THERAPEUTIC EXERCISE IN CANCER CACHEXIA: EXPLORING APPROACHES AND OUTCOMES

Matthew Maddocks BSc

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

January 2010

Dedicated to my mentor

Simon Peter Mockett

We did it!

ABSTRACT

Cachexia is common in patients with incurable cancer, particularly of the lung and upper-gastrointestinal tract, and impacts adversely on treatment options, morbidity, quality of life and survival. Current management of cancer cachexia is inadequate and progress is required. This thesis explores the use of exercise as a proactive supportive therapy with a focus on maintaining physical function.

The first piece of work was a systematic review of the use of therapeutic exercise in patients with or cured of cancer. Across 65 exercise studies, the median [IQR] rates of uptake, adherence and completion were 63 [33–80]%, 84 [72–93]% and 87 [80–96]% respectively, with no characteristic influencing the proportion of patients taking up or completing a programme. The main reasons reported for refusal were lack of interest or the impracticality of the programme and for withdrawal were medical complication or deterioration. Overall, only about half of patients offered an exercise programme completed one. This review highlighted a need to modify existing programmes or explore novel alternatives if exercise is to be acceptable to the majority of patients.

The second study explored exercise preferences in patients with incurable cancer. A questionnaire was used to determine patients' perceived capability and preparedness to undertake six different

exercise programmes, each illustrated by video clips and accompanying text, and preferences for the delivery of the most preferred programme. All 200 patients considered themselves physically capable of undertaking an exercise programme and two-thirds were prepared to undertake one at that moment in time. The most preferred type of exercise was neuromuscular electrical stimulation (NMES) 36 [35−44]%, followed by walking 22 [16−30]% and resistance training 19 [13−26]% and the majority preferred to undertake exercise at home, alone and unsupervised. This survey suggested that it is realistic to offer therapeutic exercise programmes to patients with incurable cancer and provided rationale to explore NMES in this group.

The third study was a randomised controlled pilot study of NMES in patients with non-small cell lung cancer. Sixteen patients were randomised to a control group, which received usual care, or NMES group, which received daily stimulation to the quadriceps for up to 30min (frequency 50Hz, on phase 11−25%) for four weeks. All patients found the NMES device acceptable and median (range) adherence to the recommended programme was 80% (69−100). In the NMES group, quadriceps muscle strength and free-living physical activity improved by a mean of 7.4 Newton metres (22%) and 136 steps (11%) respectively, whilst exercise endurance deteriorated by a mean of 20 metres (4%). This compared favourably with the control group however none of the differences were statistically significant. These findings suggested

NMES was an acceptable type of exercise and that further study is warranted in patients with lung cancer.

The final piece of work was a feasibility study into the use of a lightweight ActivPAL™ monitor to measure physical activity level. The aims were to determine if this form of assessment is acceptable to patients, the optimal period of monitoring and to explore the added value of the monitor's energy expenditure (EE) estimate over a simple step count. Sixty patients with lung or upper-gastrointestinal cancer wore a monitor for one week. All but one found the monitor acceptable and mean [95% CI] adherence was 98 [94−100] %. Mean daily step count and EE values measured over 2 and 4 days were significantly higher than those from 6 days ($p<0.01$). Step count was strongly related to stepping EE and non-stepping EE. The ActivPAL™ monitor was shown to be an acceptable method of assessing physical activity level. A mean daily step count obtained over 6 days was recommended for use in future cachexia studies.

Collectively, this work supports the use of therapeutic exercise and highlights a particular role for novel approaches, e.g. NMES, which may be more acceptable to patients. Findings can be used to guide future research which ultimately will determine if therapeutic exercise can help patients with cancer to maintain their level of physical activity and independence for as long as possible.

ACKNOWLEDGEMENTS

I am indebted to the many people who have helped me succeed in completing this work:

First and foremost I thank Dr Andrew Wilcock, my lead supervisor, who has always been enthusiastic, attentive and dedicated to my learning and development. I am proud to have worked alongside him and hope his high standards are reflected in this thesis.

I thank the late Simon Mockett, my personal mentor, who nurtured my initial interest in research and Grahame Pope, who took up his role and provided support within the physiotherapy department.

I thank Nottingham, Derbyshire and Leicestershire Research Alliance, Cancer Research UK and Dimbleby Cancer Care Trust for funding and all of the patients who gave up their time in the interests of others.

I thank colleagues from Hayward House, Physiotherapy Education and Oncology who assisted in recruiting patients, reviewing papers and ensuring each study ran smoothly and on time.

I thank my parents and family, who have always encouraged me, shown interest in my work and patiently followed my progress.

Finally I thank Sarah, my wife, who has always believed in me and provided endless support whilst managing her own challenging career and post-graduate studies. I am blessed to have someone as wonderful as her beside me.

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LIST OF ABBREVIATIONS

6MWT	six minute walk test
ANOVA	analysis of variance
CI	confidence interval
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
ECOG	eastern cooperative oncology group
EORTC C30	european organisation for research and treatment of cancer core questionnaire
EORTC-LC13	european organisation for research and treatment of cancer lung cancer module
ESWT	endurance shuttle walk test
FACT	functional assessment of cancer therapy
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GI	gastrointestinal
GIQLI	gastrointestinal quality of life instrument
h	hour
H	hydrogen
HR	heart rate
Hz	hertz
ICC	interclass correlation coefficient
IL-1	interleukin 1
IL-6	interleukin 6
INFγ	interferon γ

IQR	inter-quartile range
ISWT	incremental shuttle walk test
J	joules
KPS	karnofsky performance status
km	kilometre
L	litre
LMF	lipid mobilising factor
mA	milliamp
MET	metabolic equivalent task
METh	metabolic equivalent task hour
min	minute
mm	millimetre
MVC	maximum voluntary contraction
Nm	newton metre
NMES	neuromuscular electrical stimulation
NR	not reported
ns	non-significant
NSCLC	non small cell lung cancer
O_2	oxygen
PIF	proteolysis inducing factor
RT	radiation therapy
s	second
SCLC	small cell lung cancer
SD	standard deviation
SF−36	short-form 36 questionnaire

sig.	significant
SPPB	short physical performance battery
SPSS	statistical package for social sciences
TNFα	tumour necrosis factor α
$\dot{V}O_2$	oxygen uptake
$\dot{V}O_2$ max	maximum oxygen uptake
µs	microsecond
Ω	ohm

PUBLICATIONS ARISING FROM THIS WORK:

Related to studies in this thesis

Maddocks M, Mockett S, Wilcock A. Is exercise an acceptable and practical therapy for people with or cured of cancer? A systematic review. *Cancer Treatment Reviews* 2009;**35**:383−390.

Maddocks M, Lewis M, Chauhan A, Manderson C, Hocknell J, Wilcock A. Randomised controlled pilot study of neuromuscular electrical stimulation of the quadriceps in patients with non-small cell lung cancer. *Journal of Pain and Symptom Management* 2009;**38**:950−956.

Maddocks M, Byrne A, Johnson CD, Wilson R, Fearon KCH, Wilcock A. Physical activity level as an outcome measure for use in cancer cachexia trials: a feasibility study. *Supportive Care in Cancer*

Maddocks M, Armstrong S, Wilcock A. Exercise as a supportive therapy in incurable cancer: exploring patient preferences. *Psycho-Oncology*

Related to the introductory chapters in this thesis

Maddocks M, Mockett S, Wilcock A. Re: The Effect of a Physical Exercise Program in Palliative Care: A Phase II Study. *Journal of Pain and Symptom Management* 2006;**32**:514–515.

Maddocks M, Mockett S, Wilcock A. Neuromuscular electrical stimulation: a proactive supportive therapy, a reactive palliative therapy, or both? *Supportive Care in Cancer* 2007;**15**:133.

Wilcock A, Maddocks M, Lewis M, England R, Manderson C. Symptoms limiting activity in cancer patients with breathlessness on exertion: ask about muscle fatigue. *Thorax* 2008;**63**:91–92.

Wilcock A, Maddocks M, Lewis M, Howard P, Frisby J, Bell S, El Khoury B, Manderson C, Evans H, Mockett S. Use of a Cybex NORM dynamometer to assess muscle function in patients with thoracic cancer. *BMC Palliative Care* 2008;**7**:3.

Maddocks M, Petrou A, Skipper L, Wilcock A. Validity of three accelerometers during treadmill walking and motor vehicle travel. *British Journal of Sports Medicine* Published Online 13th August 2008.

Other academic output

In addition, there have been thirteen oral and seven poster presentations at national and international meetings.

CHAPTER 1:

GENERAL INTRODUCTION

1.1 General introduction

Cachexia is common in patients with incurable cancer, particularly of the lung and upper-gastrointestinal tract, in whom it becomes universal as the cancer progresses (Laviano et al, 2005; Stewart et al, 2006). It impacts adversely on treatment options, morbidity, quality of life and survival (Macdonald, 2005). Current management of cancer cachexia is inadequate and progress is required (Muscaritoli et al, 2006). Experts have suggested that a multimodal approach to include nutrition, immunomodulation and exercise, offered proactively to those most at risk of cachexia is likely to provide benefit (Fearon, 2008). However, this is a newly emerging field of enquiry and limited data exist.

1.2 Aims and objectives

The overall aim of this thesis is to examine the role of therapeutic exercise in patients with or at risk of cancer cachexia to help maintain physical function and independence for as long as possible.

More specific objectives are to:

- review the use of exercise in patients with cancer to determine if it is an acceptable and practical therapy
- identify and pilot the most acceptable type(s) of exercise in patients with incurable cancer most risk of cachexia
- identify and examine outcome measures suitable for use in studies aimed at maintaining physical function in this group.

1.3 Thesis outline

Objectives are met through a review of relevant literature leading to four original research studies. The background is divided into three chapters which consider the cachexia syndrome, the role of therapeutic exercise and the assessment of physical function respectively.

The second chapter introduces the cancer cachexia syndrome and considers the mechanisms by which it impacts adversely on physical function. This is used to identify the patient groups at whom this thesis is concerned, i.e. those with cancers in which cachexia is most common, and to highlight physical consequences of cachexia which may be addressed with interventions such as therapeutic exercise.

Chapter three examines the evidence base regarding to the use of exercise in patients during or following treatment for curable cancer and with incurable cancer. This chapter provides further support to examine the use of exercise in those with incurable cancer and highlights the lack of research in this group. It also raises issues with the acceptability of therapeutic exercise and provides a rationale to consider the broader utility of exercise before undertaking intervention studies. This led to the development of the original studies described in chapters five and six.

Chapter four completes the literature review by appraising various measures of physical function that may be used in studies aimed at patients with or at risk of cancer cachexia and comparing their respective psychometric properties and utility. The purpose of this chapter is to inform the selection of outcome measures used in the intervention studies presented in chapters seven and eight.

Chapter five describes a systematic review of the use of therapeutic exercise, which demonstrated that overall only about half of patients with or cured of cancer offered an exercise programme completed one. This highlighted a need to modify existing programmes if exercise is to be acceptable to the majority of patients. It also provided rationale to consider more novel approaches to exercise, e.g. neuromuscular electrical stimulation (NMES), which may be more practical and thus acceptable to a greater proportion of patients.

Chapter six describes a study exploring exercise preferences in 200 patients with incurable cancer. When presented with six different exercise programmes, all patients considered themselves physically capable of undertaking an exercise programme and two-thirds were prepared to undertake one at that moment in time. The most preferred type of exercise was NMES, which provided rationale to explore this approach and led to a pilot study in patients with lung cancer.

Chapter seven describes a randomised controlled pilot study of NMES in sixteen patients with lung cancer. The intervention was supported by the popularity of NMES and outcome measures were selected on the basis of the background review presented in chapter four. This chapter suggests that NMES was acceptable to participants and that further study is warranted in patients with lung cancer.

Chapter eight describes the final piece of original work relating to the use of a lightweight monitor. This can be used to assess physical activity level, which was identified in chapter three as an outcome well-suited to studies in those with or at risk of cancer cachexia aimed at maintaining physical function. The monitor was shown to be an acceptable method of assessing physical activity level and a mean daily step count obtained over 6 days was recommended for future use.

Finally, chapter nine reflects on the thesis by revisiting the original aims and objectives and drawing general conclusions in light of the main strengths and limitations of this work. These form the basis of suggestions for further work and are used to highlight the clinical implications of the overall findings.

CHAPTER 2:

THE CACHEXIA SYNDROME

2.1 Introduction

This chapter will explore the syndrome of cachexia, a major contributor to the loss of independence and quality of life in patients with cancer (Macdonald, 2005). The definition, pathophysiology and clinical impact of cancer cachexia are outlined to highlight the complexity and scale of the problem this syndrome represents. There is a more detailed overview of the mechanisms by which cancer cachexia impacts on physical function and how this relates to quality of life. Finally, current and emerging treatment options for cancer cachexia are outlined to highlight the potential role that therapeutic exercise may have in its management.

2.2 What is cachexia?

2.2.1 Definition

Cachexia is derived from the Greek '*kakos hexis'* meaning *'bad condition'* and describes a multi-factorial syndrome associated with wasting and malnutrition. The majority of the literature has used weight loss alone to define cachexia, for example the loss of ≥5% or ≥10% of the pre-morbid stable weight (e.g. Inui, 2002; Dewys et al, 1980). However, this is increasingly considered too simplistic (Fearon et al, 2006) and a much broader definition has recently been proposed by experts in the field:

"a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with wasting disease. Wasting disease is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity" (Evans et al, 2008).

This definition is accompanied by diagnostic criteria of at least 5% weight loss in the previous year in the presence of underlying illness, plus three of (Evans et al, 2008):

- decreased muscle strength
- fatigue
- anorexia
- low fat-free mass
- abnormal biochemistry, i.e. raised c-reactive protein, low albumin and anaemia.

As most of the literature in this field pre-date the consensus definition, the terms cachexia and weight loss will be used interchangeably in this thesis and the term cachectic will occasionally be used to describe patients who have lost ≥5% of their pre-morbid stable weight.

2.2.2 Prevalence

Weight loss is common in patients with solid cancers, even around the time of diagnosis with the highest levels seen in patients with upper-gastrointestinal or lung cancer (Laviano et al, 2005) (Table 1.1). One survey suggests half of all patients with cancer will lose some body weight and one third more than 5% of their pre-morbid weight (Inui, 2002). However, in many cancers weight loss will be inevitable as the disease progresses (Stewart et al, 2006).

Table 2.1 Incidence of weight loss around the time of diagnosis in various types of cancer (Laviano et al, 2005).

Cancer type	*Incidence (%)*
Pancreatic	83
Gastric	83
Oesophagus	79
Lung	50−66
Colorectal	50−60
Prostate	56
Breast	10−35

2.3 Pathophysiology

Multiple factors contribute to the cachexia syndrome in cancer (Figure 2.1). These factors are produced by the cancer or by the patient in response to the cancer (Gordon et al, 2005; MacDonald, 2005). One outcome of this is a persistent pro-inflammatory state incorporating increased levels of circulatory cytokines, e.g. Tumour Necrosis Factor-α (TNFα), Interleukins 1 and 6 (IL-1, I-6) and Interferon-γ (INFγ), which

contribute to a number of features of cachexia (Argilés et al, 2005; MacDonald, 2005; Muscaritoli et al, 2006). Additional cancer-derived catabolic factors have been identified in some cancers including proteolysis inducing factor (PIF) and lipid mobilising factor (LMF), which exacerbate the metabolic disturbance and further promote the degradation of muscle and fat tissue respectively (Gordon, 2005; Tisdale, 1997).

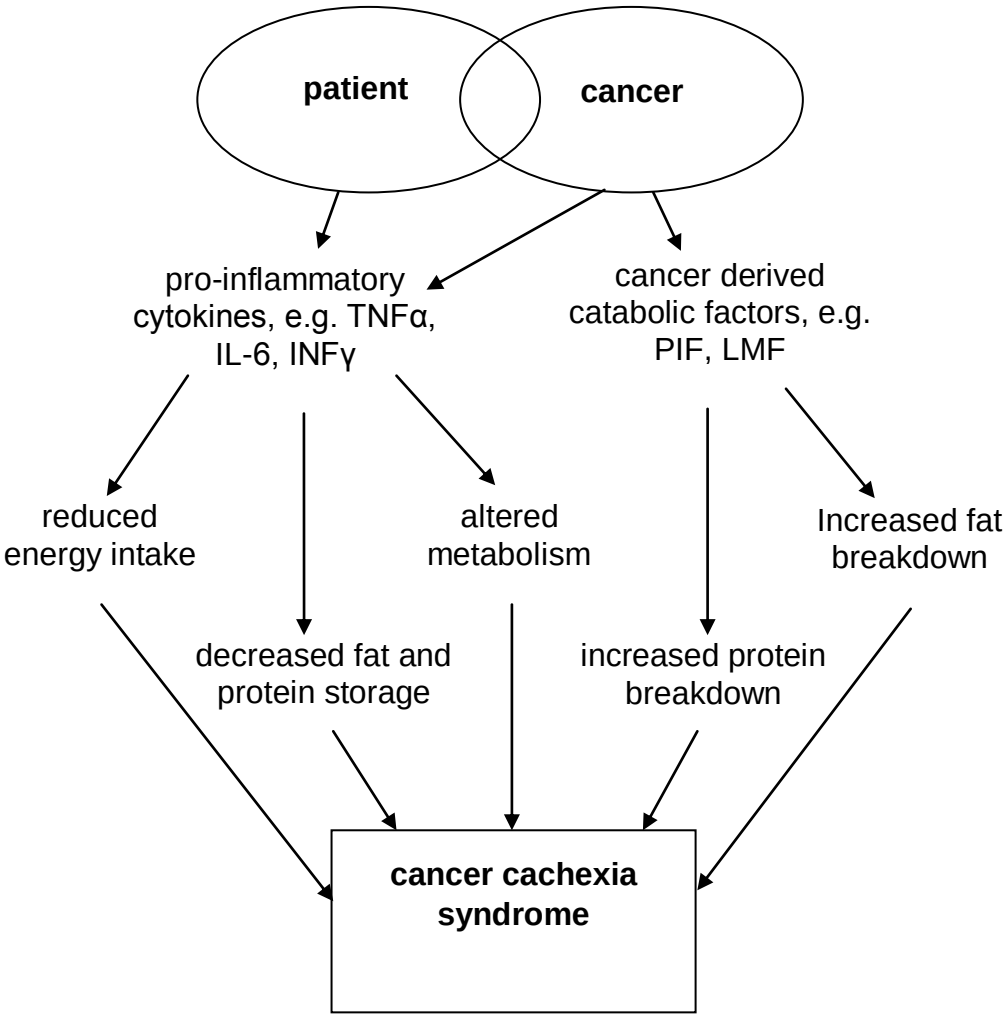


Figure 2.1 Pathogenesis of the cancer cachexia syndrome.

Both pro-inflammatory cytokines and PIF upregulate proteolytic pathways through a number of mediating ligases (Gordon et al, 2005; Tisdale, 2009). This leads to muscle tissue breakdown, the major cause of net loss of muscle tissue loss (Laviano et al, 2005; Melstrom et al, 2007). Rates of protein synthesis are also reduced, in part due to the reciprocal relationship which exists with muscle breakdown (Glass, 2005) and also to a lack of available amino acids, which are diverted to produce acute-phase proteins (Dworzak et al, 1998; Melstrom et al, 2007). In addition, there is a net loss of fat tissue, as LMF stimulates adipose tissue breakdown and the raised levels of cytokines inhibit lipase and prevent the storage of fatty acids (Gordon et al, 2005; Tisdale, 2009).

This catabolic state is often compounded by an increased and/or inefficient metabolism and a reduced food intake. An increase in resting energy expenditure has been observed in various cancers such as those of the lung and upper-gastrointestinal tract (Falconer et al, 1994; Jatoi et al, 2001). Pro-inflammatory cytokines can lead to an increase in mitochondrial uncoupling proteins, resulting in the production of heat instead of adenosine-triphosphate (Gordon et al, 2005; Muscaritoli et al, 2006). Cytokines also impact on the hypothalamus and gastrointestinal tract causing anorexia, early satiety, changes in taste and food aversions which reduce food intake (Laviano et al, 2003; Wilcock, 2005; Yavuzsen et al, 2009).

2.4 Clinical impact of cachexia

Cancer cachexia impacts adversely on patient survival, treatment options and response, morbidity and quality of life (Muscaritoli et al, 2006; Fearon et al, 2006).

2.4.1 Survival

Both the presence and the degree of weight loss around the time of diagnosis are independent predictors of survival. In a study of over 1,500 patients with locally advanced upper- or lower-gastrointestinal cancer, survival was significantly shorter in those with ≥5% weight loss at diagnosis compared to weight-stable patients (median 7.6 months vs. 11.9 months, $p<0.01$) (Andreyev et al, 1998). A multivariate analysis revealed that this degree of weight loss was associated with a 63% increased risk of death (hazard ratio 1.63, 95% CI 1.42−1.86) (Andreyev et al, 1998). In a study of over three thousand patients with variety of cancers receiving anti-cancer treatment, survival was significantly and progressively shorter in patients who had ≥5% weight loss, or >10% weight loss compared to those who had no weight loss (Dewys et al, 1980). When examined by cancer type, mean survival in patients who had lost ≥5% weight was 2−52 weeks shorter than in those who had not (Dewys et al, 1980). Thus, the presence of cachexia at diagnosis or during anti-cancer treatment has negative implications on the overall survival of patients.

2.4.2 Treatment options and response

Patients with cachexia, because of a poorer performance status, are less likely to be candidates for intensive chemotherapy or radiotherapy regimens and surgical procedures, which offer survival potential (Laviano et al, 2005; Antonelli et al, 2006). Weight loss prior to chemotherapy is associated with suboptimal dosing, more numerous and severe toxicities, more breaks from treatment and premature discontinuation of treatment (Andreyev et al, 1998; Ross et al, 2004). These events all contribute to a poorer objective response and shorter time to disease progression (Davidson et al, 2004; Ross et al, 2004).

2.4.3 Morbidity and poorer quality of life

Cancer cachexia increases morbidity as a result of the associated symptoms such as anorexia, fatigue, muscle weakness, mood disturbance and insomnia (Seruga et al, 2008), which together impact adversely on performance status and quality of life (Teunissen et al, 2007). Studies in patients with advanced upper-gastrointestinal cancer (n=119) and non-small cell lung cancer (n=106) have shown that performance status and quality of life are significantly lower in patients with ≥5% compared to those with minimal or no weight loss (Scott et al, 2002;2003; O'Gorman et al, 1998). Similarly, a group of fifty-three patients with various cancers and ≥10% weight loss rated all aspects of quality of life covered by the SF−36 questionnaire significantly lower than a reference group of age-matched healthy controls (Fouladiun et al, 2007).

2.5 Impact of cancer cachexia on physical function

Cancer cachexia has a profound effect on physical function, which encompasses the patient's level of physical capability, independence and activity. This is important not least because performance status, a global indicator of physical function, is used to assess eligibility for various anti-cancer treatments and is a strong independent predictor of survival (low performance status, HR 1.15 95% CI 1.11−1.16, Scott et al, 2003; hazard ratio 1.46 95% CI 1.12−1.88, Maione et al, 2005).

2.5.1 Primary consequences

Three primary consequences of cancer cachexia on physical function have been identified; impaired muscle function, an overall energy deficit and an increased symptom burden. These as shown in Figure 2.2, which is the authors own representation, and will be described separately in the proceeding sections of this chapter.

