm up:

Chest stretch:

- Sit tall away from the chair back.
- Reach behind with both arms and hold the chair back.
- Press your chest forwards and upwards until you feel the stretch across your chest.
- Hold for 8 seconds.

Back of thigh stretch:

- Move your bottom to the front of the chair.
- Place your right foot flat on the floor, then straighten your left leg out in front of you with your heel on the floor.
- Place both hands on the right thigh, then sit tall.
- Lean forwards and upwards until you feel the stretch in the back of your left thigh.
- Hold for 8 seconds.

- Repeat on your other leg.

Calf stretch:

- Stand behind the chair holding the chair back.
- Step back with one leg checking that both feet are pointing forward.
- Now press the heel of the back foot into the floor until you feel the stretch in your calf.
- Hold for 8 seconds.
- Repeat on your other leg.

NHS
Health Research Authority

East of England - Essex Research Ethics Committee

The Old Chapel

Royal Standard Place

Nottingham

NG1 6FS

Telephone: 0207 104 8069

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

19 July 2016

Dr John Williams
Consultant Anaesthetist and Clinical Associate Professor
University of Nottingham
Division of Medical Sciences and Graduate Entry Medicine,
University of Nottingham Medical School,
Royal Derby Hospital, Uttoxeter Road, Derby
DE22 3DT

Dear Dr Williams

Study title:	**The assessment of the feasibility of a home based post-operative exercise training programme targeting physical and cognitive function in older patients undergoing major body surgery.**
REC reference:	**16/EE/0137**
Protocol number:	**16014**
IRAS project ID:	**194914**

Thank you for your submission of 7 July 2016, 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, Helen Poole at NRESCommittee.EastofEngland-Essex@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 favorable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publicly accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster]	2	29 May 2016
Covering letter on headed paper [Covering letter]	1	02 March 2016
Covering letter on headed paper [Cover Letter]	2	29 May 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [University of Nottingham Trials Insurance]	1	08 March 2016
GP/consultant information sheets or letters [GP letter]	1	02 March 2016
Letter from sponsor [16014 Sponsor Letter]	1	29 February 2016
Other [Investigator CV]	1	01 January 2007
Other [HIFE programme]	1	02 March 2016
Other [Exercise Diary (ABCD)]	1	02 March 2016
Other [Exercise Diary (ABD)]	1	02 March 2016
Other [EQ-5D-3L questionnaire]	1	02 March 2016
Other [Geriatric Depression Scale]	1	02 March 2016
Other [IPAQ-SF Elderly Questionnaire]	1	02 March 2016
Other [Resported Edmonton Frail Scale]	1	02 March 2016
Other [MOCA form 1]	1	02 March 2016
Other [MOCA form 2]	1	02 March 2016
Other [4AT]	1.2	01 August 2014

Other [HIFE programme Acceptability Questionnaire]	1	11 March 2016
Other [Covering letter and L Carrick details]	1	11 March 2016
Other [Explanation screen for the cognitive substitution test]	1	11 March 2016
Other [Test screen for the cognitive substitution test]	1	11 March 2016
Other [Explanation screen for the cognitive simon test]	1	11 March 2016
Other [Red box test screen for the cognitive simon test]	1	11 March 2016
Other [Blue box test screen for the cognitive simon test]	1	11 March 2016
Other [Patient Summary information Sheet]	1	29 May 2016
Other [Scientific Review AGordon]	1	04 July 2016
Other [Research Protocol]	3	07 July 2016
Other [Patient Information sheet]	3	07 July 2016
Other [EQ-5]	1	07 July 2016
Other [Cover Letter]	3	07 July 2016
Participant consent form [Consent Form]	2	29 May 2016
REC Application Form [REC_Form_13062016]		13 June 2016
Referee's report or other scientific critique report [Evidence letter]	1	29 May 2016
Summary CV for student [Student CV]	1	25 February 2016
Summary CV for supervisor (student research) [Academic Supervisor CV]	2	01 January 2007
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Patient synposis]	1	02 March 2016
Validated questionnaire [DASI Questionnaire]	1	02 March 2016

Statement of compliance

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

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/EE/0137	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

HKPoole PP

Dr Alan Lamont Chair

Email:NRESCommittee.EastofEngland-Essex@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Angela Shone*

Ms Teresa Grieve, Royal Derby Hospitals NHS Foundation Trust

10 References.

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