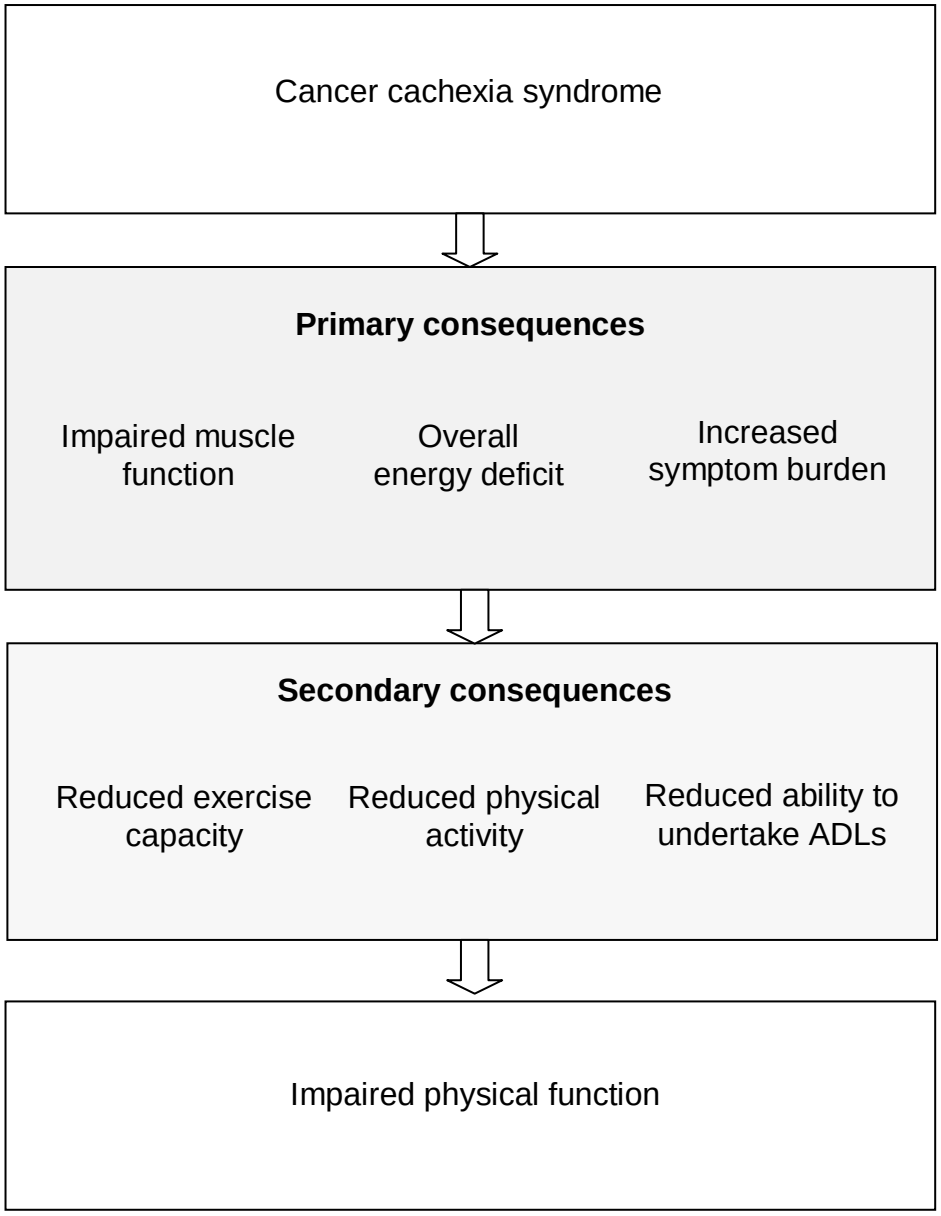


Figure 2.2. Mechanisms by which cancer cachexia impairs physical function.

2.5.1.1 Impaired muscle function

The in-depth examination of muscle function in patients with cancer is limited to a small number of studies involving patients with small cell lung cancer following potentially curative treatment (n=11) (Baracos et al, 1994), advanced non-small cell lung cancer (n=26) (Wilcock et al 2008a; Reinglas et al, 2007), or advanced upper-gastrointestinal cancer (n=64) (Reinglas et al, 2007; Weber et al, 2008). Methodology varies between the studies making direct comparison difficult, but generally the quadriceps have been studied with isokinetic testing and function compared to healthy controls or reference data sets matched for age and gender. Patients consistently produce values of peak torque (Newton metres, Nm) and total work values (Joules, J) 20−40% lower than expected. This impairment in muscular strength and endurance was greatest in patients with substantial weight loss (>10% over 6 months) (Weber et al, 2009) and least in those with a recent diagnosis (Reinglas et al, 2007) or good performance status (Wilcock et al, 2008a).

The Weber et al study also explored the mechanism of muscle function impairment and found despite a global reduction in function, parameters of microcirculation, e.g. capillary density and blood flow, and muscle metabolism, e.g. high-energy phosphates, resting pH, were comparable between patients and healthy controls. Differences in quadriceps strength disappeared when normalised for muscle cross-sectional area (mean difference [95% CI], isometric 0.03 [-0.3, 0.4] Nm

and isokinetic -0.3 [-0.7,0.2] Nm) suggesting that muscle function appears to be impaired by the quantity, i.e. mass, and not the quality, i.e. aerobic capacity, of remaining tissue (Weber et al, 2009).

2.5.1.2 Overall energy deficit

Energy expenditure is comprised of three main components: resting energy expenditure, thermogenesis related to food consumption and physical activity (Gibney, 2000). If energy expenditure exceeds energy intake, an energy deficit occurs.

Compared to age-predicted values or age-matched controls, resting energy expenditure has been found to be increased by 5−20% in studies with various sample sizes involving patients with advanced pancreatic cancer (Falconer et al, 1994 (n=21); Moses et al, 2004 (n=24)) and both local or advanced lung cancer (Gibney et al, 1997 (n=8); Jatoi et al, 2001 (n=18); Fredrix et al, 1991 (n=18); Jebb et al, 1994; Stall-van den Brekel et al, 1995 (n=87); 1997 (n=66). In health, increases in energy expenditure are generally compensated for by an increase in energy intake. However, in patients with advanced cancer, energy intake is often already reduced or cannot be increased because of anorexia; food portions generally become smaller, and meals and snacks are missed (Hutton et al, 2006). Some patients with cancer adopt a 'healthy' diet, e.g. skimmed milk, cereals, soups, etc. which also lowers energy intake (Hutton et al, 2006).

The alternative means of addressing an energy deficit is to reduce expenditure related to physical activity, which may occur voluntarily or in response to symptoms relating to the deficit, e.g. fatigue, exhaustion (Kulstad and Schoeller, 2007). There is evidence that this occurs in patients with cancer and raised resting energy expenditure. Gibney et al (1997) compared energy expenditure in 8 patients with advanced SCLC to age-predicted control values (DoH, 1991) and found patients had a significantly reduced total energy expenditure due to a lower level of physical activity (Figure 2.3). These findings were later replicated in 24 patients with advanced pancreatic cancer and ≥5% weight lost, in whom total energy expenditure was lower than age-match controls (1732 vs.1903 kcal/day, P=0.02) secondary to a reduced level of physical activity (Moses et al, 2004).

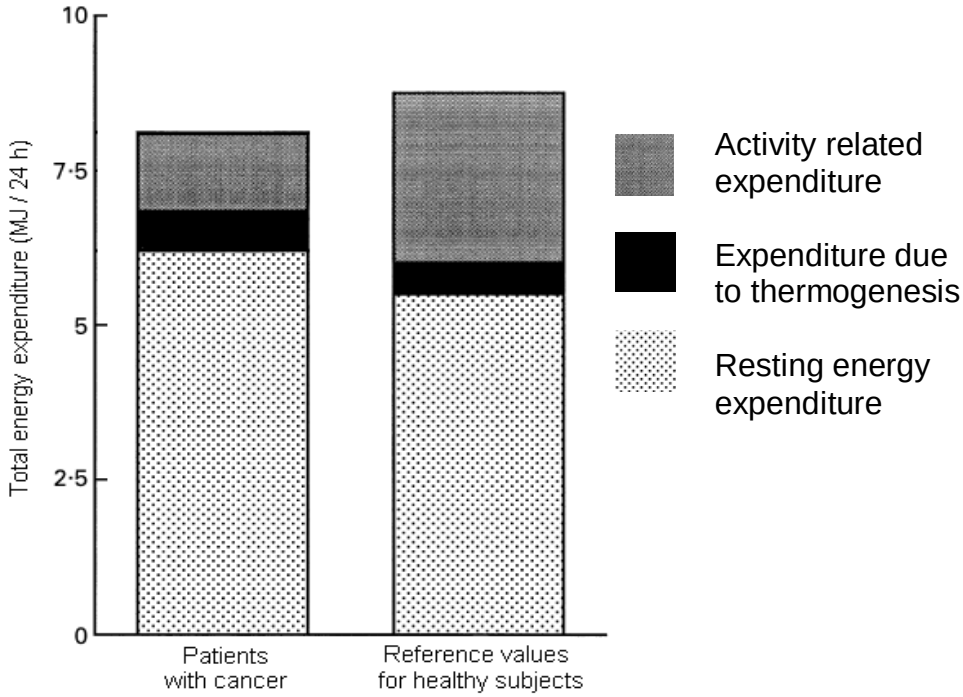


Figure 2.3 Energy expenditure in patients with advanced SCLC and healthy reference values (Gibney et al, 1997).

2.5.1.3 Increased symptom burden

The symptom burden for patients with incurable cancer is substantial. In the largest database to date, Teunissen et al (2007) examined overall symptom prevalence across 44 studies involving over twenty-five thousand patients. This sample size allowed precise 95% confidence intervals to be calculated so findings could be generalised to a population level. More than half of patients experienced symptoms related to cachexia with mean [95% CI] rates of fatigue, lack of energy, weakness and anorexia 74 [63−83]%, 69 [57−79]%, 60 [51−68]% and 53 [48−59]% respectively (Teunissen et al, 2007). The pro-inflammatory state associated with cancer cachexia may contribute to these symptom as elevated levels of cytokines increase fatigue, depression, cognitive impairment and disrupted sleep (Seruga et al, 2008). The muscle wasting and weakness associated with cancer cachexia also lead to an early onset and increased levels of leg muscle fatigue and breathlessness (Coats, 2002; Hamilton et al, 1996).

2.5.2 Secondary consequences of cachexia on physical function

The impaired muscle function, energy deficit and increased symptom burden reduce physical function through their effect on patients' exercise capacity, level of physical activity and ability to undertake activities of daily living (Figure 2.2).

2.5.2.1 Reduced exercise capacity

Exercise capacity is dependent on the ability of the ventilatory and circulatory systems to deliver oxygen to the muscle together with factors affecting muscular performance, e.g. capillarisation, oxidative capacity (Bassett et al, 2000). During exercise, the perceived effort of breathing and sensation of leg muscle fatigue gradually increase until either one or the other or both together reach a level which causes the patient to stop (Killian et al, 1992; Hamilton et al, 1996; Jones and Kiilian, 2000). In cancer cachexia, when muscle function is impaired due to wasting, a smaller amount of muscle mass is available to undertake any given workload (Stendardi et al, 2005). Thus, the sense of effort is increased and patients are prevented from exercising at levels they were previously able to manage (Killian et al, 1992; Hamilton et al, 1995).

Only two studies have formally examined exercise capacity using recommended assessment methods in patients with advanced cancer. In the first, patients with non-small cell lung cancer (n=42) undertook a maximal cycle ergometry test and peak $\dot{V}O_2$ values were compared to those predicted for age and gender using healthy control data. Despite patients having a reasonable performance status (KPS ≥70, Appendix 1.2), values were 33% lower than predicted (Jones et al, 2008). In the second, patients with pancreatic cancer (n=50) and age-matched healthy controls (n=40) undertook a symptom-limited incremental treadmill exercise test. Compared to controls, patients had less muscle

mass (9%), reached their anaerobic threshold at lower workloads (13%) and had increased levels of fatigue leading to a much reduced exercise capacity (peak $\dot{V}O_2$, 30%) (Heinz et al, 2007). In both groups, exercise capacity was shown to be moderately related to leg muscle mass (patients r=0.42; controls r=0.81, p<0.01), in keeping with Weber et al's findings that loss in muscle quantity is responsible for impaired muscle function (Weber et al, 2009).

2.5.2.2 Reduced physical activity

The energy deficit caused by cancer cachexia leads to a reduction in levels of physical activity (Gibney et al, 1997; Moses et al, 2004). The development of lightweight monitors worn on the wrist or thigh has allowed these to be examined more easily. Studies have examined physical activity levels of cachectic patients, predominantly with upper-gastrointestinal cancer, either around the time of diagnosis (n=53) or during first-line palliative chemotherapy (n=20). Compared to age-matched healthy controls, patients had significantly less activity 'counts' per minute (ActiGraph™, Fouladiun et al, 2007) or spent a median of 2h less upright and took 43% fewer steps each day (ActivPAL™, Dahele et al, 2007). In the latter study, despite spending less time upright, patients got into standing a similar number of times suggesting activity was limited by the ability to undertake prolonged periods of work. Physical activity levels have also been shown to decline over time with worsening disease (Fouladiun et al, 2007) and with increasing morbidity (Dahele et al, 2007).

Physical inactivity is both a contributor to and a consequence of impaired physical function. As patients reduce their level of physical activity, muscle disuse atrophy and cardiovascular deconditioning occur, which exacerbate existing symptoms and lead to a greater level of limitation (Biolo et al, 2005). Thus, patients are at high risk of entering a spiral of deconditioning where physical function and physical activity level decline as consequences of each another.

2.5.2.3 Reduced ability to undertake activities of daily living

Both the number of symptoms and their severity are related to patients' ability to undertake various functional activities (Sarna, 1993; Ferreira et al, 2008). When asked which symptoms interfere with daily activities, patients with advanced lung cancer and a good performance status (ECOG 0-1) reported that global fatigue and breathlessness were particularly troublesome (Sarna et al, 1993; Tanaka et al, 2002; Okuyama et al, 2001). Most commonly, these were reported to interfere with patients' ability to walk, work and complete more strenuous household chores (Sarna et al, 1993b; Tanaka et al, 2002; Okuyama et al, 2001). In patients with a variety of cancers on a specialist palliative care unit (median survival 8 weeks), symptoms of breathlessness and muscle fatigue either alone or together prevented many patients from completing many daily activities, e.g. washing and dressing. For most activities, greater proportions of patients reported being limited by muscle fatigue alone or in combination with breathlessness than by breathlessness alone (Wilcock et al, 2008b).

2.6 Relationship between physical function and quality of life

A reduction in physical function may prevent patients from completing activities they enjoy or those necessary for independent living. Figure 2.4, adapted from its original presentation (Walker et al, 1999), depicts this interaction and assumes patients will do what they wish or need to, provided they are able. In an unimpaired state (a), patients can meet all their activity related needs and, although some wishes are unattainable, e.g. running fast for a bus, most can be met. When physical function is impaired (b), initially more demanding wishes, e.g. a tiring work schedule, more active hobbies, become unattainable. As physical function deteriorates further (c), even less demanding wishes cannot be met and some needs fall beyond patients' ability, representing a loss of independence (Figure 2.4).

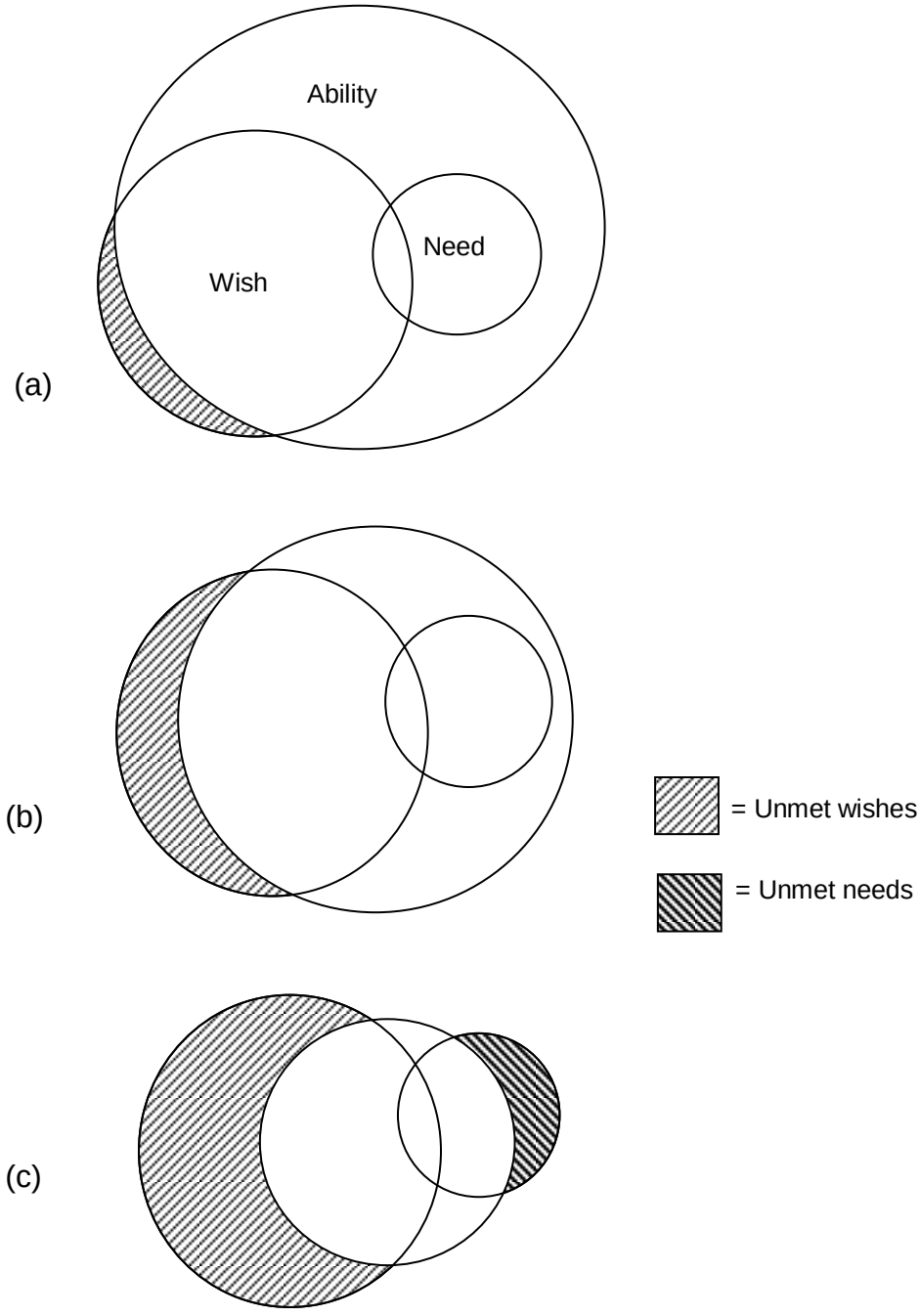


Figure 2.4 Impact of physical function on ability to meet activity-related wishes and needs.

The progressive loss of ability and independence are likely impact adversely on quality of life. This is in keeping with Stewart and King's (1999a) conceptualisation of quality of life being comprised of two main categories: function (physical abilities, dexterity, cognition, activities of daily living) and well-being (symptoms, bodily state, emotional well-being, self-concept, global perceptions). The relationship between physical function and quality of life is complex and moderated by multiple factors, e.g. how much patients' value function and well-being or adjust to illness and 'reframe' their wishes, but generally a reduction in physical function appears synonymous with a poorer quality of life. This is important as if patients with or at risk of cancer cachexia can be better managed. Maintaining or reducing the decline in their physical function may also impact on their overall quality of life.

Data supporting the notion that physical function is related to quality of life and psychological well-being exist. In older adults, accumulating evidence supports a close relationship between physical activity and these domains. Netz and Wu (2005) conducted a meta-analysis to examine the effects of increased participation in physical activity and found a causal enhancement effect on several components of well-being including emotion, self-perception and life satisfaction. Rejeski and Mihalko (2001) provided further support with a narrative review which concluded that physical activity positively influenced multiple outcomes associated with quality of life regardless of age, activity level and health status (Rejeski and Mihalko, 2001).

In cancer survivors, several large cross-sectional studies (n=300−2000) have categorised patients according to whether or not they meet physical activity guidelines, usually of 150 minutes of moderate activity each week (Haskell et al, 2007; Nelson et al, 2007). Those meeting guidelines during or following anti-cancer treatment consistently report significantly higher quality of life as assessed by a variety of measurement tools (Vallance et al, 2005, Milne et al; 2007; Stevinson et al, 2007; Blanchard et al, 2004; Lynch et al, 2008). In patients with cancer, there are limited data on physical activity but performance status appears to be moderately associated with quality of life. For example, in two studies of groups about to commence chemotherapy (Pinquart et al, 2006 (n=170); Wedding et al, 2007 (n=347)), the Karnofsky Performance Score was associated with global quality of life ($r=0.41$, $p<0.01$) and could be used to predict quality of life when used in regression modelling (Pinquart et al, 2006; Wedding et al, 2007). Furthermore, the change in Karnofsky Performance Score between 6 and 3 months prior to death in 67 advanced cancer patients was significantly correlated with change in the well-being domain ($r=0.43$, $p<0.01$) and global quality of life as measured by the FACT-G questionnaire ($r=0.36$, $p<0.05$) (Hwang et al, 2003).

2.7 Management of cancer cachexia

Despite the magnitude of problem cancer cachexia represents, progress in developing effective treatments is slow (Steer, 2004; Baracos, 2006). Studies have generally focused on either reducing the anorexia or altered metabolism and interventions have ranged from nutritional counselling (Isenring et al, 2004) and simple dietary intervention, e.g. offering small but energy-dense meals (Laviano et al, 2005), through to pharmacological therapies including progestagens (Berenstein et al, 2005), corticosteroids (Willox et al, 1984) and omega-3 fatty acid enriched oral nutritional supplements (Fearon et al, 2003; Moses et al, 2004).

Attempts to identify a sole therapy for cachexia have produced mostly disappointing results. Dietary interventions have generally failed to prevent further weight loss (Ng and Lowry, 1991; Laviano et al, 2005). Although corticosterioids and progestragens have temporarily improved appetite and/or body weight, weight gain often reflects unhelpful fluid retention and these drugs may exacerbate muscle weakness (Pascual Lopez et al, 2004; Fearon, 2008). More success has been found combining two or more treatments. For example, the combination of Ibuprofen with megestrol acetate was more effective than either alone in terms of weight gain in patients with gastrointestinal cancer (McMillan et al, 1999). Nutritional support, indomethacin (anti-inflammatory) and erythropoietin (anti-anaemia) combined has improved energy expenditure and physical function in patients with

>10% weight loss (Lundholm et al, 2004). Furthermore, interim findings of a large phase III study show more benefit from a combination of anti-oxidants, nutritional support, progestagen and an anti-inflmammatory agent compared to other study arms in which only two or three therapies are given (Mantovani et al, 2008).

These data are encouraging, but the muscle wasting associated with cancer cachexia remains irreversible with currently available treatments (Muscaritoli et al, 2006). In addition to nutritional support, immunomodulation and anabolic stimulants, exercise is likely to be an important component of any future multimodal approach to the management of cancer cachexia (Fearon, 2008; Tisdale, 2009). Exercise has the potential to help attenuate many of the the primary and secondary consequences of cachexia outlined in this chapter and depicted in Figure 2.2. The goals of exercise in other settings include reducing symptoms as well as improving muscle function, exercise capacity and the ability to undertake activities of daily living. Thus, the use of exercise in this setting may help address some of the consequences of cancer cachexia and slow down the decline in physical function and quality of life (Mascaritoli et al, 2004; 2006).

2.8 Summary

Cancer cachexia limits treatment options, increases morbidity, impairs quality of life and reduces survival. With no satisfactory treatment, it represents a major unmet need in supportive and palliative care. Despite the multitude of consequences cancer cachexia has on physical function, attempts to manage patients with or at risk of cachexia with physical therapies have only recently begun to be explored. The use of therapeutic exercise in patients with cancer and the challenges of its application are topics of the next chapter.

CHAPTER 3:

THE ROLE OF EXERCISE IN

PATIENTS WITH CANCER

3.1 Introduction

In the last chapter, the cachexia syndrome was outlined as a major contributor to the loss of physical function and independence in patients with incurable cancer, particularly of the lung and upper-gastrointestinal tract. The potential role of therapeutic exercise for those with or at risk of cancer cachexia was outlined as a means to improve the management of these patients. This chapter examines the use of exercise in patients during or following treatment for curable cancer and in patients with incurable cancer. After appraising the evidence base in these groups, the challenges of using exercise as a therapy are considered leading to an exploration of more practical novel types of exercise. This chapter provides part of the background for the first three pieces of original work presented in chapters five, six and seven, examining the acceptability of therapeutic exercise, patients' preferences around exercise and the use of neuromuscular electrical stimulation as a novel exercise therapy.

3.2 Current use of exercise in cancer

A search was conducted to identify published reviews and studies examining the use of exercise in adults with or cured of cancer. Medline, Embase, Cochrane Central Register of Controlled Trials and Cinahl electronic databases were searched from their respective inceptions to July 2009 using search terms based on exercise (physical activity, exercise therapy, physical training, aerobic, strength, walking) and clinical studies (study, programme, intervention, scheme, trial). In

addition, reference lists of relevant reviews and studies already located were searched and experts in the field were contacted to identify grey literature. The evidence bases relating to patients during or following treatment for curable cancer and those with incurable cancer were appraised separately as detailed below.

3.2.1 Patients during or following treatment for curable cancer

The majority of studies into the use of exercise in the field of cancer have involved patients during or following curative treatment. In the earliest studies, resistance training led to increased excretion of creatinine, a marker of muscle mass, in patients following bone marrow transplantation (Cunningham et al, 1986) and endurance training improved physical function in patients with resectable breast cancer receiving adjuvant chemotherapy (MacVicar and Winningham, 1988). The amount of work examining exercise has grown exponentially and there are currently >70 primary studies of varying quality. The safety of therapeutic exercise in this setting has not been formally examined, although no serious adverse events relating to exercise have been reported suggesting that it is a safe therapy if used appropriately (Jones et al, 2009). Potential adverse events may include an injury when exercising or post-exercise muscle soreness and general fatigue, however, the risks of these can be effectively managed with adequate instruction, training and supervision (McNeely et al, 2006a). Numerous reviews of the efficacy of exercise in this setting have been undertaken. Most have adopted more inclusive inclusion criteria to

involve a greater number of studies (Courneya, 2003; Oldervoll et al, 2004; Stevinson et al, 2004; Holtzman et al, 2004; Galvao and Newton, 2005; Shmitz et al, 2005; Knols et al, 2005; Conn et al, 2006). A smaller number have focused on a particular effect of exercise, e.g. fatigue (Jacobsen et al, 2007; Cramp and Daniel, 2008) or quality of life (Courneya and Friedenreich; 1999). Others have focused on a particular group of patients, e.g. with breast cancer (McNeely et al, 2006b) or those receiving anti-cancer treatment (Young-McCaughan and Arzola, 2007).

Conn et al (2006) provide the most current and comprehensive synthesis of these data with a systematic review and meta-analysis of 30 studies that provided sufficient data to calculate an effect size. This was more studies than other reviews had located using similar criteria underscoring a comprehensive search strategy. Most studies in this review concerned groups consisting entirely (n=13) or predominantly (n=5) of patients with curable breast cancer during or following treatment. The exercise programmes offered to patients varied, however the majority were based at a centre and supervised (n=21) and included either aerobic (n=18), resistance (n=11) or flexibility (n=9) training components undertaken at moderate intensity (n=21). Sessions lasted for a median [IQR] of 30 [25−30] minutes and were completed 3 [2−5] times each week for 10 [9−14] weeks (Conn et al, 2006).

To compare outcome across studies, Conn et al (2006) used standardised mean differences to construct overall effect sizes with 95% confidence intervals. One strength of the methodology used was that the analysis plan weighted studies such that larger samples had proportionally more impact on the effect sizes. An effect size provides a generic numerical measure of the effectiveness of an intervention, which can be interpreted as small (>0.1), moderate (>0.3) or large (>0.5) (Cohen, 1988). It can also be converted into statements which use percentage values to describe the overlap between two groups to infer a degree of change or difference. For example, an effect size of 0.1, 0.3 or 0.5 indicates that the score or performance of the average patient following an intervention, in this case exercise, would exceed that of 54%, 62% and 69% of patients in the respective control groups (Cohen, 1988).

From uncontrolled studies, a large effect size from exercise was found for physical function, which included aspects such as muscular strength or physical fitness, and moderate effect sizes were found for fatigue, mood, other physical symptoms and quality of life, all of which were statistically significant (Table 3.1). When data from controlled studies were pooled, effect sizes reduced and 95% confidence intervals became wider such that only the effect of exercise on physical function remained significant (Table 3.1).

Outcome	Uncontrolled / pre- vs. post-exercise			Controlled / exercise vs. control		
	Effect size	*[95% CI]*	*p*	*Effect size*	*[95% CI]*	*p*
Fatigue	0.40	[0.12, 0.67]	<0.01	–	–	–
Mood	0.34	[0.19, 0.49]	<0. 01	0.19	[-0.12, 0.50]	ns
Exercise behaviour	0.21	[-0.35, 0.96]	ns	0.04	[-0.52, 0.60]	ns
Physical function	0.72	[0.43, 1.00]	<0.01	0.52	[0.25, 0.78]	<0.001
Quality of life	0.43	[0.29, 0.58]	<0.01	–	–	–
Physical symptoms	0.44	[0.09, 0.81]	<0.05	0.35	[-0.30, 0.99]	ns

CI = confidence intervals, ns = not significant (P>0.05)

Table 3.1 Effect sizes for exercise programmes in patients during or following treatment for curable cancer (Conn et al, 2006).

The review also examined if cancer type (breast/non-breast), presence of exercise prescription, supervision, inclusion of a fitness test and timing relative to treatment (during/following) were moderating variables for an effect from exercise (Conn et al, 2006). This analysis was largely limited by the small number of studies with adequate data from which to calculate effect sizes, however, there were indications that higher effect sizes were found in groups of patients with a diagnosis of breast cancer and when exercise was delivered following anti-cancer treatment. However, perhaps owing to the wide heterogeneity in samples and study design, none of the moderator effects were found to be significant (Conn et al, 2006).

This well-conducted review provides support for the use of exercise in patients during or following treatment for curable cancer (Conn et al, 2006). The main finding of an improvement in physical function following exercise is in keeping those of others (Courneya and Friedenreich, 1999; Oldervoll et al, 2004; Mock 2004) and the small-to-moderate effect size estimates encompass reported in previous meta-analyses of these data (Holtzman et al, 2004; Stevinson et al, 2004; Cramp and Daniel, 2008). It is difficult to draw more focused conclusions due to the quantity and quality of studies to date. Conn et al (2006) did not use a formal instrument to assess the methodological quality of included studies, e.g. CONSORT checklist, but reported whether studies had features associated with a robust design. Many studies had pitfalls which may introduce bias, for example, around half were not randomised and few described allocation and/or concealment protocols, blinded assessors to treatment allocation or described the handling of data from patients who withdrew from a study. Outcomes were also assessed by a variety of tools, some of which had not undergone appropriate psychometric testing which the authors acknowledged but did not take into account in their analysis (Conn et al, 2006) As larger, higher quality studies emerge it should become possible to estimate effect sizes with more precision, examine additional effects from exercise, e.g. on sleep (Burnham and Wilcox, 2002) and potentially determine the most beneficial type of exercise programme, e.g. session duration or frequency, or the minimum amount of exercise required to produce a beneficial effect.

3.2.2 Patients with incurable cancer

Only a limited number of studies have examined exercise programmes offered to patients with incurable cancer (Table 2.2). Five studies, three of which were uncontrolled, and three case studies have reported on a total of 119 patients. The cancer diagnosis has varied between and within studies but in general patients offered exercise have been reasonably fit and independent (ECOG performance score 0−2 or KPS ≥60) reflecting the use of exercise as a proactive therapy to maintain or slow down the loss of physical function. The content and structure of programmes has been inconsistent. Programmes have used either aerobic (n=3) or resistance (n=3) training or a combination of the two (n=2). Discounting the case studies, three of the five studies have offered exercise at hospital in a group setting and two have offered home-based programmes to be undertaken alone. Individual sessions of exercise have lasted up to 120 minutes, been completed from twice-weekly to several times daily and programmes have lasted for 4−52 weeks (Table 3.2).

The safety and feasibility of therapeutic exercise in patients with incurable cancer is still being explored. As is the case in patients with curable cancer, no serious adverse events relating to exercise have been reported suggesting it is a safe therapy when used appropriately (Jones et al, 2009). Similarly, it appears feasible to use exercise in this group as studies have been completed in a range of patients, including those receiving concurrent anti-cancer treatment (Headley et al, 2004;

Oldervoll et al, 2006; Porock et al 2000). Nonetheless, these aspects should be examined formally with adequately powered phase II studies before large efficacy studies are attempted.

Overall, data suggest that some patients with incurable cancer are able to complete an exercise programme and benefit from improvement in physical function and aspects of quality of life. Of three studies in which physical function was assessed objectively, muscle strength or functional capacity improved in two (Oldervoll et al, 2006; Renk et al, 2005) and was maintained in the other (Temel et al, 2009). Several case studies which have measured parameters of cardiorespiratory fitness have also found improvements, e.g. increased peak workload, peak $\dot{V}O_2$, or resting heart rate (Crevenna et al 2003a and 2003b; Kelm et al, 2003). In addition, several studies found improvements in one or more domains of quality of life following exercise, e.g. dyspnoea, function, emotion and social domains (Crevenna et al, 2003a; Temel et al, 2009; Oldervoll et al, 2006), or a higher overall quality of life score (Porock et al, 2000; Kelm et al, 2003; Headley et al, 2004)

These preliminary findings suggest a potentially beneficial effect from exercise but should be considered in light of the heterogeneity in study design, setting and patient group and the methodological limitations inherent in collecting pilot data (Lowe et al, 2009). Most studies have not been statistically powered to examine efficacy and

lack a control group therefore improvements may be accounted for by motivational or learning effects alone. For example, Renk et al (2005) concluded that exercise was a ‘very effective method to prevent muscle wasting’ despite reporting on a limited group of 10 patients. In addition, benefit appears to be limited to a select group of patients who were able and willing to complete the exercise programme being offered. When patient flow data was reported, only about a half of those approached about an exercise study started the programme (Porock et al, 2000, Oldervoll et al, 2006), thus reducing the ability to generalise findings to a larger group of patients. Adherence to the recommended programme of exercise was also an issue in some studies, particularly involving patients with non-small cell lung cancer (Temel et al, 2009). This suggests those most at risk of cancer cachexia and potentially able to gain the most from exercise, may also find it least acceptable as a therapy. Temel et al (2009) suggested that offering community based programmes may improve adherence but it is clearly necessary to further explore the utility of exercise in this setting before embarking on larger efficacy studies.

Table 3.2 Summary of exercise studies in patients with incurable cancer.

Study			*Programme*		*Main findings*
Author	*Design*	*Patients*	*Content*	*Outcomes*	*(mean group % change, patients first)*
Headley et al (2004)	RCT (n=38)	Breast cancer receiving chemotherapy Mean age: 51	Home-based seated exercises. 30 minutes, three times each week for 12 weeks	Fatigue and overall quality of life: FACT fatigue scale Perceived exercise intensity: Borg rating scale	Sig. slower decline in fatigue and overall quality of life in exercise group
Renk et al (2005)	Patients (n=10) and age/gender-matched healthy controls (n=10)	Gastrointestinal cancer and ≥5% weight loss	Hospital-based isokinetic resistance training.75% 1RM twice weekly for 8 weeks	Muscle strength: isokinetic dynamometry Body cell mass: bioimpedance Thigh CSA: magnetic resonance imaging	Both groups: sig. ↑isometric (20% and 22%) and isokinetic (14 and 10%) quadriceps strength, body cell mass and thigh CSA
Oldervoll et al (2006)	Uncontrolled (n=34)	Variety of cancers Mean age: 65 KPS ≥60	Hospital-based aerobic and resistance circuit training. 50 minutes, twice a week for 6 weeks	Functional capacity: timed sit-to-stand and 6MWT Quality of life: EORTC-C30	Sig. ↑functional capacity (sit-to-stand 24%, 6MWT 6%) ↑ dyspnoea, functional, emotional and social domains of quality of life (subscales 13−40%)
Temel et al (2009)	Uncontrolled (n=25)	Newly diagnosed non-small cell lung cancer Median age: 68 ECOG 0−1	Hospital based aerobic and resistance training. 120 minutes, twice weekly for 8 weeks	Functional capacity: 6MWT Muscle strength: isokinetic dynamometry Quality of life: FACT lung cancers symptom and fatigue scales	Only eleven patients attended all sessions: sig. ↓ symptoms and no change in functional capacity or muscle strength

Porock et al (2000)	Uncontrolled (n=9)	Variety of cancers Mean age: 60 ECOG 1−3	Home-based short sessions of walking, seated exercises and dancing (individualized) several times daily for 4 weeks	Multidimensional Fatigue Index, Hospital Anxiety and Depression Scale, Symptom Distress Scale, Quality of Life Scale	Non-sig. trends towards ↓ fatigue (activity, motivation and mental subscales), anxiety and ↑ quality of life over programme
Crevenna et al (2003a)	Case study (n=1)	Male (age 55) with metastatic hepato-cellular cancer (lung and brain 2°)	Home-based stationary cycling (60% HR_{max}), 60 minute sessions, twice weekly for 6 weeks	Peak work: cycle ergometry Sub-maximal exercise capacity: 6MWT Quality of life: SF-36	↑ peak work capacity (24%) and sub-maximal exercise capacity (20%) SF−36: ↑ physical functioning (31%), vitality / fatigue (100%), ↓ general health (-5%) and pain (-86%)
Crevenna et al (2003b)	Case study (n=1)	Female (age 48) with metastatic breast cancer (lung, liver and bone 2°)	Home-based stationary cycling (60% HR_{max}), 60 minute sessions, three times weekly for 52 weeks	Peak $\dot{V}O_2$ and work capacity: cycle ergometry Lung function: spirometry Quality of life: SF−36	↑ peak $\dot{V}O_2$, (53%) and peak work capacity (36%)
Kelm et al (2003)	Case study (n=1)	Male (age 58) with metastatic rectal cancer (liver 2°)	Hospital-based resistance (20 reps of 40−60% 1RM) and aerobic training (30 minutes) 1-2 sessions weekly for 13 weeks.	Exercise endurance: reduction in resting heart rate Lung function: spirometry Quality of life: GIQLI	↓ resting heart rate (-10%) ↑ FEV_1 (13%) ↑ FVC (11%) ↑ overall quality of life (22%)

ECOG = Eastern Cooperative Oncology Group, EORTC-C30 = European Organisation for Research and Treatment of Cancer core questionnaire, FACT-G = functional assessment of cancer therapy, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, GIQLI = Gastrointestinal Quality of Life Instrument, HR = heart rate, SF−36 = Short-Form 36, Sig = significant, 6MWT=six minute walk test.

3.3 Challenges of using exercise as a therapy

3.4.1 Issues with acceptability and practicality

Exercise takes time and effort to perform and participation in an exercise programme requires a high level of commitment and motivation (Oldervoll et al, 2005; Chao et al, 2000). Even in healthy older adults, only a minority of the population undertake sufficient exercise and physical activity to maintain their current level of health and it is difficult to increase levels of exercise over a sustained period of time (Thurston and Green, 2004; Nelson et al, 2007). For example, the majority of older adults (>65 years) prescribed home-based exercise admit to partial or complete non-adherence (Yardley and Donovan-Hall, 2007) and more than half of healthy older adults who start an exercise programme drop out during the first six months (Dishman, 1990).

Cancer and its treatment may make it even more challenging to undertake therapeutic exercise. In patients during or following anti-cancer treatment for curable cancer, rates of uptake, adherence and completion across twelve exercise studies have been examined (Oldervoll et al, 2004). Of 1697 eligible patients invited to take part in an exercise programme, more than half declined (53%). Of those who started a programme, a mean (range) of 14% (0−34%) of did not complete (Oldervoll et al, 2004). Among those patients who were able to completed a programme, adherence was generally high (72−100%), suggesting a high level of motivation. However, overall, less than half

were able and willing to complete an exercise programme (Oldervoll et al, 2004).

In patients with incurable cancer, the successful undertaking of studies into exercise represents even more of a challenge and patient flow data reflect this. In Oldervoll et al's study (2006), of 101 patients approached about participation in the exercise programme, 38 immediately refused and a further sixteen withdrew consent before starting. The most common reasons for refusal related to travel to the programme (n=9) or patients already exercising (n=3) or lacking energy (n=4) and in most patients who withdrew consent this was due to a medical reason (n=12). During the course of the programme a further thirteen patients dropped out (medical problems n=10, social reasons n=2, or death n=1) such that, overall, only one third of those approached and about half of those interested managed to complete the programme (Oldervoll et al, 2005). The study by Temel et al (2009) in patients with incurable non-small cell lung cancer provides another example. Data on the number of patients approached were not presented but of 25 patients (who took three years to recruit), six did not start the programme, two only completed one exercise session, and only eleven patients completed the 8 week programme. The reasons for withdrawing from the exercise programme included hospitalization (n=3), toxicities relating to either chemotherapy (n=2) and deterioration in overall health (n=2) (Temel et al, 2009).

3.3.2 Barriers to exercise in patients with cancer

Multiple barriers may prevent patients from taking up and completing an exercise programme and/or study (Figure 3.1) (Sherwood and Jeffery, 2000).

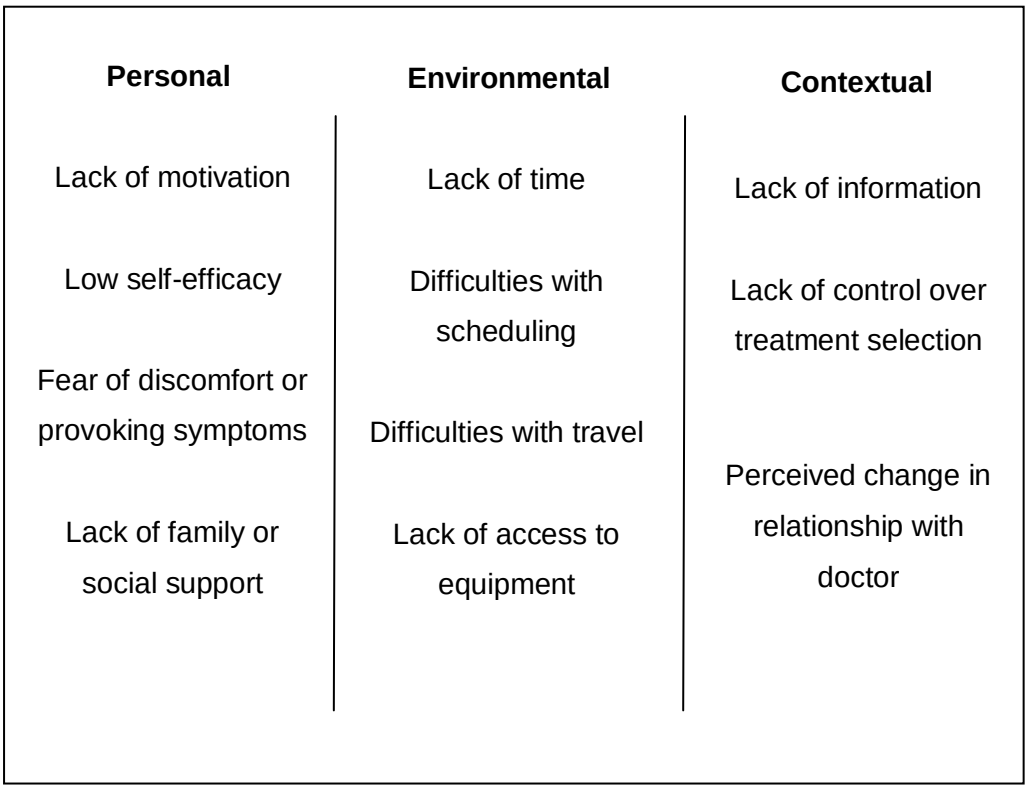


Figure 3.1 Potential barriers to participation in an exercise study

Personal barriers include a lack of motivation and low self-efficacy. Patients require motivation in order to be willing to take up exercise and need to be convinced that the benefits will offset the inconvenience associated with it (Sherwood and Jeffery, 2000; Yardley and Donovan-Hall, 2007). They also need to have sufficient self-efficacy, i.e. belief in their own capability, which may be compromised by current physical symptoms, the perceived demands of an exercise

programme and the opinions of friends, family and other significant others (Carron et al, 1996; Leddy, 1997; Courneya and Friedenreich, 1999). Environmental factors will also impact on the practicality of an exercise programme. Lack of time is a common barrier as participation in exercise requires the time for travel, preparation as well as the prescribed period exercise (Booth et al, 1997; Godin, 1994). Other environmental barriers include scheduling difficulties, poor access to equipment and, for patients on treatment with compromised immune function, the need to avoid crowded public spaces (Doyle et al, 2006). Finally, the context of an exercise programme as part of a research study may prevent patients from taking it up. Several barriers to the study accrual process have been identified. These include a perceived lack of information or control when entering a study involving a random process and a perceived change in the relationship with the patient's physician, who is now bound by a study protocol rather than clinical judgement (Mills et al, 2006; Castel et al, 2006).

The review by Oldervoll et al (2004) cited earlier in this section provided a useful insight into the acceptability of exercise programmes in the cancer setting. However, owing to the recent growth in this literature, its findings only represent around a fifth of the available studies in patients with curable cancer (12 of >70) and do not encompass more recent studies in patients with incurable cancer. Furthermore, this piece of work did not consider the most common barriers to exercise reported by patients in these groups, which may

help to develop exercise as a more acceptable therapy. In view of this, an updated version of this work, with a more detailed exploration of the factors influencing rates of uptake and reasons for declining or withdrawing from an exercise programme, was undertaken and is presented in chapter 5.

3.4 Strategies to improve the acceptability of exercise

Attempts can be made to overcome some of the barriers to exercise to help improve acceptability and unlock the potential benefits to more patients. These include improving education and awareness around exercise participation, eliciting preferences for exercise and exploring novel and more practical forms of exercise.

3.4.1 Improving education and awareness

Education may help address any misconceptions about the demands of undertaking exercise and promote the potential benefits among patients and clinicians. Clinical guidelines for the use of exercise are limited and, due to poor knowledge about specific types or amounts of exercise, those that do exist are broad and non-specific. For example, the American Cancer Society is limited to recommending that “physical activity be encouraged” during and following anti-cancer treatment (Doyle et al on behalf of the American Cancer Society, 2006). In the United Kingdom, there are no specific guidelines on exercise prescription but the National Institute of Clinical Excellence recommend that ‘rehabilitation training programme should be provided’ (NICE,

2004). Recommendations in the public domain are equally sparse, lack clarity and are often inconsistent (Humpel and Iverson, 2005). More detailed guidance requires greater understanding of the role of exercise in patients with curable and incurable cancer.

A more intensive method of education involves individual exercise counselling. This provides patients with one-to-one sessions with an exercise specialist to explore their self-efficacy and motivations around exercise participation (Dishman, 1990). Exercise counsellors then employ behavioural strategies, e.g. cognitive behavioural approaches, in an attempt to address low levels of motivation, unwillingness to change or social barriers and improve levels of exercise participation (McNeely et al, 2006). This approach is beginning to be explored by some of the large clinics in North America but requires extensive resource and expertise, is not suited to all patients and a measured effect has yet to have been demonstrated (Courneya et al, 2008).

3.4.2 Eliciting patient preferences

An understanding of exercise preferences can inform the type, location and delivery of exercise to help make future programmes more congruent with the interests and needs of patients (Booth et al, 1997). This could help to facilitate uptake to studies and minimise loss of patients due to low levels of motivation (Jones et al, 2007). This strategy has been successfully used in healthy older adults where, in

response to patient preferences, changes to community-based exercise programmes led to higher levels of adherence (Ward, 1998; Dunlop and Barry, 1999; Carnall, 2000). These included offering programmes on more days of the week, improving flexibility around scheduling and making content more varied and tailored to each individual's capability (Dunlop and Barry, 1999; Carnall, 2000).

Preliminary work in cancer has examined preferences in patients with various types of curable cancer (Jones and Courneya, 2002), non-Hodgkin's lymphoma (Vallance et al, 2006) and brain cancer (Jones et al, 2006). In each study, the majority of patients reported a preference to start exercise after anti-cancer treatment had been completed and to exercise at home without formal supervision. Walking was preferred by more than half of all patients and equal proportions of patients wished to complete exercise sessions alone, as part of a group or did not have a preference (Jones and Courneya, 2002; Vallence et al, 2006; Jones et al, 2007). Although there is general agreement among these studies, they do not represent many common types of cancer, i.e. only seventeen of nearly 850 patients had upper-gastrointestinal or lung cancer. In view of this limitation, further work to examine the preferences of patients with common incurable cancers would be of value and an original study to address this area of need is presented in chapter 6.

3.4.3 Novel exercise therapies

Another strategy is to explore more novel therapies, e.g. neuromuscular electrical stimulation or whole-body vibration, which may be more practical to some patients. Although passive as they are assisted and initiated by an external stimulus, both fulfil the American College of Sports Medicine's broader definition of exercise, i.e. 'planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness' (Thompson et al, 2010). The former uses a portable device and electrodes to cause a slow, controlled contraction and relaxation of the underlying muscles whilst seated (Robertson et al, 2006) and can lead to improvements in muscular performance and exercise capacity (Bax et al, 2005; Dehail et al, 2008). The latter uses a portable platform on which patients stand for short period of time, e.g. ≤5 minutes, whilst it vibrates and can lead to neural and hormonal changes and, in the longer term, metabolic changes within the muscle, e.g. increased blood flow and oxidative capacity (Rehn et al, 2007; Cardinale and Wakeling, 2005).

Compared to traditional types of exercise such as walking, stationary cycling or resistance training, these novel types of exercise are more passive and require less time and/or effort to complete. Both whole-body vibration and neuromuscular electrical stimulation are well suited to the home environment, generally require low levels of physical ability and, as they do not involve vigorous movements or changes in posture, are unlikely to provoke symptoms such as breathlessness and

fatigue (Sillen et al, 2008). Thus, programmes using these therapies may require lower levels of motivation or less of a change in lifestyle to complete than programme using traditional types of exercise, e.g. walking and stationary cycling (Ambrosino and Srambi, 2004; Maddocks et al, 2007). As a result, such approaches may be acceptable to a greater number of patients. There is no empirical data supporting these as more acceptable types of exercise, however, there is growing interest in their use in healthy older adults and patient groups such as those with COPD and chronic heart failure. On the basis of practicality, neuromuscular electrical stimulation has the most potential in patients with or at risk of cancer cachexia and a more detailed exploration of this therapy follows.

3.5 Neuromuscular electrical stimulation

Neuromuscular electrical stimulation (NMES) uses a portable device to deliver current to tissue via surface electrodes, causing excitation of peripheral nerves and muscular contraction (Robertson et al, 2006). When the current of electrons produced from the stimulator unit interfaces with the skin it is converted into a flow of ions, which move across nerve membranes causing depolarization and an action potential. A sufficient number of action potentials will create a muscular contraction which, when repeated, can be used for purposes of training (Robertson et al, 2006; Dehail et al, 2008).

Within a training programme, current is usually delivered in phases so a period of muscle contraction is followed by a period of rest to help prevent muscular fatigue. The ‘duty cycle’ reflects the proportion of time that the stimulation is active, defined as a percentage of overall time. The current itself is characterised by the width of each pulse (microseconds, μs), their frequency (hertz, Hz) and their intensity (milliamps, mA) which, in combination, create an effect on muscle that can be normalised to a patient’s maximum voluntary contraction (%MVC). The frequency and pulse width may be important in determining the changes brought about by training. For example, use of higher frequencies, e.g. ≥40Hz, has been reported to preferentially target type II fibres and lead to greater improvements in muscle strength compared to endurance (Kit-lan, 1991; Harris et al, 2003; Bax et al, 2005; Vivodtzev et al, 2008). Conversely, low frequencies, e.g. ≤10Hz, may preferentially target type I muscle fibres impacting predominantly on muscle endurance. No universal agreement exists on the optimal training programme and stimulation parameters, which may explain in part the wide range used in studies (Table 3.3).

Table 3.3 NMES training programmes and stimulation parameters used in different patient groups.

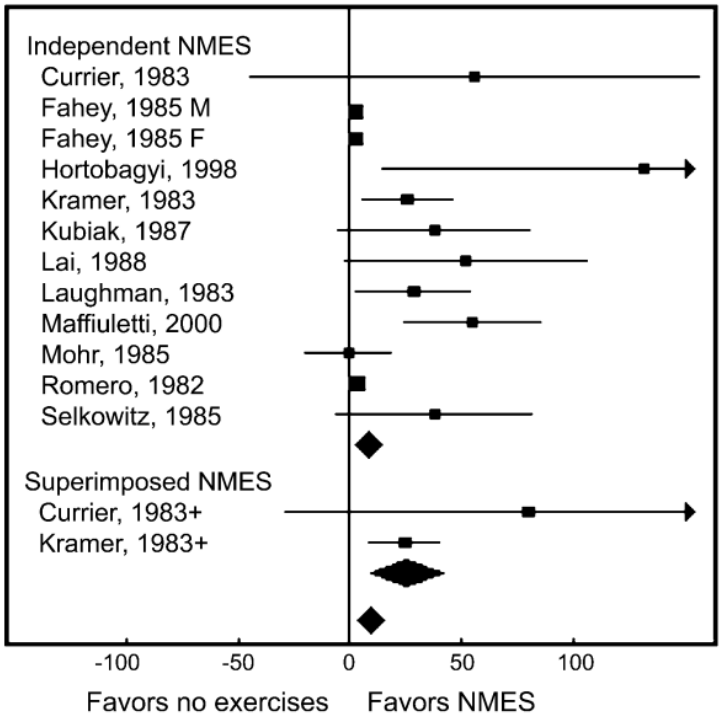
Variables	Healthy subjects	COPD	Chronic heart failure	Cancer
Training programme				
Duration, weeks	4−8	4−6	5−10	4
No. of sessions	15−32	20−30	25−70	20
Session duration, min	10−30	30	30−240	60
NMES parameters				
Pulse duration, µs	300−400	300−400	200−700	400
Frequency, Hz	45−75	35−50	10−25	63
Intensity, mA	10−120	10−100	30−100	−
Intensity, %MVC	50−85	−	25−30	−
Contraction phase, s	5−12	0.2−10	2−20	3.5
Resting phase, s	8−20	1.5−30	4−20	4.5
Duty cycle, %	25−60	10−45	20−50	44

µs = microsecond, Hz=hertz, mA= milliamp, MVC=maximum voluntary contraction, s = second

3.5.1 Healthy volunteer studies

Bax et al (2005) examined the efficacy of NMES using data from randomised controlled studies comparing NMES of the quadriceps to either no treatment, sham treatment or a volitional exercise programme. Seventeen reasonably small studies (mean (range) sample size 20 (12−40)) mostly completed in young adults (mean (SD) age 28(8) years) were indentified Training programme and stimulation parameters are described in Table 3.3. Pooled data (12 studies, n=235) revealed a significant improvement in maximum voluntary contraction following NMES compared to no intervention or sham treatment, with a mean [95% CI] weighted difference of 8.0Nm [2.8, 13.2]. However, when compared to volitional exercise (8 studies, n=155) NMES was less effective, with a mean weighted difference was -1.6 Nm [-24.3, 1.13]. Only two studies compared NMES as an adjunct superimposed onto a volitional exercise programme (n=37) and produced comparable findings; NMES alone produced a strengthening effect but did not appear to enhance volitional training. Figure 3.2 presents these findings with forest plots of NMES versus no exercise (a) and versus volitional exercise (b). The squares represent the mean outcome of each study with the corresponding horizontal lines depicting 95% confidence intervals and the diamonds represent pooled outcomes with the width of the diamond corresponding to the 95% confidence interval. For an effect to be statistically significant, the pooled 95% confidence intervals must not cross the vertical zero line, therefore none of the pooled effects were found to be statistically significant (Figure 2.2).

(a)



(b)

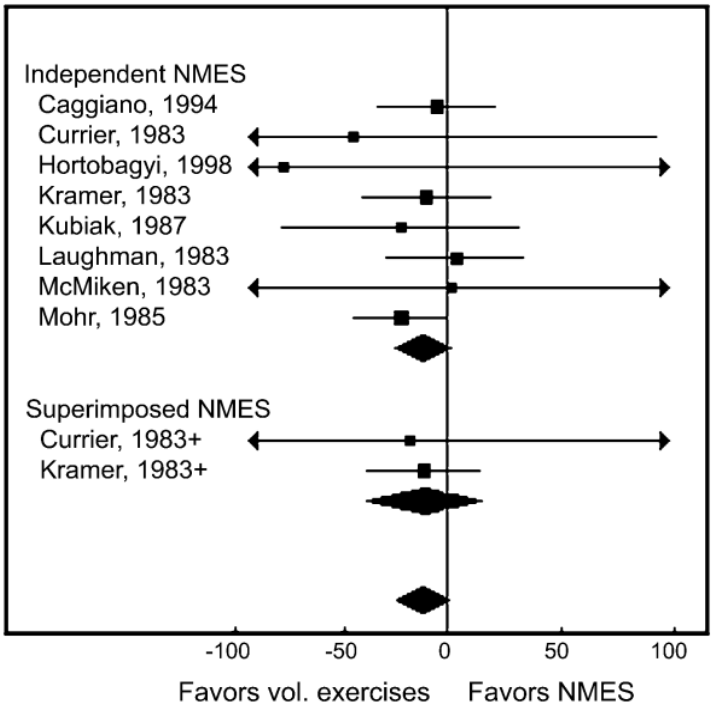


Figure 3.2. Effect of NMES on mean peak torque [95% CI] compared to (a) no exercise or (b) volitional exercise (Bax et al, 2005).

Overall, this review supports a strengthening effect of NMES applied to the quadriceps but also suggests that volitional exercise programmes are generally more effective. Therefore for healthy subjects who are able and willing to undertake volitional strength training programme, NMES may be an appropriate adjunct therapy but cannot be recommended as an alternative therapy to improve quadriceps strength. Nonetheless, for weak patients who experience difficulties undertaking traditional types of exercise, NMES may be a useful alternative therapy. Given that their baseline strength is likely to be lower than the young healthy controls examined by Bax et al (2005), such patients may also benefit proportionally more from any given improvement in muscle strength.

3.5.2 Patients with COPD or chronic heart failure

A number of studies have examined NMES patients with COPD (5 studies, n=91) or chronic heart failure (9 studies, n=210), groups who are also at risk of cachexia (Tisdale, 2009). In controlled settings, NMES has been compared to usual care (no treatment), a sham treatment or a stationary cycling programme, or superimposed onto an exercise programme (Tables 2.4 and 2.5). Interventions varied but typically consisted of 30−60 minute sessions of quadriceps stimulation, 5–7 times each week for 4−6 weeks. The full range of training programmes and stimulation parameters is shown in Table 3.3.

Data for studies in patients with COPD have been subject to a recent meta-analysis, which concluded moderate improvements in muscle function and exercise performance from NMES compared to control, sham or intervention groups (Roig and Reid, 2009) (Table 3.4). Four out of 5 studies reported significant improvements in outcomes relating to muscle function and, overall, NMES groups demonstrated significantly greater improvements in peak torque compared to control groups (mean difference = 9.7Nm; 95%CI 1.2, 18.1) (Roig and Reid, 2009). Programmes also led to a beneficial effect on sub-maximal exercise capacity such that, compared to control groups, differences in improvements in 6MWT distance following NMES (mean difference = 48m; 95% CI 9,86) were close to the minimal clinically important difference of 54m [95% CI 37,71] (Wise and Brown, 2004). Evidence for a hypertrophic effect of NMES was more equivocal, as although global measures of muscle mass did not change, one study found a small increase in thigh circumference (Vivodtez et al, 2006) and another, an increase in the cross sectional area of type II muscle fibres (Dal Corso et al, 2007).

Studies in patients with chronic heart failure have not been pooled but findings appear to be similar and suggest benefits following a programme of NMES if a similar nature and magnitude (Table 3.5). All but one of the nine studies demonstrate a significant improvement in muscle function following NMES with a median [IQR] improvement of 23 [17−43]% and, where measured, maximal and sub-maximal exercise

capacity improved by 9 [5−32]% (Table 3.5). Two studies demonstrated changes in thigh cross-sectional area (Maillefert et al, 1998; Quittan et al, 2001). Another found histochemical changes following NMES, which were not present in a sham–stimulation group, providing robust evidence for an effect on muscle tissue (Nuhr et al, 2004).

In summary, NMES appears to be an acceptable therapy in patients with COPD and chronic heart failure. Four to ten week programmes have been well tolerated by patients (adherence to programmes not presented but frequently ≥90%) and have lead to potentially meaningful changes in muscle function and whole-body exercise capacity. Stronger recommendations supporting the use of NMES are limited by the small number of studies with small sample sizes and methodological differences between studies, which may in part explain differences in findings. Therefore, NMES remains a promising experimental therapy in patients with COPD or chronic heart failure until further studies, ideally using larger samples and longer follow-up periods, are undertaken (Ambrosino and Strambi, 2004). These groups have a number of characteristics that are similar to the patients this thesis is concerned with. They suffer from chronic illnesses and are at risk of developing cachexia and experience the associated range of symptoms including severe muscle wasting and weakness. Therefore, the beneficial effects from NMES in these groups provide strong support for exploring the use of this therapy in patients with incurable cancer.

Table 3.4 Summary of NMES in patients with COPD.

Study			*Intervention*		*Significant findings*
Author	*Design*	*n*	*Parameters*	*Programme*	*(within group changes; NMES first)*
Neder et al (2002)	RCT Crossover NMES vs. control	15	300-400μs, 50Hz, 10-25% duty cycle, 0−100mA	Quadriceps, 30min sessions, 5 times/week for 6 weeks	Between-group differences favouring NMES in isokinetic muscle strength (43 vs. 10%) and endurance (52 vs. -2%), peak $\dot{V}O_2$ (20 vs. 11%), exercise endurance (87 vs. -15%) and dyspnoea during daily activities.
Bourjeily-Habr et al (2002)	RCT NMES vs. sham	18	50Hz, 8% duty cycle, 0−120mA. Sham: NMES not switched on.	Quadriceps and hamstrings, 20min sessions, 3 times/week for 6 weeks	Between-group differences favouring NMES in quadriceps (39 vs. 9%) and hamstring (34 vs. 3%) isokinetic muscle strength, and peak $\dot{V}O_2$ (36 vs. 2%)
Zanotti et al (2003)	RCT Active limb mobilisation ± NMES	24	350μs, 35Hz	Quadriceps and glutei, 30min sessions, 5 times/week for 4 weeks	Between-group differences favouring NMES in isotonic quadriceps muscle strength (131 vs. 68%), respiratory rate (-10 vs. -2%) and time to sit out of bed (11 vs. 14 days).
Vivodtez et al (2006)	RCT Treadmill and peripheral exercise ± NMES	17	400μs, 35Hz, 45% duty cycle, 0−80mA	Quadriceps, 30min sessions daily for 4 weeks	Between-group differences favouring NMES in isokinetic muscle strength (35 vs. 14%) Both groups: ↑ thigh circumference (3 vs. 1%) and sub-maximal exercise capacity (11 vs. 6%)
Dal Corso et al (2007)	RCT Crossover NMES vs. sham	17	400μs, 50Hz, 16−33% duty cycle, 0−60mA Sham:; 50μs, 10Hz, 0−10mA	Quadriceps, 15−60min sessions, 5 times/week for 6 weeks	NMES group: ↑type II fibre CSA (9%) and ↓ type I fibre CSA (15%)

Table 3.5 Summary of NMES in patients with chronic heart failure.

Study			*Intervention*		*Significant findings*
Author	*Design*	*n*	*Parameters*	*Programme*	*(within group changes; NMES first)*
Quittan et al (2001)	RCT NMES vs. control	42	700μs, 50Hz, 25% duty cycle, 25−30% MVC	Quadriceps and hamstrings, 30−60min, 5 times/week for 8 weeks	Between-group differences favouring NMES in isometric (23 vs. -7%) and isokinetic (23 vs. -8%) quadriceps muscle strength and CSA (16 vs. 2%) NMES group: ↑ health-related quality of life for all SF-36 subscales
Nuhr et al (2004)	RCT NMES vs. sham	32	500μs, 15Hz, 33% duty cycle, 25−30% MVC Sham: intensity limited	Quadriceps and calves or sham, 4h sessions daily for 10 weeks	Between-group differences favouring NMES in peak $\dot{V}O_2$ (32 vs. -10%) and sub-maximal exercise capacity (32 vs. 3%) NMES group ↑ citrate synthase activity (30%), ↓ glycerol-dehydre-phosphate dehydrogenase activity (17%), and shift from fast to slow myosin heavy chain isoforms
Harris et al (2003)	RCT NMES vs. stationary cycling	46	25Hz, 50% duty cycle	Quadriceps and calves or cycling at 70% HR_{max}, 30min sessions, 5 times/week for 6 weeks	Both groups: ↑in quadriceps muscle strength (15 and.12%) and endurance (17 and 12%), peak $\dot{V}O_2$ (3 and 5%) and sub-maximal exercise capacity (10 and 10%).

Dobšák et al (2006a)	Parallel groups NMES vs. stationary cycling	30	200µs, 10Hz, 50% duty cycle, 0−60mA	Quadriceps and calves, 1h sessions daily for 8 weeks *or* Cycling 40min sessions, 3 times/week for 8 weeks	Between-group difference favouring stationary cycling in peak $\dot{V}O_2$ (5 vs. 7%) Both groups: ↑ sub-maximal exercise capacity (9 and 14%)
Míkova et al (2004)	Uncontrolled	10	200µs, 10Hz, 50% duty cycle, 0−60mA	Quadriceps, 1h sessions daily for 5 weeks	↑ isometric muscle strength (113%)
Dobšák et al (2006a)	Uncontrolled	15	200µs, 10Hz, 50% duty cycle, 0−60mA	Quadriceps and calves, 1h sessions daily for 6 weeks	↑ isometric (51%) and isokinetic (43%) muscle strength and resting peripheral blood flow (36%)
Maillefert et al (1998)	Uncontrolled	14	200µs, 10Hz, 50% duty cycle, 0−60mA	Quadriceps and calves, 1h sessions, 5 times/week for 5 weeks	↑ muscle CSA (6%), peak $\dot{V}O_2$ (14%), and sub-maximal exercise capacity (ESWT) (10%)
Quittan et al (1999)	Uncontrolled	7	700µs, 50Hz, 25% duty cycle, 25−30% MVC	Quadriceps, 30−60min sessions, 5 times/week for 8 weeks	↑ isometric (9%) and isokinetic (21%) muscle strength and muscle endurance (20%)

CSA = cross sectional area, HR_{max} = maximum heart rate, Hz=hertz, mA= milliamp, MVC=maximum voluntary contraction, s = second, µs = microsecond, $\dot{V}O_2$ = oxygen uptake

3.5.3 Patients with cancer

The use of NMES in patients with cancer is limited to a case report by Crevenna et al (2007), who reported beneficial effects in a patient with metastatic lung cancer and brain secondaries. The authors used NMES due to concerns around the increased risk of seizures due to hyperventilation and pathological fractures due to bone disease with more active forms of exercise. The programme, offered post- brain irradiation, consisted of stimulation of the quadriceps and glutei for one hour sessions, five times each week for a month (stimulation parameters Table 2.3). The patient found the programme sufficiently practical and tolerable such that she was able to integrate sessions into her daily life and adhered to the full recommended programme. This led to clinically meaningful improvements in sub-maximal exercise capacity (6MWT distance), mobility (timed up and go test, 20%) and the physical functioning domain of quality of life (SF-36, 35%).

Although promising, this case study remains a weak form of evidence and the case was not typical of a patient with lung cancer; she was relatively young (47 years), had slowly developing disease and a reasonable performance status despite a being diagnosed several months previously. Other limitations that should be considered when interpreting these findings include the failure to include a practice 6MWT and the lack of reporting on the use of corticosteroids peri-irradiation. The former could

have lead to a learning effect, which may have accounted for the beneficial change in sub-maximal exercise capacity (Troosters et al, 2002) and the later may have contributed to muscle weakness that would have improved on their cessation (Maddocks et al, 2007). Nonetheless, it is reasonable to suggest that NMES may benefit patients with incurable cancer by improving muscle strength and exercise performance and a pilot study in patients with incurable lung cancer is presented in chapter 6.

3.6 Summary

There is convincing evidence that in patients with curable therapeutic cancer exercise can lead to improvements in a broad range of symptoms culminating in beneficial changes in physical function and psychological well-being. Preliminary work suggests these benefits may also be realised in some patients with incurable cancer and further study is warranted. However, there are multiple barriers to exercise participation in this group and issues relating to poor acceptability and practicality, which must be carefully considered. Chapters five and six begin to address some of these issues by examining the acceptability of exercise programmes previously offered to patients with cancer and preferences for different types of exercise in patients with incurable cancer. The next chapter completes the background to this thesis by appraising various assessments of physical function to inform the selection of outcome measures used in the studies presented in chapters seven and eight.

CHAPTER 4:

ASSESSMENT OF PHYSICAL FUNCTION

4.1 Introduction

This chapter provides an overview of measures of physical function that may be used in studies aimed at patients with or at risk of cancer cachexia. Its purpose is to inform the selection of outcome measures used in chapters six and seven. Initially, different aspects of physical function and the attributes of an ideal outcome measure are described. Thereafter, a range of measurements used to assess various aspects of physical capacity and activity are appraised in relation to their psychometric properties and utility.

4.2 Aspects of physical function

The majority of assessments used in cancer cachexia studies to date have focused on the nutritional status of the patient reflecting the nutritional intervention being examined. Some outcomes, e.g. weight loss, have been derived from simple measurements such as body weight whilst others, e.g. lean body mass, have required more detailed forms of measurement such as bioimpedence analysis or dual-energy X-ray absorptiometry (Dahele and Fearon, 2004).

For studies examining therapeutic exercise, outcome measures will also need to consider the patient's physical function. Assessments of physical function can consider both physical capacity, i.e. what a person can do in an exercise test, and physical activity, i.e. what a person actually

does in day-to-day life (Figure 4.1). Assessment of physical capacity may focus on the performance of one body system, e.g. muscular strength, or whole body performance, e.g. maximum workload. Assessments of physical activity may directly measure and quantify bodily movement in terms of its type, duration or frequency, or seek to determine the patient's energy expenditure, which is the energy cost associated with the physical activity they perform (Irwin and Ainsworth, 2004; Valanou et al, 2006).

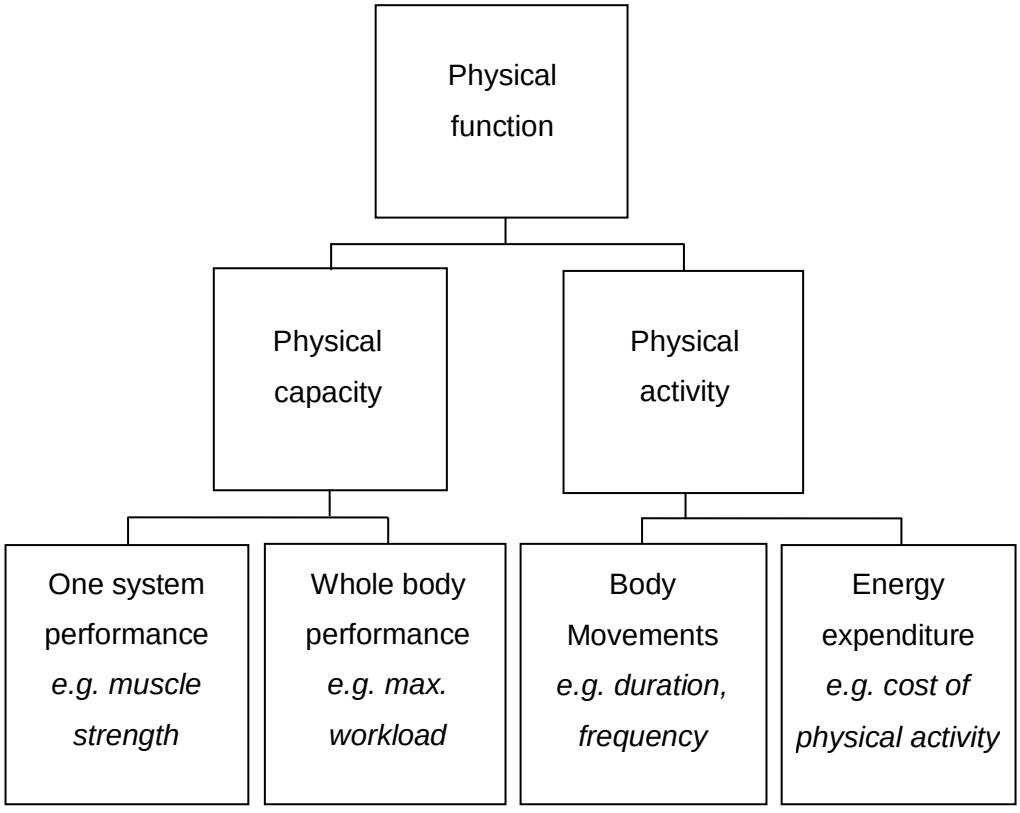


Figure 4.1 Aspects of physical function to be assessed.

4.3 Attributes of an outcome measure

The ideal outcome measure would be valid and reliable in the patient group being examined, sensitive and responsive to change, whilst being useful and practical to apply.

The validity and reliability of an outcome measure determines the confidence that can be placed in the inferences drawn from its use. Validity is the degree to which a measurement reflects the 'true' value of what is being measured. Components of validity include:

- criterion validity: the degree to which outcomes of one instrument correlate with outcomes of a criterion or 'gold standard' measure
- construct validity: the degree to which the construct trying to be measured is assessed by a measure
- content or face validity: the degree to which the appearance or content of an outcome portrays it as a reasonable measure
- convergent validity: the degree to which two instruments are able to measure the same construct (Portney and Watkins, 2000; Lang and Secic, 2006).

Reliability reflects the ability of an outcome measure to reproduce the same results under the same conditions or the degree of consistency with which a variable is measured. Components of reliability include:

- inter-rater reliability: the degree to which two or more raters can obtain the same ratings for a given variable
- intra-rater reliability: the degree to which one rater can obtain the same rating on multiple occasions
- test−retest reliability: the degree to which a measure provides the same outcome under the same conditions when repeating the measure (Portney and Watkins, 2000; Lang and Secic, 2006).

The sensitivity of an outcome measure is the degree to which it can measure an amount or difference. A more sensitive outcome measure will be able to detect smaller amounts or differences, irrespective of whether they are meaningful to the patient or clinically relevant (Lang and Secic, 2006). Responsiveness is a similar attribute, but is the degree to which a meaningful or clinically important amount or difference can be measured (Streiner and Norman, 2003).

In addition to being valid, reliable and sensitive/responsive, the optimal outcome measure would also have qualities that make it useful. A useful outcome measure would be practical, affordable, simple to administer, feasible to use and potentially have some meaning or value to the patient.

4.4 Assessments of physical capacity

4.4.1 Physician-rated performance scales

These provide a global indication of physical capacity based on the patient's level of independence, physical ability and activity levels, which are estimated from a subjective assessment. Popular scales for assessing performance status are the World Health Organisation (WHO, 1979), Eastern Cooperative Oncology Group (ECOG) (Oken et al, 1982) and Karnofsky Performance Scales (KPS) (Karnofsky and Burchenal, 1949). The scores of each scale are broadly comparable with an ECOG performance score of 0−1 equating to a KPS score of 100−80, ECOG 2 to KPS 70−60, and ECOG 3−4 to KPS 50−10 ($r=-0.83$ to -0.90, $P<0.01$) (Buccheri et al, 1996) (Table 4.1).

Table 4.1 Scores and descriptions from physician-rated performance scales (Oken et al, 1982, Karnofsky and Burchenal, 1949)

WHO / ECOG Performance Status		*Karnofsky Performance Scale*	
0	Fully active, able to carry on pre-disease performance without restriction	100	Normal with no complaints or evidence of disease
		90	Able to carry on normal activity but with minor signs of illness present
1	Restricted in physically strenuously activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work	80	Normal activity but requiring effort. Signs and symptoms of disease more prominent
		70	Able to care for self but unable to work or carry on other normal activities
2	Ambulatory and capable to all self-care but unable to carry out any work activities. Up and about >50% of waking hours	60	Able to care for most needs but required occasional assistance
		50	Considerable assistance and frequent medical care required; some self-care possible
3	Capable only of limited self care, confined to bed or chair >50% of waking hours	40	Disabled; requiring special care and assistance
		30	Severely disabled; hospitalisation required but death not imminent
4	Completely disabled, cannot carry on any self-care. Totally confined to bed or chair	20	Extremely ill; supportive treatment and/or hospitalisation required
		10	Imminent death
5	Dead	0	Dead

WHO = World Health Organisation, ECOG= Eastern Cooperative Oncology Group

Performance status is the most common form of functional assessment in oncology and provides a simple global reference for clinical practice. Performance scales are quick to administer, easy to interpret and are well-suited to the clinical environment. Scores are also clinically meaningful, as a patient's performance status is a key determining factor in deciding their eligibility for many anti-cancer treatments, e.g. chemotherapy or high dose radiotherapy. For hospital in-patients, KPS scores have been related to other measures of physical capacity, e.g. dressing, walking, outdoor mobility, supporting the scale's construct validity (Mor et al, 1984). However, the reliability of performance scales has been questioned. In prospective studies using the ECOG performance scale, r values for inter-rater reliability between physicians and between physicians and patients were r=0.44 (Sorensen et al, 1993) and r=0.45 (Blagden et al, 2003) respectively. Thus, only around one-fifth (r^2) of the variance in scores from one rater can be explained by the score of another. Other disadvantages to performance status include scales having a limited number of categories and thus being insensitive to change and scores being third-party rating and suffering from judgement bias (Dahele and Fearon, 2004).Thus, for research studies, performance status provides a useful descriptor to help 'ground' a sample to a clinical population but cannot be recommended to evaluate an intervention due to issues with reliability and sensitivity.

4.4.2 Patient-rated questionnaires

Patient-rated questionnaires can be used to assess a range of components of physical capacity. Only one questionnaire, the Functional Assessment of Anorexia/Cachexia Therapy questionnaire, considers physical capacity in the context of the cachexia syndrome (Ribaudo et al, 2000). The assessment of physical capacity in patients with cancer is generally otherwise undertaken as part of a holistic assessment of quality of life, e.g. EORTC C-30 or FACT-G (Aaronson et al, 1993; Cella et al, 1993), or in the context of other symptoms, e.g. Brief Fatigue Inventory (Mendoza et al, 1999; Jordhøy et al, 2007).

Advantages of such questionnaires include their ease of use and the availability of large comparative datasets (Victorson et al, 2008). Common questionnaires are usually developed in large groups of patients using systematic criteria which establish good levels of validity and reliability. For example, in the development of the EORTC C-30, 305 patients with incurable lung cancer were studied and all sub-scales had to demonstrate (i) an acceptable level of internal consistency (Conrbach's $\alpha \geq 0.7$), (ii) clinical validity, i.e. discriminate between those with clinically distinct features, and (iii) responsiveness in the clinical setting, e.g. change following anti-cancer treatment. Conceptually related scales, e.g. physical functioning and fatigue, also had to correlate to each other ($r \geq 0.4$) (Aaronson et al, 1993). Nicklasson and Bergman (2007) examined the

EORTC C-30 in 112 patients with advanced thoracic cancer in the palliative care setting. Scores from each of the sub-scales were compared between patients to examine clinical validity in this group. Those with a poorer performance status (ECOG 3-4) were found to have worse physical functioning and symptom scores ($p<0.05$) supporting the criterion validity of this sub-scale (Nicklasson and Bergman, 2007).

When selecting a questionnaire for a study, it should be specific to both the patient group being examined and the components of quality of life of most concern, i.e. those the intervention is attempting to influence. For the purpose of this thesis, the EORTC C-30 fulfils these criteria as it has been validated in patients with advanced lung cancer and has a sub-scale specifically concerned with physical function (Aaronson et al, 1993; Nicklasson and Bergman, 2007). This core questionnaire can also be supplemented with the LC-13 a lung cancer specific module, which assesses frequently occurring physical symptoms that may moderate the effect of an intervention on overall quality of life (Bergman et al, 1994).

The main disadvantage to using questionnaires to assess physical capacity is that responses are subjective thus can suffer from recall and response bias. Scores may also lack substantive meaning as, for most questionnaires, the impact of a high or low score has not been connected to external criteria, e.g. ability to perform a task (Mallinson et al, 2006). In

addition, some questionnaires can be time consuming to complete and frequently require the patient to answer questions of little relevance to them, e.g. they will enquire about high level function despite previous responses indicting substantial impairment (Helbostad et al, 2009).

4.4.3 Functional performance tests

Functional performance tests involve asking the patient to perform one or more practical tasks and rating their ability. One example used in patients with cancer is the Simmonds Functional Assessment (Simmond, 2002). This combines a questionnaire regarding physical symptoms and function together with a series of nine functional tasks, e.g. tying a belt, putting on a sock and walking 50 feet, generally completed under timed conditions (Simmonds, 2002). Both inter-rater and test-retest reliability are high with intra-class correlation coefficients (ICCs) of >0.98 and >0.69 respectively. However, the relationship between performance in the physical tasks and questionnaire responses is low ($r=0.25-0.45$, $p<0.01$) demonstrating poor convergent validity (Simmonds, 2002). Responsiveness has not been studied to the same extent but studies have found significant differences in task performance between reasonably fit patients with lung cancer (ECOG 0-1) and age-matched healthy controls suggesting some degree of sensitivity (Yadav et al, 2003; Montoya et al, 2006).

Performance tasks are not reliant on the patient estimating their ability as with questionnaire and thus these potentially provide a more valid form assessment. However, they are still influenced by a variety of factors including the patient's current mood, level of motivation and anxiety and the environment in which they are completed. Their success also depends on selecting appropriate tasks that can discriminate between patients of differing ability without suffering from floor and ceiling effects (Streiner and Norman, 2003). The utility of performance tests is also limited by the need to train assessors for purposes of standardisation, the time taken to complete them, and in less able patients, the number of tasks that can be performed before fatigue limits performance.

4.4.4 Muscle function assessments

Isokinetic dynamometers can be used to assess muscle function through joint range at a pre-determined speed whilst matching any force that the subject exerts in real-time. Common examples of isokinetic dynamometers include the Cybex and Kin-Com® systems. These provide the gold standard measure of peak torque (Newton metres, Nm), which is the maximum force generated by the muscle(s) being tested indicating muscular strength (Thompson et al, 2010). In healthy younger adults, assessments of peak torque for the quadriceps and hamstrings are highly reliable with median (range) test-retest ICCs across studies of 0.93 (0.83−0.99) and 0.92 (0.58−0.88) respectively (Perrin 1986; Montgeomery

et al,1989; Li et al, 1996; Maffiuletti et al, 2007; Imprezelli et al, 2008). Assessments in patients with advanced upper-gastrointestinal and lung cancer are equally reliable, with test-retest ICCs of 0.91−0.99 for quadriceps testing (Reinglas et al, 2007; Trutschnigg et al, 2007; Wilcock et al, 2008a) and 0.86 for hamstrings testing having been reported (Wilcock et al, 2008a).

Isokinetic dynamometry can also be used to assess muscular endurance; the ability of a muscle to maintain a given or expected power output (Thompson et al, 2010). Muscular endurance can be assessed using absolute parameters, e.g. total work (joules, j) / time to a specified reduction in performance, or relative parameters, e.g. work ratios / slope of decline in performance (Kannus et al, 1992). Absolute parameters are generally more reliable with median (range) ICCs for quadriceps testing of 0.92 (0.84−0.98) compared to 0.48 (0.21−0.85) for relative parameters (Perrin 1986 ; Burdett and van Swearingen, 1987; Montgeomery et al,1989; Li et al, 1996; Pincivero et al, 2001; Maffiuletti et al, 2007; Wilcock et al, 2008a). On this basis, the use of absolute parameters is recommended. Nonetheless, the most common of these, total work, is largely dependent on the patient's strength as stronger patients will undertake more work during the course of a test irrespective of the decline in their performance. Therefore, the most reliable outcome measures are limited as they do not adequately differentiate between muscular strength

and endurance. More general disadvantages to isokinetic dynamometry include the size and expense of the equipment, assessments being time consuming and the expertise required to examine patients and interpret findings (Gleeson and Mercer, 1996; Brown and Weir, 2001).Thus, the use of isokinetic dynamometry has generally been limited to research settings.

Portable dynamometers are available, which are less expensive and more practical than isokinetic dynamometers for the assessment of muscle function, however, can only be used to assess isometric or static strength. For hand-grip strength testing, the patient is asked to grip and squeeze a dynamometer as hard as they can and for other muscle groups, an assessor generally holds a dynamometer against a patient's limb and asks them to exert force against their resistance for 3−4 seconds (Bohannon, 2002). Test-retest reliability for portable dynamometry has been shown to be high for the assessment of hand-grip strength within a session (Trutschnigg et al, 2007, r=0.99) and quadriceps strength both within a session (Mathur et al, 2004, ICC 0.94) and between sessions up to one week apart (O'Shea et al, 2007 ICC 0.79; Mathur et al, 2004 ICC, 0.88). However, when comparing the measurement of muscle function using isokinetic and portable dynamometry, between instrument ICCs have been moderate to high for hand-grip strength testing in patients with advanced cancer (Trutschnigg et al, 2007, r=0.89) and quadriceps strength testing in both older adults (Reed et al, 1993, r=0.72−0.85) and patients

with COPD (Martin et al, 2006, r=0.91). Discrepancies tend to arise from an underestimation of muscle strength using portable dynamometers, for example, Martin and colleagues found a mean error of -15Nm (Martin et al, 2006). Despite standardised protocols, this is most likely reflects the difference in measurement technique, with reliance on the assessor to constantly match the patient's strength to maintain a steady testing position with the portable dynamometer (Bohnannon, 1996; Curb et al, 2006). Therefore, when there is a choice between assessments using portable and isokinetic dynamometers, the later is preferred because of its superior validity.

4.4.5 Exercise capacity testing

Cardiopulmonary exercise testing involves measuring oxygen uptake ($\dot{V}O_2$) whilst the patient performs a progressive exercise test until their maximum oxygen uptake ($\dot{V}O_2$ max) is reached (Jones et al, 2008). The gold standard tests use incremental treadmill or cycle ergometry protocols and directly measure $\dot{V}O_2$ by having the patient continually breathe through a mask into a respiratory gas analyser (Jones et al, 2008; Thompson et al, 2010). Although accurate, these tests require specialised equipment and experienced assessors to undertake and use forms of exercise which can be unfamiliar to patients (Irwin and Ainsworth, 2004). $\dot{V}O_2$ max can also be estimated from performance in walking tests, which are easier to perform and more familiar to patients. The incremental shuttle walk test (ISWT) is

one example in which the patient walks around a 10m course, with their walking speed dictated by a pre-recorded audio signal, following a 12−level protocol using walking speeds of 0.5−2.4 m/s (Singh et al, 1992). The patient continues until they can no longer maintain the walking speed or their symptoms become limiting and $\dot{V}O_2$ max is predicted from their performance. Predicted values relate strongly to those measured directly using a mask both during the ISWT (using a portable respiratory gas analyser unit) and a treadmill test (r=0.88 and r=0.81 respectively) demonstrating high criterion validity (Singh et al, 1994). A single practice ISWT provides sufficient familiarisation to account for a learning effect, after which test-retest reliability is high with mean differences between subsequent tests of 2m in patients with COPD (Singh et al, 1992) and 1.4m in patients with advanced cancer (Booth and Adams, 2001).

Submaximum exercise tests can also be used to assess cardiopulmonary fitness (Jones et al, 2008). These usually comprise of a self-paced test in which the patient walks as far as possible within a set time or at a set pace. The 6 minute walking test (6MWT) involves the patient walking around two cones, placed 40m apart, and covering the furthest distance possible over the duration of the test (American Thoracic Society, 2002). Although more practical to administer than a maximal exercise test, the 6MWT requires a large clear space, is difficult to standardise and suffers from a large learning effect (Guyatt et al, 1984;

Gibbons et al, 2001). The learning effect is generally greatest between the first two tests, with mean increases of 0–17% reported, which encompasses that thought to represent the minimal clinically important difference of around 10% (American Thoracic Society, 2002; Redelmeier et al, 1997). Thus, even though the American Thoracic Society guidelines only suggest that a practice 6MWT test 'should be considered', a practice walk and standardised encouragement at set intervals, e.g. after every 30sec or every minute have been recommended (Toosters et al, 2002, Solway et al, 2001). The endurance shuttle walk test (ESWT) is an alternative to the 6MWT and minimises the influence of motivation and encouragement by pacing the speed of walking externally. In this test the patient walks around a shorter 10m course at an 'endurance' walking speed equivalent to 85% of the $\dot{V}O_2$ max predicted from an ISWT (Revill et al, 1999). Although there is no criterion measure to validate the ESWT outcomes of time or distance walked against, the test has been shown to be highly reliable in patients with COPD with a mean (2SD) difference between two tests completed ten days apart of 13 (5)m (<5% of mean distance walked, $p>0.05$) (Revill et al, 1999).

4.5 Assessments of physical activity

In addition to measures of physical capacity, the assessment of physical activity can provide additional, perhaps more meaningful, evidence of the functional impact of an intervention.

4.5.1 Doubly labelled water

Doubly labelled water is the gold standard method to assess energy expenditure in free-living conditions and is based on the rates of O_2 consumption and CO_2 production (Dahele and Fearon, 2004). For this method, stable isotopes ^{2}H and ^{18}O are used to label water, which the patient consumes. Samples of urine or blood are collected at the beginning and end of the assessment period during which isotopes are lost from the patient's body as either water in urine and perspiration (both ^{2}H and ^{18}O) or CO_2 (^{18}O only). As the ^{18}O is lost from the body as both water and CO_2, its washout curve is steeper than that of ^{2}H and the difference represents CO_2 production, which is an indirect measure of metabolic rate (Dahele and Fearon, 2004).

Mean measurement error using the doubly labelled water method is estimated to be <5% (Montoye et al, 1996; Starling, 2002). It is non-intrusive and performed over a prolonged period of time, usually one to two weeks, thus more likely to provide an accurate reflection of a patient's habitual energy expenditure. However, the wider use of doubly labelled

water is limited by its expense (around £1000 per patient) and technical complexity (Valanou et al, 2006). Therefore, its use remains generally confined to small scale studies examining metabolism in detail or validation studies where it is used as a criterion measure.

4.5.2 Questionnaires and diaries

Questionnaires may be posted, handed out in person or completed by telephone and are frequently used to assess physical activity level. They typically ask the patient to provide either a global rating of their physical activity level or details about the type, duration and frequency of activities performed over a given time period, usually a week or a month (Ainsworsth, 2008). Common questionnaires include the Baecke questionnaire (Baecke et al, 1982), seven day recall (Blair et al, 1985) and International Physical Activity Questionnaire (IPAQ, 2005). Diaries provide a more detailed account of physical activity but are typically completed for a shorter period of time, usually less than one week (Ainsworth, 2008). Diary entry methods range from logging each activity on completion to recording activities at specified time intervals, e.g. every minute or every four hours (Valanou et al, 2006). Once details about physical activities have been captured, questionnaires or diaries either provide a score to represent the patient's overall physical activity level or estimate energy expenditure by considering the time spent in each activity and its intensity. To identify the intensity, a compendium can be used which details the

relative energy cost of various types of physical activity using metabolic equivalent of task (MET) values. These reflect the energy cost of physical activities expressed as a multiple of the resting metabolic rate. In adults, this is equal to 3.5 ml O_2 kg^{-1} min^{-1}, with MET values ranging from 0.9 (sleeping) to 18 (running at 17.5 km/h) (Ainsworth et al, 2000).

Self-report questionnaires and diaries are practical, low cost and, when completed retrospectively, do not alter the patient's habitual level of physical activity. However, some intrinsic properties make them less valid than direct assessment of physical activity (Ainsworth, 2008). A recent systematic review synthesised 187 individual questionnaire or diary validation studies and revealed low-to-moderate correlations with objective assessments of physical activity (mean (SD) r=0.37 (0.25)) (Prince et al, 2008). A wide range include of positive and negative values were found reflecting both over- and under-estimates of physical activity level and energy expenditure (r=-0.71 to 0.96) (Prince et al, 2008). This may be because subjective assessments suffer from recall and response bias and few questionnaires or diaries assess low intensity physical activity or capture incidental, intermittent activity characteristic of sedentary populations, e.g. household chores and family care (Tudor-Locke and Myers, 2001; Shephard, 2003).

4.5.3 Pedometers

Pedometers are small, battery operated motion sensors that are attached to the waistband in the midline of the thigh and measure the number of steps a person takes during walking. They count steps using a horizontal spring-suspended level arm which, during walking, moves up and down with vertical accelerations of the pelvis and opens and closes an electrical circuit (Berlin et al, 2006). Pedometers range in cost from £5−£80, with more expensive models offering additional measures based on the patient's stride length, e.g. distance walked. Pedometers do not have internal clocks so are unable to log stepping activity against time, nor do they take into account the degree of movement of the lever arm, so are unable to distinguish different walking patterns of speeds (Berlin et al, 2006).

The validity and reliability of pedometers varies depending on the brand and model. The Yamax™ pedometers (Yamax USA Inc. Texas) are generally considered the most accurate and produce valid measurements at walking speeds typical of younger adults (>1.2m/s) with good intra- and inter-instrument agreement (Bohannon, 1999; Shepherd et al, 1999; Le Masurier et al, 2004; Schneider et al, 2004). However, even these tend to underestimate the number of steps taken at slower walking speeds (≤0.9m/s) and in patients with irregular gaits, where measurement error can exceed 35% (Bassett et al, 1996; Schmalzried et al, 1998; Swartz et

al, 2003; Le Masurier and Tudor-Locke, 2003; Cyarto et al, 2004; Le Masurier et al, 2004). This loss of accuracy limits their value in older adults and patients with altered gait.

4.5.4 Accelerometers

Accelerometers use more sensitive technology than pedometers to detect change in the body's centre of mass. During acceleration, a small mass within the accelerometer applies a force to a spring, causing it to stretch or compress. The displacement of the spring is measured and used to calculate the applied acceleration. Most models use piezoresistive materials which respond to gravitational acceleration as well as acceleration due to movement, so are also able to detect changes in their position (Mathie et al, 2004; De Bruin et al, 2008). Accelerometers vary in cost from £50-£1000. Common models include the ActiGraph™ and TriTrac−R3D (worn on the wrist or waist), StepWatch™ (worn on the ankle) and ActivPAL™ (worn on the thigh). They record physical activity in 'counts', which reflect the frequency and intensity of accelerations during movement. Counts are displayed over time either in raw form or once characterised into different activities, e.g. sitting, walking or running, using supporting software. Some models also provide an estimate of energy expenditure by applying MET values to the various types of physical activity they characterise in the same manner as activity questionnaires (Montoye et al, 1996).

Psychometric properties and utility differ depending on the accelerometer model, the patient population and the activities performed. Accelerometers are more accurate than pedometers at measuring steps during slow walking. The ActiGraph™ step count function has been validated in healthy volunteers against direct observation at various walking speeds (1.3−2.8m/s) on a treadmill (r=0.85−0.92, Welk et al, 2000). The ActivPAL™ step count and cadence functions have been validated during treadmill walking across a range of slower speeds (0.60−1.78m/s) and during outdoor walking at self-selected slow, normal and fast paces in healthy younger subjects (Ryan et al, 2006; Maddocks et al, 2008). The ActivPAL™ monitor's measurement of time spent in different postures during everyday activities has also been shown to be valid in both healthy and frail older subjects (mean error <1%) (Grant et al, 2006; Stene et al, 2008). In direct comparison studies, accelerometers out-perform pedometers with consistently low measurement error (<3%) during slow walking (≤1m/s) (Schnieder et al, 2004; Le Masurier and Tudor-Locke, 2003). On the other hand, many models of accelerometer are 'over sensitive' and record more erroneous steps than pedometers during non-ambulatory activities, e.g. motor vehicle travel (Gotshall et al 2003; Le Masurier & Tudor-Locke, 2003) (Table 4.2).

*Table 4.2 Mean number of erroneous steps [95% CI] recorded with various models of pedometer and accelerometer during motor vehicle travel.**

Device type / model	Erroneous steps per 10km of travel
Accelerometers	
ActivPAL™	*0 [0−0]*
PALlite™	*267 [243−293]*
ActiGraph™	*89 [76−102]*
Pedometers	
Yamax DigiWalker™	*26 [7−45]*
Yamax SW-200™	*6 [3−9]*
Yamax LS-2100™	*27 [18−34]*

**For comparative purposes data have been standardised to a 10km distance.*

Accelerometers tend to underestimate energy expenditure during free-living conditions (Leenders et al, 2006). This may be due to the MET values supporting software assigns to various types of activity, or the lack of consideration for upper limb activities or external factors which may increase expenditure, e.g. uneven terrain (Leenders et al, 2006). Many studies claiming to validate energy expenditure outcomes use restricted physical activity regimens which do not reflect free-living activity and their findings should be treated with appropriate caution (Swartz et al, 2000; Leenders et al, 2006). Other issues with accelerometers relate to their expense in terms of acquisition and data management, methodological

inconsistency across studies, e.g. monitoring period, handling of missing data, and the tendency for patients to initially increasing their habitual level of physical activity in response to being monitored (Ward et al, 2005; Clemes et al, 2008). Patient acceptability must also be considered and may be a factor in determining the most appropriate model, i.e. some are easily placed whilst others require specialist fitting and some use only one sensor whilst others use multiple sensors worn at the same time.

Our group compared the relative accuracy of three accelerometers during treadmill walking and motor vehicle travel, in order to help inform our choice of accelerometer for use in future studies (Maddocks et al, 2008). We focused on determining the most accurate step count function as this is important not only as an outcome per se, but also because it is used in the calculation of other outcomes, e.g. distance walked, time spent walking (Mathie et al, 2004; De Bruin et al, 2008). Forty healthy volunteers (15 male, mean (SD) age 28 (8) years, height 169 (8) cm, BMI 22.9 (2.4) Kg/m^2) were recruited and undertook either treadmill walking or motor vehicle travel wearing an ActivPAL™,, PALlite™ (PAL Technologies, UK) and a SW–401 Yamax Digi-Walker™ (New Lifestyles Inc, Missouri, USA). For the treadmill walking, subjects undertook five treadmill walks, each of 5min duration, starting at 0.6m/s and increasing to a maximum of 1.4m/s, reflecting the range of comfortable walking speeds in the healthy elderly (Bohannon, 1997). For motor vehicle travel, subjects occupied the seat of

a car, which followed a standardised route incorporating town, housing estate and single carriage way driving for as close to 15min as possible dependent upon finding a safe place to stop. Step counts recorded by each accelerometer were noted after each walk or car journey and actual step counts were determined from video recordings, viewed independently by two researchers at half-speed and using a zero value respectively. Mean percentage error for treadmill walking was calculated using individual error values regardless of directionality, i.e. under- or over estimates of step count, and for motor vehicle travel, 15min erroneous step counts were multiplied by four to calculate 1h estimates. Measurement errors and their 95% confidence intervals were compared between devices by one-way ANOVA and Students t-test. The sample size of 20 was sufficient to detect a 10% difference between actual and measured step counts (β 0.8, p=0.05).

During treadmill walking, the mean number of steps for twenty subjects ranged from 375 (0.6 m/s) to 578 (1.4 m/s) with estimated stride lengths of 0.51cm and 0.73cm respectively. Mean measurement error was low (<4%) and did not differ between the ActivPAL™ and the PALlite™ monitors. Compared to the ActivPAL™ and PALlite™, the Digi-Walker™ tended to underestimate the number of steps taken and was significantly less accurate at speeds of ≤1m/s (Table 4.3).

Table 4.3 Mean percentage error (95% CI) recorded during treadmill walking (Maddocks et al, 2008).

Speed (m/s)	Steps taken	ActivPAL ™	PALlite ™	Digi-Walker
0.6	375	1.7 (0.5–2.9)	3.4 (1.8–4.9)	40.4 (23.9–60.0)*
0.8	449	0.7 (0.3–1.2)	2.9 (0.3–5.5)	16.4 (9.0–23.9)*
1.0	450	1.4 (0.9–1.9)	1.6 (0.9–2.2)	5.8 (3.3–8.3)*
1.2	541	1.8 (0.9–2.7)	3.9 (1.5–9.2)	6.4 (2.8–10.4)
1.4	578	0.7 (0.3–1.1)	1.1 (0.3–1.8)	3.7 (0.3–7.8)

*significantly different to other step counts (p<0.01)

Ten motor vehicle journeys, each with two subjects, were undertaken lasting a mean duration of 15min 3sec (range 14min 59sec to 15min 11sec) over distances of 9.3–9.8km. The ActivPAL™ did not record any erroneous steps. Both the PALlite™ and Digi-Walker™ recorded erroneous steps, the former 10-fold more than the latter (Table 4.4).

Table 4.4 Mean number of erroneous steps (95% CI) recorded during motor vehicle travel (Maddocks et al, 2008).

Duration	ActivPAL	PALlite	Digi-Walker
15min	0 (0–0)	254 (231–278)*	25 (7–43)*
1h (estimate)	0 (0–0)	1016 (925–1107)*	101 (26–175)*

*significantly different to actual step count (p<0.01)

In this comparison, the ActivPAL™ accelerometer performed best, with the accuracy of the other two accelerometers compromised either during slow walking (Digi-Walker™) and/or motor vehicle travel (PALlite™ and Digi-Walker™) (Maddocks et al, 2008). Differences in accuracy in these circumstances may relate to differences in the sensitivity threshold, site of attachment, and the algorithms used in the processing of movement data (Mathie et al, 2004; Valanou et al, 2006). This study added to previous work by examining the accuracy of accelerometers at walking speeds which are representative of elderly patient groups, and providing a direct comparison of accelerometers of varying cost. In addition, it highlighted the importance of accurate measurement during motor vehicle travel, an aspect of free-living physical activity which should be routinely evaluated in validation studies. On this basis of this and previous studies, we decided to further explore the utility of the ActivPAL™ accelerometer by using it in the study presented in chapter 7 and formally examining its acceptability and identifying the optimal period of monitoring in chapter 8.

4.6 Summary

A variety of assessments can be used to provide outcome measures for various aspects of physical capacity and activity. No assessment is perfect and the selection of an assessment for use in a study will reflect a balance between its validity, reliability and responsiveness and how affordable and practical it is. Throughout this chapter assessment methods have been

appraised and compared as a means to determine the most suitable outcomes for use in the intervention studies within this thesis. Objective assessments have generally been shown to be more valid, reliable and sensitive than subjective assessments but these can be difficult to undertake and more burdensome to patients. These will be adopted for use in chapters seven and eight but there remains a need to carefully examine how acceptable and feasible they are to patient groups who are likely to be the focus of future cancer cachexia studies.

CHAPTER 5:

IS EXERCISE AN ACCEPTABLE AND PRACTICAL THERAPY FOR PEOPLE WITH OR CURED OF CANCER? A SYSTEMATIC REVIEW

5.1 Introduction

Physical exercise is reported to be therapeutic in patients with or cured of cancer, enhancing physical functioning and psychological well-being (Conn et al, 2006; Stevinson et al, 2004). However, rates of uptake, adherence and completion of exercise programmes vary widely, suggesting that not all patients find exercise an acceptable or practical therapy. This appears more so for those undergoing anti-cancer treatment or with advanced and incurable disease (Oldervoll, 2006; Stevinson, 2006), reasons for which may include the impact of cancer and its treatment on functional status, symptoms, and self-efficacy (Lagman, 2005). Therefore, if exercise is to be developed as a therapy suitable for the majority of patients with cancer, a greater understanding of the factors influencing its utility is required.

Only one review has considered the acceptability of exercise programmes offered to patients with or cured of cancer, and this predates the majority of work in this field, encompassing only around one-fifth of studies to date (Oldervoll et al, 2004). To explore acceptability further, this review examines all exercise programmes offered to this group of patients in order to identify rates of uptake, adherence and completion together with reasons for declining or withdrawing from exercise programme. It also explores whether the characteristics of an exercise programme or the group of patients it is offered to influence how acceptable it is.

5.2 Methods

5.2.1 Search strategy and selection criteria

Medline, Embase, Cochrane Controlled Trials Register and CINAHL electronic databases were searched from their respective inceptions to July 2008 for studies of exercise programmes for people with or cured of cancer. Searches used key words based on: cancer (carcinoma, neoplasm, tumour, chemotherapy, radiation therapy, surgery), exercise (physical activity, exercise therapy, physical training, aerobic, strength, walking) and clinical trials (programme, intervention, scheme, trial) modified according to the specific vocabulary of each database. In addition, hand searches were conducted in European Journal of Cancer Care, Psycho-Oncology and Journal of Clinical Oncology, and the reference lists of relevant reviews and studies already located were checked.

To be eligible, the exercise intervention studies had to contain a minimum of five patients, 18 years or older, who had previously or were currently receiving treatment for cancer. Studies were excluded if they did not report patient flow data for either the number of eligible patients who were approached or the number of patients who were lost from the study. To determine eligibility, full reports of readily available studies were reviewed. Abstracts of remaining articles were assessed and full texts of potentially relevant articles obtained.

5.2.2 Data extraction and validity assessment

Studies were identified by first author, year of publication and trial design. Where possible, data were extracted on age, gender, cancer type and stage, prior and current treatment, characteristics of the exercise programme (location, type of exercise, length and frequency of sessions, overall duration), the number of eligible patients approached and the number declining, starting, withdrawing and completing the exercise programme. Reasons given for declining or withdrawing were documented along with their frequency. Patient flow data for follow-up periods (time points beyond the first post-intervention assessment) were not included. The mean level of adherence to the intervention across the sample and assessment methodology was recorded. Data were extracted by one researcher then verified by one of two assistants, by cross-referencing proformas containing the review data with original texts.

5.2.3 Statistical analysis

Data were expressed as mean (SD) or median [IQR] as appropriate. Percentage rates were calculated for proportions of eligible patients entering an exercise study on being approached and, when allocated to an active study arm, completing the programme. Adherence to programmes was expressed as percentage adherence to the recommended exercise schedule and compared according to the assessment method used (self-report, objective) with a Mann Whitney U test of difference.

To determine the influence of patient or programme characteristics on uptake and completion of programmes, patient and study characteristics were transformed into binary data. For some characteristics, e.g. treatment status (on / off treatment) and study design (randomised / single arm), a reduction in the level of data was not necessary as these naturally fitted within one of two groups. For data regarding cancer diagnoses (breast cancer / other cancer) and exercise settings (home / centre), dichotomous divisions were based on the evidence base regarding exercise in people with cancer, e.g. predominantly patients with breast cancer either in the home or a community or hospital setting. For remaining exercise programme characteristics; exercise intensity (low / mod–high), session length (less / more than 30min), session frequency (less / more than 3 times weekly), and programme duration (less / more than 6 weeks), groupings were

based on exercise prescription guidelines for healthy elders of at least three 30min bouts of moderate exercise each week for 6 weeks (Haskell et al, 2007; Nelson et al, 2007). To examine if each characteristic influenced the acceptability of exercise, rates of uptake and completion for each binary pair were compared using a Student's t-test or Mann Whitney-U test as appropriate.

Reasons provided by patients when declining or withdrawing from an exercise programme were listed by category in order of prevalence by study and by number of patients. Calculations were performed using Statistical Package for the Social Sciences (SPSS) version 15.0. A p value of <0.05 was regarded as statistically significant.

5.3 Results

5.3.1 Included studies

The literature search yielded 1373 separate article titles. Of these, 97 trials of exercise interventions were retrieved for potential inclusion and 65 were included in the review (Figure 5.1).

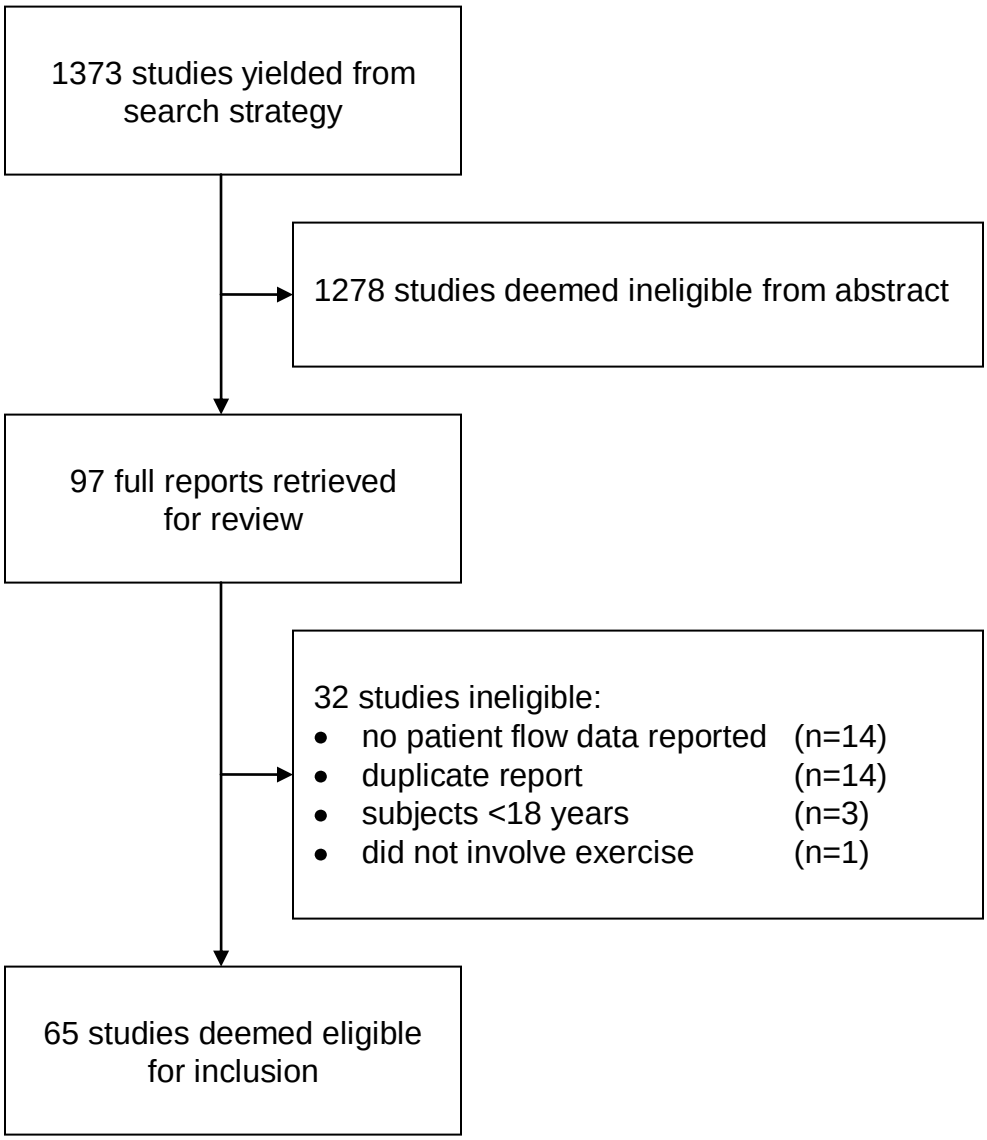


Figure 5.1. Study selection diagram.

5.3.2 Study descriptions

The majority of included studies contained patient groups made up entirely (n=29) or predominantly (n=18) of patients with breast cancer. Of the remainder, groups consisted of patients with hematological (n=5), prostate (n=4), lung (n=4), gastro-intestinal (n=2), head and neck (n=2), or skin (n=1) cancer. In studies reporting disease stage (n=29), the study groups generally consisted of patients with early stage disease with only one or two patients with advanced disease (n=20). The remaining nine studies consisted of patients only with early (stage I–II) (n=8) or advanced (stage III–IV) (n=1) stage disease. Thirty-one studies involved patients receiving concurrent anti-cancer treatment such as adjuvant chemo- or radiation therapy (n=14), radical or palliative chemo- or radiation therapy (n=12) or biological or hormone treatment (n=5). In the 50 studies reporting prior treatment, the majority of patient groups had undergone surgery (n=44) ± adjuvant chemo- or radiation therapy (n=23). Others had received bone marrow transplantation (n=4) or chemo- or radiation therapy (n=3) (Table 5.1).

Patients were randomly allocated to either a control group or an exercise programme in 42 of the 65 studies. Programmes generally consisted of either one aerobic exercise (e.g. walking (n=10), cycling (n=8), or patient selected (n=14)), resistance exercises (with (n=4) or without (n=4) weights), or a combination of the two (n=25), undertaken at

low to moderate intensities. Walking was employed as the main or a contributory exercise in over three-quarters of the exercise programmes. Less traditional programmes included Tai Chi and trunk stability exercises (e.g. Pilates), generally used to promote patient relaxation and well-being.

Programmes were delivered in the home setting (n=24) or at an alternative centre (n=41), such as hospital, health centre, private gym, or community hall. Generally, patients were recommended to complete or attend 3 to 5 sessions each week (n=43) lasting 15 to 30 minutes (n=29). The frequency of sessions ranged from 1 to 7 times per week and session length ranged from 10 to 120 minutes, with longer sessions usually concerning low intensity types of work, e.g. relaxation exercises, Tai Chi. Most programmes were of 6 to 12 weeks duration (n=36) with shorter programmes, i.e. ≤3 weeks, generally being offered to inpatients, and longer programmes, i.e. ≥20 weeks, tending to be based on promoting an active lifestyle (Table 5.2).

Table 5.1. Study participant characteristics.

Study	(n)	Random	Gender (m : f)	Mean age	Group	Stage	Previous treatment	Current treatment
Adamsen et al, 2001	17	N	17:0	57	Mixed	NR	NR	NR
Adamsen et al, 2003	23	N	9:14	40	Mixed	NR	Chemotherapy / RT	Chemotherapy
Adamsen et al, 2006	82	N	26:56	40	Mixed	NR	Surgery / RT	Chemotherapy
Berglund et al, 1993	60	Y	2:58	54	Mixed	NR	Surgery / chemotherapy / RT	Post active Rx
Berglund et al, 2004	199	Y	0:199	53	Mixed	NR	Surgery / chemotherapy / RT	Post active Rx
Bobbio et al, 2008	12	N	10:2	71	Lung	I–II	NR	Pre-surgery
Burnham & Wilcox, 2002	21	Y	3:18	53	Mixed	NR	Surgery / chemotherapy / RT	Post active Rx
Campbell et al, 2005	22	Y	0:22	48	Breast	NR	Surgery	Chemotherapy / RT
Cesario et al, 2007	25	N	NR	NR	Lung	NR	Surgery	Post-surgery
Coleman et al, 2003	24	Y	14:10	55	Multiple Myeloma	NR	NR	Chemotherapy, stem cell transplant
Coleman et al, 2008	135	Y	70:65	55	Multiple myeloma	NR	NR	Chemotherapy
Courneya et al, 2002	108	Y	16:92	52	Mixed	I–IV	Surgery / chemotherapy / RT	Chemotherapy / RT / none
Courneya et al, 2003a	52	Y	0:52	59	Breast	NR	Surgery / chemotherapy / RT	Post active Rx
Courneya et al, 2003b	100	Y	59:41	60	Colorectal	NR	Surgery	Chemotherapy / none
Courneya et al, 2007	242	Y	0:242	49	Breast	I–III	Surgery	Chemotherapy
Daley et al, 2007	108	Y	0:108	51	Breast	NR	Surgery / chemotherapy / RT	Post active Rx
Decker et al, 1989	12	N	9:3	43	Leukemia	–	BMT	Post-BMT
Denmark-Wahnefried et al, 2008	90	Y	0:90	42	Breast	I–III	Surgery	Chemotherapy
Dimeo et al, 1996	20	N	11:9	36	Hematological	NR	BMT / chemotherapy	Post-BMT

Dimeo et al, 1997a	36	N	11:21	42	Mixed	NR	Chemotherapy / RT	Chemotherapy, stem cell transplant
Dimeo et al, 1997b	70	Y	19:51	40	Mixed	NR	Chemotherapy	Post active Rx
Dimeo et al, 1999	59	N	22:37	40	Mixed	–	NR	Chemotherapy, stem cell transplant
Galvao et al, 2006	11	N	11:0	70	Prostate	NR	NR	Androgen deprivation therapy
Headley et al, 2004	38	Y	0:38	51	Breast	IV	NR	Chemotherapy
Hwang et al, 2008	40	Y	0:40	46	Breast	NR	Surgery	RT
Heim et al, 2007	63	Y	0:63	NR	Breast	NR	Surgery / chemotherapy / RT	Post active Rx
Irwin et al, 2008	75	Y	0:75	56	Breast	I–III	Surgery / chemotherapy / RT	Post active Rx
Jones et al, 2007	25	N	6:19	65	Lung	I–III	NR	Pre-surgery
Kolden et al, 2002	51	N	0:51	55	Breast	I–III	Surgery / chemotherapy / RT	Post active Rx
Korstjens et al, 2006	665	N	140:525	51	Mixed	NR	Surgery / chemotherapy / RT	Post active Rx
Ligibel et al, 2008	101	Y	0:101	52	Breast	I–III	Surgery / chemotherapy / RT	Post active Rx
MacVicar & Winningham, 1989	62	Y	0:62	45	Breast	II	Surgery	Chemotherapy
Matthews et al, 2007	36	Y	0:36	51	Breast	I–III	Surgery / chemotherapy / RT	NR
May et al, 2008	147	Y	24:123	49	Mixed	NR	Surgery / chemotherapy / RT	None
McNeely et l, 2004	17	Y	14:3	61	Head and neck	–	Surgery	Post–surgery
McNeely et al, 2008	52	Y	37:15	52	Head/neck	I–IV	Surgery	Post active Rx
Mello et al, 2003	18	Y	8:10	29	Hematological	–	Bone marrow transplant	Post–BMT
Midtgaard et al, 2006	61	N	16:45	43	Mixed	NR	NR	Chemotherapy
Milne et al, 2008	58	Y	0:58	55	Breast	I–III	Surgery / chemotherapy / RT	Post active Rx
Mock et al, 1994	18	Y	0:18	44	Breast	I–II	Surgery	Chemotherapy
Mock et al, 1997	50	Y	0:50	49	Breast	I–II	Surgery	RT
Mock et al, 2001	52	N	0:52	48	Breast	I–III	Surgery	Chemotherapy / RT
Monga et al, 2007	21	Y	21:0	68	Prostate	NR	NR	RT

Mutrie et al, 2007	203	Y	0:203	NR	Breast	I–III	NR	Chemotherapy / RT
Na et al, 2000		Y	NR	58	Stomach	–	Surgery	Post-surgery
Ohira et al et al, 2006	86	Y	0:86	53	Breast	I–III	Surgery / chemotherapy / RT	Post active Rx
Oldervoll et al, 2006	34	N	15:19	65	Mixed	NR	Surgery / chemotherapy / RT	Chemotherapy, HRT, none
Payne et al, 2008	20	Y	0:20	65	Breast	NR	Surgery / chemotherapy / RT	Hormone therapy
Pickett et al, 2002	52	Y	0:52	48	Breast	I–III	Surgery	Chemo/radiotherapy
Pinto et al, 2003	24	Y	0:24	53	Breast	I–II	Surgery / chemotherapy / RT	Hormone therapy
Pinto et al, 2005	86	Y	0:86	53	Breast	I–II	Surgery / chemotherapy / RT	Post active Rx
Porock et al, 2000	9	N	3:6	60	Mixed	NR	Surgery / chemotherapy / RT	Post active Rx
Schulz et al, 1998	39	N	0:39	54	Breast	NR	Surgery	Chemotherapy / none
Schwartz, 1999	31	N	0:31	47	Breast	I–IV	Surgery	Chemotherapy
Schwartz, 2000	31	N	0:31	47	Breast	I–IV	Surgery	Chemotherapy
Schwartz et al, 2001	72	N	0:72	47	Breast	NR	Surgery	Post-surgery
Schwartz et al, 2002	12	N	NR	44	Melanoma	III	Surgery	Interferon-α
Segal et al, 2001	123	Y	0:123	51	Breast	I–II	NR	Chemotherapy / RT / hormone therapy
Segal et al, 2003	155	Y	155:0	68	Prostate	I–IV	NR	Androgen deprivation therapy
Segar et al, 1998	30	Y	0:30	49	Breast	NR	Surgery	Post-surgery
Stevinson & Fox, 2006	12	N	5:7	59	Mixed	NR	Surgery / chemotherapy / RT	Chemotherapy / RT / none
Thorsen et al, 2005	111	Y	36:75	39	Mixed	NR	Surgery / chemotherapy / RT	Post active Rx
Van Weert et al, 2005	81	Y	13:68	52	Mixed	I–IV	Surgery / chemotherapy / RT	Post active Rx
Wall, 2000	104	Y	56:48	65	Lung	I–III	NR	Post surgery
Windsor et al, 2004	66	Y	66:0	68	Prostate	–	NR	RT

Key: Y = yes, N = no, NR = not reported, RT = radiation therapy, "mixed" cancer type denotes ≥3 cancer types used in the study

Table 5.2. Exercise programme characteristics and patient flow data.

Study	Location	Type of exercise	Intensity	Session length (min)	Frequency (per week)	Duration (weeks)	Uptake (%)	Completion (%)
Adamsen et al, 2001	Centre	Tai chi, balance	Low	60	1	16	NR	59
Adamsen et al, 2003	Centre	Cycling, resistance, relaxation	Low / moderate	90	3	6	NR	85
Adamsen et al, 2006	Centre	Aerobic, resistance	High	90	3	6	NR	71
Berglund et al, 1993	Centre	Mobility, relaxation	Low	120	1.5	7	80	83
Berglund et al, 2004	Centre	Mobility, resistance, aerobic	Low	120	1.5	7	68	92
Bobbio et al, 2008	Centre	Cycling	Moderate	90	5	4	NR	100
Burnham & Wilcox, 2002	Centre	Aerobic	Low / moderate	15–30	3	10	NR	100
Campbell et al, 2005	Centre	Aerobic (chosen)	Moderate	10–20	2	6	NR	75
Cesario et al, 2007	Centre	Cycling	Moderate / high	30	5	4	12	100
Coleman et al, 2003	Home	Aerobic, resistance	Moderate	60	3–5	24	NR	78
Coleman et al, 2008	Home	Walking, resistance	Low moderate	NR	3–5	15	NR	88
Courneya et al, 2002	Home	Aerobic (chosen)	Moderate	20–30	3–5	10	80	85
Courneya et al, 2003a	Centre	Cycling	Moderate	15–35	3	15	16	96
Courneya et al, 2003b	Home	Aerobic (chosen)	Moderate	20–30	3–5	16	35	90
Courneya et al, 2007	Centre	Aerobic, resistance	Moderate	15–45	3	18	33	94
Daley et al, 2007	Centre	Aerobic	Moderate	50	3	8	25	97
Decker et al, 1989	Home	Cycling	Moderate	30	3	NR	NR	58
Denmark-Wahnefried et al, 2008	Home	Aerobic, resistance	Moderate	60	3	24	81	90
Dimeo et al, 1996	Centre	Treadmill walking	Moderate	30	5	6	91	70
Dimeo et al, 1997a	Centre	Treadmill walking	Moderate	15–30	5	6	90	89
Dimeo et al, 1997b	Centre	Bed cycling	Low	30	7	NR	NR	94
Dimeo et al, 1999	Centre	Bed cycling	Low	30	7	NR	NR	83

Galvao et al, 2006	Centre	Resistance	Low / moderate	60	2	20	41	91
Headley et al, 2004	Centre	Walking, resistance	Moderate	NR	5	NR	41	NR
Hwang et al, 2008	Home	Arm and leg (seated)	Moderate	30	3	16	NR	NR
Heim et al, 2007	Centre	Aerobic, resistance	Moderate	50	3	5	NR	100
Irwin et al, 2008	Centre / home	Aerobic	Moderate	15–30	3–5	24	20	97
Jones et al, 2007	Centre	Cycling	Moderate / high	15–30	5	4–6	71	92
Kolden et al, 2002	Centre	Aerobic, resistance	Moderate	60	3	16	NR	78
Korstjens et al, 2006	Centre	Aerobic, resistance	Low / moderate	120	2	12	NR	100
Ligibel et al, 2008	Home	Aerobic. resistance	Low / moderate	30–50	2–5	16	86	78
MacVicar & Winningham, 1989	Centre	Aerobic, cycling	Moderate	NR	3	10	NR	NR
Matthews et al, 2007	Home	Walking	Moderate	20–40	3–5	12	13	100
May et al, 2008	Centre	Aerobic, resistance	Low / moderate	120	2	12	91	92
McNeely et l, 2004	Centre	Resistance	Moderate	45	3	12	80	80
McNeely et al, 2008	Centre / home	Resistance	Low / moderate	45	2–3	12	47	88
Mello et al, 2003	Centre	Arm and leg, treadmill walking	Low / moderate	40	7	6	NR	100
Midtgaard et al, 2006	Centre	Aerobic, resistance, cycling	Low / moderate	540/week	NR	6	NR	93
Milne et al, 2008	Centre	Aerobic, resistance	Low / moderate	60	3	12	44	100
Mock et al, 1994	Home	Walking	Moderate	10–45	4–5	NR	NR	50
Mock et al, 1997	Home	Walking	Low / moderate	20–30	4–5	6	77	88
Mock et al, 2001	Home	Walking	Low / moderate	10–15	5–6	6	NR	92
Monga et al, 2007	Centre	Aerobic	Moderate	45	3	8	71	84
Mutrie et al, 2007	Centre	Aerobic, resistance	Moderate	NR	3	12	27	93
Na et al, 2000	Centre	Cycling, resistance	Low / moderate	30	5	2	NR	71
Ohira et al et al, 2006	Centre	Resistance	NR	30	2	26	65	91
Oldervoll et al, 2006	Centre	Aerobic, resistance	Low / moderate	50	2	6	52	95
Payne et al, 2008	Home	Walking	Moderate	20	4	12	35	90

Pickett et al, 2002	Home	Walking	Moderate	10–30	5	6	NR	88
Pinto et al, 2003	Centre	Aerobic (chosen), resistance	Moderate	30	3	12	NR	75
Pinto et al, 2005	Home	Aerobic (chosen)	Low / moderate	30	2–5	12	70	91
Porock et al, 2000	Home	Walking, arm and leg	Low	NR	7	4	11	82
Schulz et al, 1998	Centre	Walking, core stability	Low / moderate	90	2	10	NR	72
Schwartz, 1999	Home	Aerobic (chosen)	Low / moderate	15–30	3–4	8	89	87
Schwartz, 2000	Home	Aerobic (chosen)	Low	15–30	3	8	NR	87
Schwartz et al, 2001	Home	Aerobic	Low / moderate	15–30	3–4	8	NR	92
Schwartz et al, 2002	Home	Aerobic (chosen)	Low	15–30	4	16	NR	100
Segal et al, 2001	Home	Walking	Low / moderate	NR	5	26	33	79
Segal et al, 2003	Centre	Resistance	Moderate	30–40	3	12	31	90
Segar et al, 1998	Centre	Aerobic (chosen), resistance	Low / moderate	30–40	4	10	100	80
Stevinson & Fox, 2006	Centre	Aerobic and resistance	Low / moderate	30–60	5	10	39	82
Thorsen et al, 2005	Home	Aerobic (chosen)	Moderate	30	2	14	63	86
Van Weert et al, 2005	Centre	Cycling, resistance	Low / moderate	90	2	15	NR	78
Wall, 2000	Home	Walking, resistance, breathing	Low	30–40	7	1–3	NR	92
Windsor et al, 2004	Home	Walking	Moderate	30	3	4	86	97

Key: "centre" indicates setting other than patient's home, NR = not reported.

5.3.3 Acceptance and adherence data

Overall, 7224 eligible patients were approached about participation in an exercise programme and 4524 accepted and enrolled. The median [IQR] rate of uptake was 63% [33–80]. Allowing for randomisation of some patients to a control group, this left 3220 patients commencing an exercise programme. Of these, 2824 completed the programme, a median [IQR] programme completion rate of 87% [80–96].

Most studies assessed adherence by either a patient diary (n=19) or an attendance register (n=21) for programmes located in the home or a centre respectively, although a range of methods were employed (telephone or face-to-face interview, accelerometer). Median [IQR] adherence to the recommended programme was 84% [72–93]. No statistical difference was found between adherence measured by self-report or independent assessment methods (p=0.42).

5.3.4 Factors influencing acceptability

No characteristic was found to significantly influence the uptake to an exercise programme. Non-significant trends suggested patients with or cured of breast cancer were less inclined to take up exercise than those with other types of cancer and that greater proportions of patients agreed to undertake programmes which recommended walking as the main exercise, used shorter bouts of low intensity exercise and had a shorter overall duration. Once enrolled and allocated to an exercise group, no characteristic was found to influence the proportion of patients completing the exercise programme (Table 5.3).

Table 5.3. Median [IQR] uptake and completion data according to patient or exercise programme characteristics.

Characteristic	Rate of uptake (%)	p value	Rate of completion (%)	p value
Cancer type:				
Breast cancer	51 [35–80]		90 [82–93]	
Other cancer	67 [24–80]	0.87	91 [86–94]	0.90
Treatment status:				
On treatment	56 [33–82]		90 [86–93]	
Off treatment	63 [35–80]	0.96	90 [82–94]	0.76
Study design:				
Randomised	64 [33–80]		90 [85–95]	
Single arm	51 [40–90]	0.54	87 [76–92]	0.16
Exercise type:				
Walking	74 [38–88]		88 [83–91]	
Other exercise	47 [31–80]	0.20	91 [83–94]	0.34
Location:				
Home	63 [35–81]		88 [85–91]	
Centre / hospital	58 [32–80]	0.85	91 [82–94]	0.97
Intensity:				
Low	60 [45–88]		85 [81–92]	
Low / Moderate	49 [27–80]	0.08	90 [86–96]	0.97
Session length:				
≤ 30min	70 [35–86]		90 [86–92]	
> 30min	49 [33–80]	0.55	90 [82–95]	0.70
Session frequency:				
≤ 3 per week	57 [33–80]		91 [86–95]	
> 3 per week	70 [34–88]	0.79	88 [81–92]	0.50
Programme duration:				
≤ 6 weeks	74 [47–89]		89 [73–96]	
> 6 weeks	47 [33–80]	0.23	90 [84–93]	0.79

5.3.5 Reasons for refusal or withdrawal

Common reasons for refusal included the impracticality of undertaking the exercise programme; time commitment associated with exercise, travel requirements and disinterest in exercise. These were reported by over three-quarters of patients who did not take up an exercise study. Once randomised to an exercise programme, the main reasons for withdrawal from a study included development of a medical complication, including adverse responses to treatments, e.g. chemotherapy, and acute events such as pulmonary emboli, deterioration in medical condition and personal or social problems (Table 5.4). In cases of a medical condition or deterioration in condition, this was reported to be related to anti-cancer treatment rather than participation in the exercise programme studied.

Table 5.4. Main reasons for refusing or withdrawing from an exercise programme

Reason	Number of studies reporting	% of studies reporting	Number of patients reporting	% of all patients reporting
Refusing				
Too busy / no time	17 / 36	47	203	17
Too far to travel	15 / 36	42	261	22
Lack of interest	15 / 36	42	477	40
Worried about physical ability	7 / 36	19	63	5
Already managing exercise	7 / 36	19	21	2
Too much of a strain	4 / 36	11	34	3
Declined randomisation	7 / 36	19	40	3
Wanted a break	2 / 36	6	11	1
Wanted medical approval	2 / 36	6	37	3
Reminder of illness	1 / 36	3	4	<1
Work commitments	3 / 36	8	35	3
Personal reason	1 / 36	3	1	<1
Withdrawing				
Medical complication	18 / 63	29	42	29
Deterioration of condition	18 / 63	29	32	23
Personal / social reasons	11 / 63	17	22	15
Time commitment too much	7 / 63	11	11	8
Problems with travel	7 / 63	11	5	3
Exercises too strenuous	3 / 63	5	9	6
Cancer recurrence	4 / 63	6	22	15
Not strenuous enough	1 / 63	2	1	1

5.4 Discussion

The acceptability of therapeutic exercise in this patient group has not recently been subject to a systematic review. Although rates of uptake and completion of exercise programmes varied, overall, only about half of patients approached and allocated to an exercise group undertook and completed the exercise intervention. Median [IQR] rates of uptake, adherence and completion across 65 studies were 63% [33–80], 84% [72−93] and 87% [80–96] respectively. These are in keeping with previous findings of Oldervoll et al (2004) who reported median rates of 63% and 86% for uptake and completion relating to a smaller group of patients (1697 vs. 7224 eligible patients) across twelve studies.

The main reasons reported for declining a programme concerned either a lack of interest or the impractical nature of the exercise offered, for example the time, travel, strain and commitment a programme demands (Table 5.4). This reflects findings from other patient groups offered exercise rehabilitation programmes including those with cardiac disease (Evanson and Fluery, 2000) and COPD (Taylor et al, 2007) where factors known to discourage participation include problems with access, e.g. travelling long distances, poor parking facilities, time and scheduling conflicts. A greater understanding of these factors and how they contribute to a patient's decision making is required if exercise programmes are to become more practical in nature. In contrast, the experimental design of

many of the studies which can be a barrier to participation (Castel et al, 2006; Mills et al, 2006), did not appear to have a major influence on uptake and was cited as the main reason for refusal by only 3% of all patients.

Once enrolled, the adherence and completion rates were high (>80%) and the main reason for withdrawal was the occurrence of a medical complication, generally associated with an anticancer treatment, suggesting that patients were highly motivated. The rates are similar to those reported by studies involving healthy elders (Thurston and Green, 2004), which may reflect that the majority of patients were receiving potentially curative or adjuvant treatment for early stage breast cancer. It also suggests that patients who started an exercise programme found sufficient benefit from the initial sessions to maintain their interest and continue participating regularly. This highlights the importance of the initial approach to patients about participation in an exercise study. As the evidence base for therapeutic exercise in patients with incurable disease is limited, it is inappropriate to suggest that this group will benefit from a programme. However, it may help improve uptake if the potential benefits are discussed and explored in some detail.

Because studies which did not explicitly report rates of uptake and completion were excluded, these data should be accurate and valid. However, missing data may influence the validity of other results in this

review. Adherence was recorded by about one-third of studies and the main reason for declining or withdrawing from a programme was recorded in about half and one-thirds of patients respectively. The high proportion of reports failing to provide full details of patient flow data and study characteristics highlights the importance of thorough documentation. Hopefully reporting will improve following consensus documents on minimum datasets for scientific reporting such as those from the CONSORT group.

Factors such as duration of exercise, setting, programme length and disease status have been suggested as possible influences on uptake and completion (Thurston and Green, 2004; Chao et al, 2000; Sherwood and Jeffery, 2000). We found no significant relationships between the characteristics of a patient group or exercise programme we considered and rates of uptake and completion. The most likely explanation for this is the wide ranges seen in these rates across a relatively small number of studies resulting in overlap. Another reason could be the nature of our analysis and the arbitrary cut off points we selected for the dichotomous divisions. The use of multiple linear regression models would have been our preferred means of analysis as these consider the independent contribution of each characteristic being examined whilst accounting for multi-colinearity (Portney and Watkins, 2000). However, based on Lang and Secic's (2006) recommendation of at least ten studies for each

independent characteristic being considered in a model, the number of studies was deemed insufficient and simple tests of difference were used. Another methodological decision regarded the reduction of some characteristics from ratio, interval or ordinal level data into nominal level data, which may have resulted in a loss of precision (Portney and Watkins, 2000). However, when transforming data, all decisions regarding cut-off points were all determined *a priori* and were based on epidemiological and clinical grounds or current public health and exercise prescription guidelines, e.g. 3 times per week, 6 weeks duration (Haskell et al, 2007; Nelson et al, 2007).

It remains plausible that in a more homogenous population those patients who are willing to participate in an exercise programme may differ from those who decline with regard to characteristics such as age, gender and treatment status. It is also possible that other characteristics which were not considered in this review, e.g. depression, education, social status and pre-diagnosis exercise behaviour, may influence rates of uptake and completion. These variables have been highlighted as barriers to exercise (Rogers et al, 2007; 2008) and have also been associated with a reduced level of interest in exercise counselling (Jones and Courneya, 2002). However, as only a minority of studies reported on such demographics, these were not considered. Authors are encouraged to provide these details to allow for synthesis in the future.

This review can be used to compare the acceptability of future exercise studies to median rates of uptake across all studies and similar previous programmes. It also helps inform the planning of future research studies by providing an approximation of the proportion of patients likely to be interested in taking up exercise. Finally, by outlining the most common reasons for patients declining or withdrawing from an exercise programme, it provides a basis on which strategies to make exercise acceptable can be formed. To develop exercise as a therapy, it appears that traditional exercise programmes need to be modified or tailored to each patient to increase practicality, e.g. delivered in a local centre or scheduled around existing commitments. Another approach would be to explore novel types of exercise which are such as neuromuscular electrical stimulation, which may be less demanding and required less of a change in lifestyle thus be acceptable to a greater proportion of patients.

In conclusion, although aiming for universal acceptability is unrealistic, these findings suggest that there is a need to modify current programmes or explore novel alternatives if exercise is to be acceptable and practical for the majority of patients with or cured of cancer. Future work is needed examine in more detail the factors influencing uptake in patients with a wide range of cancers and stage of disease.

CHAPTER 6:

EXERCISE AS A SUPPORTIVE THERAPY IN INCURABLE CANCER: EXPLORING PATIENT PREFERENCES

6.1 Introduction

Therapeutic exercise programmes improve physical fitness, psychological well-being and quality of life in patients receiving curative treatment for cancer (Conn et al, 2006). Patients with incurable cancer may also benefit from exercise, but the evidence in this group is limited and further study is required (Oldervoll et al, 2006; Stevinson and Fox, 2006). Which types of exercise to explore in this group requires careful consideration as the rates of uptake and completion for programmes based on 'traditional' exercises are only about two-thirds and one half respectively (Chapter 5; Maddocks et al, 2009). For an exercise to be a practical therapy for patients with incurable cancer, the majority should be capable of undertaking it and find it acceptable.

One approach to improve acceptability is to develop exercise programmes based on patients' exercise preferences in order they are congruent with the needs and interest of patients (Booth et al, 1997). Although some work on exercise preferences has been carried out, this is limited to patients with less common cancers, e.g. brain, non-Hodgkin lymphoma, ovarian, and exercise has not been presented to patients with details of the intensity, duration and frequency likely to be required to provide a therapeutic effect (Vallance et al, 2006; Jones and Courneya, 2002; Jones et al, 2007; Stevinson et al, 2009). Further, little is known about preferences for more novel and more passive forms of exercise, e.g. neuromuscular electrical stimulation and whole-body vibration, which may be preferred by some patients.

This study has determined the acceptability of six exercise programmes based on different types of exercise to patients with incurable common cancers. This included identifying the most acceptable delivery method, location and time relative to anticancer treatments, and exploring if the choice for a particular exercise programme was influenced by various patient characteristics, e.g. habitual exercise behaviour, performance status or presence of co-morbidities.

6.2 Methods

6.2.1 Subjects

Over a one-year period commencing January 2008, patients with histologically confirmed incurable cancer and an Eastern Cooperative Oncology Group (ECOG) Performance Status (Oken et al, 1982) of 0 to 2 attending oncology outpatient clinics or a daycase chemotherapy suite at Nottingham University Hospitals NHS Trust were identified by their medical records. Whilst attending a scheduled clinic or chemotherapy appointment, patients were approached and invited to take part unless nursing staff considered it inappropriate to do so, e.g. because of high levels of psychological distress or confusion. All gave written informed consent and the study was approved by Nottingham Research Ethics Committee 1 (ref. 07/H0403/116).

6.2.2 Questionnaire

A 19-item questionnaire was developed with the help of the Nottingham Cancer Patients' Support Group and the University of Nottingham Survey Unit used KeyPoint© version 5.5 (Speedwell, Cambridgeshire, UK) to provide a self-contained questionnaire with standardised instructions which could be presented on a laptop computer (Appendices 1.5 and 1.6). The questionnaire covered three broad themes:

Exercise behaviour: current and pre-diagnosis exercise behaviours were estimated using items from the Godin Leisure Time Exercise Questionnaire (Godin and Shepard, 1985; Godin et al, 1986). An independent evaluation found this to compare favourably to nine other physical activity questionnaires with test-retest ICCs over two weeks of 0.62−0.74 having been reported (Jacobs et al, 1993). Patients were asked to report the number of times they did strenuous, moderate and mild intensity exercise for at least 15 minutes during a typical week, on a five-point scale (0, 1−2, 3−4, 5−6 or ≥7 times per week). An activity score was calculated by multiplying the lower value of the patient's response by nine, five and three for strenuous, moderate and mild intensity exercise respectively and summing these together. A higher score indicates greater levels of physical activity.

Preference for type of therapeutic exercise programme: To introduce the purpose of therapeutic exercise, participants were informed that 'Exercise has been used as a therapy to improve people's physical condition, mood and quality of life. We are going to show you a selection of exercise therapies that may provide benefit.' Six different therapeutic exercise programmes were then illustrated in turn by a looping short video clip with accompanying text describing the content, intensity and frequency of sessions and duration of the exercise programme (Table 6.1). For example, for the exercise programme based on walking, patients were informed that 'each session would

consist of three 10 minute walks with rest periods in between and this would be for three days a week for six weeks'.

Table 6.1 Description of the exercise programmes.

Exercise type	*Intensity*	*Single session content*	*Session frequency (times/week)*	*Duration (weeks)*
Walking	Moderate, i.e. brisk walking on the flat	Three 10min walks with rest periods between	3	6
Treadmill walking	Moderate, i.e. brisk walking on the flat	Three 10min walks with rest periods between	3	6
Stationary cycling	Moderate but not exhausting	20−30min	3	10
Resistance training	Low to moderate	Four leg exercises 2 sets of 8 repetitions	3	6
Whole-body vibration	Low to moderate	Three 3min stands with rest periods between	3	10
Neuromuscular electrical stimulation	Low to moderate	30−45min stimulation to both thighs	5	6

Programmes based on walking, treadmill walking, cycling or resistance training were selected because of reported benefit in patients with or cured of cancer (Conn et al, 2006) and those utilizing neuromuscular electrical stimulation or whole-body vibration because of reported benefit in other patient groups, e.g. chronic heart failure, chronic obstructive pulmonary disease (Vivodtzev et al, 2008; Rehn et al, 2007). To minimise bias in the presentation of exercise programmes, video clips were filmed independently (Black Hawk Productions Ltd,

UK) using a standardised setting, model and clip length. The descriptions for each programme were also presented uniformly in order that participant's could interpret the differences between the six programmes in terms their content, e.g. session length and frequency (Appendix 1.6).

Patients were asked to indicate if, at that moment in time, they were physically capable of undertaking such an exercise programme and, if so, whether they would be prepared to undertake the programme. If they were not prepared, they were asked to give reasons for this using free-text. After providing responses for all six exercise programmes, patients were asked to indicate which, if any, of the programmes they would be most prepared to undertake, providing reasons where possible using free-text.

Programme delivery preferences: for the programme they would be most prepared to undertake, patients were asked to indicate their preferences for the delivery method (alone or in a group, supervised or unsupervised), location (home, hospital, community centre, gym) and timing relative to any anticancer treatments received (during or immediately after chemotherapy or radiation therapy).

6.2.3 Protocol

A member of the research team obtained demographic data verbally or from the medical records and introduced the questionnaire. The patient

was asked to complete the questionnaire unaided, in a setting of their choice, e.g. consulting room, treatment bay, with the member of the research team providing assistance only if requested. Data were captured in real-time using an Apache Webserver, version 2.2 (Apache Software Foundation) and uploaded to a central database.

The sample size was based on the precision to which patients' preferences for each type of exercise programme could be estimated and assumes the estimated preference for each type of exercise lies within the range 10-60%. With a sample size of 200, two-sided 95% confidence intervals for preferences for each type of exercise can be estimated to within ±7% when a large sample normal approximation is used (nQuery Advisor® version 6.0).

6.2.4 Statistical analysis

Normally distributed continuous data and skewed data were summarised by mean (SD) or median [IQR] respectively. Change from pre-diagnosis to current physical activity level was calculated using a Wilcoxon signed-rank test. Frequency counts and percentages with 95% confidence intervals were calculated for responses to questionnaire items; perceived physical capability and preparedness to undertake each type of exercise programme, most preferred exercise therapy programme, delivery method, location and time. Responses to open-ended questions were pooled and grouped into themes using content analysis.

Multiple logistic regression was used to examine the associations between gender, age, performance status, current activity score and presence of co-morbidities with being capable and prepared to undertake each of the exercise programmes. Age, performance status and activity score were categorised arbitrarily using cuts off points of 65 years, 1 and 15 respectively; the latter equivalent to three sessions of moderate exercise a week. For each exercise programme, a single logistic regression model containing all independent variables was used to estimate odds ratios, 95% confidence intervals and P values.

All calculations were performed using Statistical Software for the Social Sciences (SPSS) version 15.0 with the exception of confidence intervals, which were calculated using Wilson's method (Wilson, 1927) and Confidence Interval Analysis (CIA) version 2.1.2 (Trevor Bryant, University of Southampton). A p value of <0.05 was regarded as statistically significant.

6.3 Results

6.3.1 Participants

Of 225 eligible patients approached, 200 (89%) enrolled and completed the study. Twenty five patients declined participation citing that they lacked interest (n=19), felt active enough (n=3), were too tired (n=2) or in discomfort (n=1). Participants had a range of common cancers and groups at highest risk of cancer cachexia were well represented, for example, 46 (23%) and 39 (20%) had lung and upper-gastrointestinal cancer respectively. The majority were currently receiving palliative chemotherapy and compared with pre-diagnosis, participants' current physical activity scores were significantly lower (median [IQR] fall 10 [4−16], $p<0.01$). (Table 6.2).

Table 6.2 Patient details. Reported as counts unless stated otherwise.

Demographic	
Sex (male / female)	97 / 103
Age (mean (SD) years)	64 (9)
Diagnosis	
Lung (non-small cell, small cell, mesothelioma)	46 (29, 15, 2)
Breast	40
Upper-GI (pancreatic, oesophageal, gastric, gallbladder)	39 (20, 9, 9, 1)
Colorectal	34
Urological (prostate, renal, bladder)	21 (14, 5, 2)
Gynaecological (ovarian, endometrial, cervical, falopian tube)	16 (12, 2, 1, 1)
Other (head and neck, non-Hodgkin lymphoma, leiomyosarcoma)	4 (2, 1, 1)
Current treatment	
Chemotherapy	185
Radiotherapy	0
Previous treatment	
Chemotherapy	63
Radiotherapy	86
Co-morbidities	
COPD	27
Diabetes	21
Ischaemic heart disease	18
Arthritis	11
ECOG Performance status	
0	29
1	121
2	50
Exercise behaviour (median [IQR] activity score)	
Pre-diagnosis	24 [20−33]
Current	14 [9−21]

Upper-GI = upper-gastrointestinal; COPD = Chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group.

6.3.2 Physical capability to undertake an exercise programme

All 200 patients considered themselves physically capable of undertaking one or more of the exercise programmes. More than 80% felt physically capable of undertaking exercise programmes utilizing resistance training, whole body vibration or neuromuscular electrical stimulation, whereas only about half felt capable of undertaking programmes using walking, treadmill walking or cycling (Table 5.3). Specific reasons given for not feeling capable included the presence of breathlessness (n=89), tiredness/fatigue (n=62), pain (n=49), leg weakness (n=43), poor balance (n=18), joint stiffness (n=13), concern regarding the exercise equipment (n=12) and both breathlessness and leg weakness (n=9). Non-specific comments were also common, e.g. “I would not be able to do that” (n=66).

6.3.3 Preparedness to undertake an exercise programme

Two-thirds (n=133) of patients reported being prepared to undertake one or more exercise programmes at that moment in time. Individually, this was highest for neuromuscular stimulation (60%) and lowest for treadmill walking (33%) (Table 5.3). For all exercise programmes, reasons given for being capable but not prepared included a lack of interest (n=47), being content with current levels of activity/not perceiving a need for exercise (n=33), completing an activity without purpose (n=19), time commitment/scheduling difficulties (n=15), the programme being insufficiently challenging (n=13), wanting to avoid exercise-induced symptoms (n=6), or having other priorities, e.g. family

or work (n=4). For patients prepared to undertake exercise, the decision did not appear to be influenced by the timing of the programme in relation to anticancer treatments (Table 6.3).

One-third (n=67) were not prepared to undertake any of the exercise programmes. Across the six programmes reasons given by this group included a lack of interest (n=109), being content with current levels of activity/not perceiving a need for exercise (n=63), time commitment/scheduling difficulties (n=20), other priorities, e.g. family or work (n=16), completing an activity without purpose (n=7), the programme being insufficiently challenging (n=6), or wanting to avoid exercise-induced symptoms (n=4). Although numbers are smaller, again the decision did not appear to be particularly influenced by the timing of the exercise programme in relation to anticancer treatments (Table 6.3).

Table 6.3 Current physical capability and preparedness to undertake an exercise programme.

	Frequency yes/no	% yes	[95% CI]
Do you think you are physically capable of undertaking this type of exercise therapy programme?			
Walking	107/93	54	[47 to 60]
Treadmill walking	97/103	49	[42 to 55]
Stationary cycling	81/119	41	[34 to 46]
Resistance training	183/17	92	[87 to 95]
Whole body vibration	163/37	82	[76 to 86]
Neuromuscular electrical stimulation	191/9	96	[92 to 98]
Would you be prepared to undertake an exercise therapy programme similar to this?			
Walking	57/50	53	[44 to 62]
Treadmill walking	32/65	33	[24 to 43]
Stationary cycling	38/43	47	[36 to 58]
Resistance training	91/92	50	[43 to 57]
Whole body vibration	95/68	58	[51 to 66]
Neuromuscular electrical stimulation	114/77	60	[50 to 64]
For each of the treatments you have received, would you be prepared to undertake an exercise therapy programme at these times?			
Patients prepared to undertake one or more exercise programmes:			
During chemotherapy	121/7	95	[89 to 97]
After chemotherapy	120/8	94	[88 to 97]
During radiotherapy	40/14	74	[61 to 84]
After radiotherapy	39/15	72	[59 to 82]
During combined chemotherapy and radiotherapy	7/2	78	[45 to 94]
After combined chemotherapy and radiotherapy	7/2	78	[45 to 94]
Patients not prepared to undertake any exercise programme:			
During chemotherapy	0/63	0	[0 to 1]
After chemotherapy	5/58	8	[3 to 17]
During radiotherapy	2/18	10	[3 to 30]
After radiotherapy	1/19	5	[1 to 24]
During combined chemotherapy and radiotherapy	0/3	0	[0 to 56]
After combined chemotherapy and radiotherapy	0/3	0	[0 to 56]

6.3.4 Most preferred type of exercise programme and delivery

For the 133 patients willing to undertake exercise, the most preferred type of exercise to undertake at that moment in time was neuromuscular electrical stimulation, followed by walking and resistance training (Figure 6.1 and Table 6.4). Reasons given for selecting the preferred programme included the practicality or convenience of the type of exercise (n=33), previous experience of the exercise (n=22), enjoyment (n=20), wanting to improve leg strength (n=19), curiosity or interest (n=15), being within their capabilities (n=13), having a focus on general fitness (n=12), or the positive physical challenge it presented (n=9).

The majority of patients expressed a preference to undertake the exercise programme at home, alone and unsupervised. A minority (n=15, 12%) preferred group exercise, with a community centre the preferred meeting place (Table 6.4).

Table 6.4 Patients preferred type of exercise programme and delivery preferences (n=133).

	Frequency	%	[95% CI]
Which type of exercise programme would you be most prepared to undertake at this moment in time?			
Walking	29	22	[16 to 30]
Treadmill walking	5	4	[2 to 9]
Stationary cycling	9	7	[4 to 12]
Resistance training	25	19	[13 to 26]
Whole body vibration	18	14	[14 to 20]
Neuromuscular electrical stimulation	47	36	[35 to 44]
How would you most prefer to undertake the exercise programme?			
Alone, unsupervised	106	80	[72 to 86]
Alone, supervised	5	4	[2 to 9]
In a group, unsupervised	7	5	[3 to 11]
In a group, supervised	15	12	[7 to 18]
Where would you most prefer to undertake an exercise programme?			
Home	110	83	[75 to 88]
Hospital	5	4	[2 to 9]
Community centre	11	8	[5 to 14]
Gym	7	5	[3 to 11]

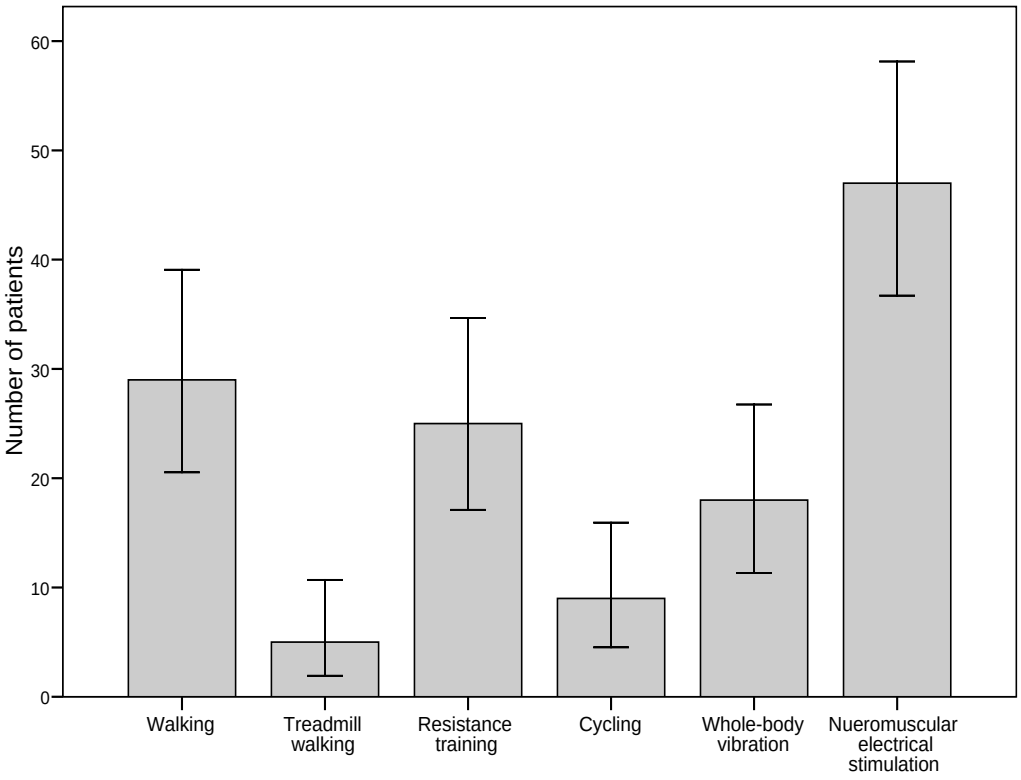


Figure 6.1 Most preferred type of exercise programme by number of patients with 95% confidence intervals.

6.3.5 Influence of patient characteristics on exercise programme preference

Older patients and those with a low performance status were less likely to be capable of and prepared to undertake the cycling exercise programme (odds ratios 0.36 and 0.21 respectively, $p<0.05$) and patients with a low performance status were less likely to be prepared to undertake the programme of treadmill walking (odds ratio 0.19, $p<0.05$) (Table 6.5). There were non-significant indications that older patients, males and those with low performance status, activity scores and comorbidities felt less capable of and prepared to undertake exercise programmes utilising walking, treadmill or cycling and generally more likely to undertake programmes utilising resistance training, whole body vibration or neuromuscular electrical stimulation (Table 6.5). These characteristics were also non-significantly associated with being less prepared to undertake at least one exercise programme.

Table 6.5 Influence of patient characteristics on preparedness to undertake each type of exercise programme expressed as odds ratios [95% confidence intervals].

Characteristic (baseline category second)	*Walking*	*Treadmill walking*	*Stationary cycling*	*Resistance training*	*Whole body vibration*	*Neuromuscular electrical stimulation*
Gender: male vs. female	0.74 [0.38, 1.41]	0.84 [0.37, 1.82]	0.93 [0.44, 1.98]	1.17 [0.66, 2.07]	1.22 [0.69, 2.15]	1.27 [0.72, 2.25]
Age: ≥65 vs. <65	0.68 [0.36, 1.31]	0.65 [0.29, 1.43]	0.36 [0.17, 0.79]*	0.69 [0.39, 1.23]	1.15 [0.65, 2.04]	1.00 [0.56, 1.78]
Performance status: 2 vs. 0–1	0.37 [0.14, 1.01]	0.19 [0.04, 0.87]*	0.21 [0.06, 0.78]*	0.67 [0.33, 1.38]	0.64 [0.31, 1.32]	0.79 [0.38, 1.61]
Current activity score: <15 vs. ≥15	0.62 [0.31, 1.25]	0.97 [0.42, 2.20]	0.99 [0.45, 2.19]	1.63 [0.87, 1.23]	0.80 [0.43, 1.48]	1.27 [0.68, 2.38]
Comorbidities: ≥1 vs. 0	0.77 [0.37, 1.58]	0.67 [0.27, 1.69]	1.75 [0.80, 3.86]	1.06 [0.57, 1.97]	1.03 [0.56, 1.91]	1.23 [0.66, 2.29]

* statistically significant ($p<0.05$)

6.4 Discussion

This is the most in-depth survey of the exercise preferences of patients living with a range of common cancers. When provided with the full details of exercise programmes utilizing various types of exercise and reflecting common regimens, two-thirds of patients appeared capable of and prepared to undertake at least one of them. This proportion is in keeping with the median [IQR] uptake of 63 [33−80]%, reported by a recent systematic review of therapeutic exercise in people with or cured of cancer across a range of settings (Chapter 5; Maddocks et al, 2009). Of those patients prepared to undertake a programme, the most preferred type of exercise was neuromuscular electrical stimulation (36%) followed by walking (22%), resistance training (19%) and whole body vibration (14%) with treadmill walking and stationary cycling selected by less than 10% of patients. This suggests that to engage the majority of patients with common incurable cancers in their most preferred form of exercise, a range of therapeutic exercise programmes may need to be offered, taking into account the clear preference for the exercise to be undertaken at home and unsupervised.

Patients' preferences regarding the delivery of exercise were generally in keeping with those of other patients with or cured of cancer. In a group of non-Hodgkin's lymphoma survivors, over half felt able (53%), and interested (55%), in participating in an exercise programme and the majority had preference to complete exercise sessions at home (Vallence et al, 2006). Similarly, in a group of mixed cancer survivors,

the majority reported a preference towards recreational types of exercise, particularly walking, and undertaking exercise at home and unsupervised (Jones and Courneya, 2002). One advantage to the present study is that patients who were not prepared to undertake any of exercise programmes were not asked about the delivery of a fictitious exercise programme as in previous studies (Vallance et al, 2006; Jones and Courneya, 2002; Jones et al, 2007).

The evidence base regarding the exercise programmes we examined is limited in people with incurable cancer, particularly for the more novel forms of exercise, e.g. neuromuscular electrical stimulation. Our results can be used to help inform the selection of appropriate types of exercise in which to examine uptake, adherence and efficacy in this group and, on the basis of its popularity, neuromuscular electrical stimulation appears worthy of study. Patients cited practicality and convenience as the main reason for selecting this as their preferred choice and, compared to many exercises, neuromuscular electrical stimulation is relatively passive and requires less motivation and change in lifestyle, e.g. it can be undertaken whilst sitting watching television, reading etc. Nonetheless, this choice is likely to have been based mainly on the information given rather than actual experience of neuromuscular electrical stimulation and further work is required to explore the acceptability of its use. Except for walking, there will also be varying degrees of experience with the other types of exercise and this knowledge could have further informed our findings.

One third of patients surveyed were not prepared to undertake any of the exercise programmes, which is also in keeping with the findings of the systematic review (Chapter 5; Maddocks et al, 2009). The main reason given for being unprepared to exercise was a lack of interest, and there was a tendency for older or male patients and those with a low performance status or activity score to be the least prepared to undertake exercise. There is always likely to be a proportion of patients for whom any form of exercise is unacceptable, even when able and aware of the potential benefits. Indeed, Clark et al (2007) surveyed 128 patients with advanced cancer receiving palliative chemotherapy and found that although most patients could identify an immediate benefit from exercise, only a third were interested in receiving support to increase their exercise participation. Some authors have suggested offering exercise as an integrated component of cancer treatment as a means to improve patient interest (Irwin et al, 2008). However, whether this could improve uptake to exercise programmes remains to be seen.

This work builds on a review of the acceptability of exercise as a therapy in which a need to determine the most acceptable types of exercise was identified. Although we asked about the most common types of exercise, some patients may have had a preference towards an alternative, e.g. yoga or swimming, and further work may include an option to report alternative preferences. Another limitation was the potential for researcher bias in the questionnaire. Attempts were made

to minimise bias, for example, video clips were filmed independently, each type of exercise was presented using a standardised format and the six programmes were reasonably comparable in terms of their content. Nonetheless, we were limited by the lack of available evidence in this group and it may be that one or more of the programmes are shown to provide little therapeutic benefit in the future. Finally, although all participants had incurable disease and a similar performance status, there was heterogeneity in the sample in terms of cancer type. Therefore, it remains possible that patients with specific types of cancer have preferences that went undetected. We plan to focus future work on patients with lung and upper gastro-intestinal cancers to address this particular issue.

Future studies expanding on this work could explore factors contributing to preparedness to exercise in more depth, e.g. motivation, confidence, educational level and social status, along with any willingness or preference to undertake other types of exercise not represented in the six programmes. Although we gave participants the opportunity to provide some free-text responses to questionnaire items, a more in-depth exploration of which activities patients' participate in and why, which factors lead to a lack of interest to exercise and whether tailoring programmes would alter preparedness to exercise would all have added to the richness of the data obtained. Some selective follow-up interviews and/or focus groups with participants would have made a useful contribution but was overlooked.

The longer term aim is to develop therapeutic exercise for people with incurable cancer as part of a proactive rehabilitation programme in order to optimise physical function, independence and psychological well-being for as long as possible. Intuitively, success is more likely the sooner it commences after diagnosis rather than waiting until significant loss in function has occurred. Thus, we explored the views of patients with a reasonable performance status, many of whom were receiving or had received chemotherapy or radiotherapy as part of their cancer management. Although all patients had a good performance status, their exercise levels had already fallen from pre-diagnosis levels, supporting our rationale for early intervention.

In conclusion, these findings suggest that it is realistic to consider exercise as a supportive therapy for patients with incurable cancer, including those receiving anticancer treatments. Further work to examine the safety, adherence and efficacy of exercise is required and these data can inform future studies so the most popular forms of exercise are examined.

CHAPTER 7:

RANDOMISED CONTROLLED PILOT STUDY OF NEUROMUSCULAR ELECTRICAL STIMULATION OF THE QUADRICEPS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

7.1 Introduction

Cachexia is particularly common in patients with incurable non-small cell lung cancer (NSCLC) leading to muscle wasting and weakness, which impair physical function and quality of life (Laviano and Meguid, 1996; Courneya and Freidenreich, 1999; Rejeski and Mihalko, 2001). Anti-cancer treatments causing fatigue can also lead to physical inactivity and further muscle deconditioning (Muscaritoli et al, 2006). Effective treatments are lacking and new approaches are required.

Therapeutic exercise may be one component of a multimodal approach to the management of patients with or at risk of cancer cachexia (Fearon et al, 2008). However, there are issues with acceptability and only about half of patients with or cured of cancer are willing and able to complete an exercise programme (Chapter 5 Maddocks et al, 2009). Further, patients experiencing breathlessness and/or fatigue at low levels of exertion may find more active types of exercise, e.g. walking, circuit training, too demanding (Irwin and Ainsworth, 2004; Oldervoll et al, 2006). One approach which avoids some of these difficulties is neuromuscular electrical stimulation (NMES) of the quadriceps muscles. NMES can be self-administered at home while seated and, being a passive intervention, it demands less motivation and change in lifestyle than traditional forms of exercise. Thus, it may help overcome some of the practical barriers identified in the systematic review presented in Chapter 5 (Maddocks et al, 2009). In support of this, when therapeutic programmes using NMES were

directly compared to more traditional types of exercise, e.g. walking, stationary cycling, they were preferred by patients with incurable cancer because of their perceived practicality and convenience (Chapter 6; Maddocks et al, in press).

Stimulation is administered by a small battery operated unit, which, via self-adhesive electrodes, produces a controlled contraction and relaxation of the underlying muscle equivalent to 20−50% of the patient's maximum voluntary contraction. Treatment regimens generally consist of a 30 minute period of stimulation 5–7 times a week. In healthy subjects, NMES leads to similar changes in muscle biochemistry (Nuhr et al, 2004; Dal Corso et al, 2007; Sillen et al, 2008) and improvements in strength as found with volitional resistance training (Bax et al, 2005). NMES has increased quadriceps muscle strength by 10–40% in patients with chronic obstructive pulmonary disease (COPD) or heart failure, with improvements in exercise capacity and health-related quality of life seen in some studies (Nuhr et al, 2004; Dal Corso et al, 2007; Neder et al, 2002; Bourjelly-Habr et al, 2002; Quittan et al, 2001; Dobšák et al, 2006a). NMES has not been formally examined in patients with cancer to our knowledge. Thus, the primary aim of this pilot study was to explore if it is a feasible and tolerable intervention for patients with NSCLC. Secondary aims were to examine efficacy around muscle strength, exercise endurance, physical activity levels and health-related quality of life for the purpose of informing the design of future studies.

7.2 Methods

7.2.1 Subjects

Patients with NSCLC and an ECOG performance status of 0 or 1 were recruited from thoracic oncology clinics. Medication had to have been stable for at least one week and patients were excluded if they had received radio- or chemotherapy within the last four weeks, lost >10% of their pre-morbid body weight, had ischaemic heart disease, a cardiac pacemaker, or any problem that might affect their ability to undertake a walking exercise test. Patients gave written informed consent and the study was approved by Nottingham Research Ethics Committee (ref. 05/Q2402/62) and registered with Current Controlled Trials (ISRCTN 86814835).

7.2.2 Measurements

7.2.2.1 Acceptability

Acceptability of NMES was assessed by patients' adherence to the recommended duration and frequency of NMES, recorded in a self-report daily diary (Appendix 1.7). Patients' experiences of NMES, recorded using a semi-structured evaluation form, were also captured on completion of the programme. The form used an open question to obtain any good or bad comments about NMES, e.g. any difficulties with its use, and specifically asked patients to record if they would be prepared to use it again in the future (Appendix 1.8).

7.2.2.2 Quadriceps muscle strength

Assessed with a Cybex NORM dynamometer (Cybex, division of Lumex Inc, New York, USA; software version 2.06) using a protocol previously used in patients with NSCLC (Wilcock et al, 2008a). Equipment set up and test settings were standardized for each patient during all tests. The dynamometer was set up to only allow isokinetic exercise, i.e. for any force exerted the machine produced an equivalent resistance and thus the lower leg could only move at a prefixed speed. Patients were seated with the padded lever arm of the dynamometer placed just above the ankle of the dominant leg, i.e. the one preferred to kick a ball with, and undertake 30 maximal isokinetic contractions through a fixed range of movement from knee flexion to extension at a fixed speed of 180°sec^{-1}. The speed was pre-determined to replicate joint movements during functional movements, e.g. stair climbing or postural adjustments during gait. The first five repetitions are for familiarisation purposes and maximum strength is indicated by the peak torque (Newton metres, Nm) obtained in the remaining 25 repetitions (Wilcock et al, 2008a; Kannus, 1994). This protocol has been shown to be acceptable to sixteen patients with thoracic cancer, all of whom were prepared to repeat the test, and highly reliable with a between day test-retest ICC [95% CI] of 0.91 [0.82−0.95] (Wilcock et al, 2008a).

7.2.2.3 Exercise endurance

Assessed using the ESWT (Department of Respiratory Medicine, Glenfield Hospital, Leicester, UK) (Revill et al, 1999). Patients walk

around two cones 10m apart at a constant pace dictated by an external audio signal from a tape cassette player. The test kit contains eight cassettes, covering a range of walking speeds from 1.78 to 6km/h. For each patient, the walking speed is selected to be closest to a workload equivalent to 85% of the patient's predicted peak oxygen uptake. This is calculated from the maximum walking speed achieved by the patient in a prior ISWT. This is carried out in an identical manner to the ESWT except that the frequency of the audio signals and walking speed progressively increases (Singh and Morgan, 1992; Singh et al, 1994). The ESWT is continued until the patient is unable to maintain the pace or if the maximum duration of the test is reached (20 minutes) and the distance walked in metres is recorded as the test outcome. Although the ESWT has not yet been used in patients with cancer, it has also been shown to be reliable with a mean [95% CI] difference in distance walked of 15m [1−29] found in patients with COPD completing sequential tests on two separate days (Revill et al, 1999). The ISWT was also shown to be acceptable to 41 patients with advanced disease (Booth and Adams, 2001).

7.2.2.4 Free-living physical activity

Assessed as mean daily step count measured over a period of one week using an ActivPAL™ monitor (PAL technologies Ltd, Glasgow, UK). This small, lightweight (20 x 30 x 5mm, 20g) uni-axial accelerometer is applied to the mid-thigh using adhesive pads and is worn continuously except for when showering / bathing or during

NMES. The ActivPAL™ step count has been shown to be accurate across a range of walking speeds (0.6-2.4m/s) with measurement error of <5% (Grant et al, 2006; Ryan et al, 2006; Maddocks et al, 2008). Unlike other accelerometers, it also does not record erroneous steps during motor vehicle travel (Gotshall et al 2003; Le Masurier & Tudor-Locke, 2003; Maddocks et al, 2008).

7.2.2.5 Spirometric values

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured with participants seated as the best of three recordings using a dry wedge spirometer (Vitalograph Type R Spirometer, Buckingham, UK).

7.2.2.6 Health-related quality of life

Assessed using the EORTC QLQ C-30 core questionnaire and LC-13 lung cancer module (Aaronson et al, 1993; Bergman et al, 1994; Nicklasson and Bergman, 2007). From the core questionnaire, the global quality of life and physical functioning sub-scales were used and the lung cancer module provided an additional scale concerning physical symptoms. The physical functioning and symptom questions use a four-point response scale, the global quality of life question uses a seven-point scale, and all total raw scores are linearly converted to a 0–100 score. For global quality of life and physical functioning, a high score represents a better quality of life or level of function. For the symptom scale, a high score represents a greater level of symptom

distress. Both instruments have been widely used in patients with cancer and have recently been validated in patients with thoracic cancer in a palliative care setting as described previously (chapter 4, Nicklasson and Bergman, 2007).

7.2.3 Neuromuscular electrical stimulation

Delivered by a MicroStim Exercise Stimulator MS2v2 (Odstock Medical Ltd, Wiltshire, UK) using two 7cm round PALS® Platinum self-adhesive electrodes (Axelgaard Manufacturing Co Ltd, Denmark) placed on the anterior thigh over the body of the quadriceps muscle. The programme consisted of daily stimulation to one thigh at a time for 15 minutes, increasing to 30 minutes after one week. One treatment session for both thighs would therefore last 30–60 minutes in total. Pulse waveform (symmetrical biphasic squared), frequency (50Hz) and width (350microseconds) were constant throughout the four week period. The amplitude (device output 0–120mA, tested across 1000Ω) was initially set to elicit a visible and comfortable muscle contraction; patients were encouraged to subsequently increase the amplitude as tolerated. The proportion of the treatment duration which was active stimulation, i.e. the duty cycle, increased on a weekly basis from 11% to 18% to 25%, remaining constant thereafter.

The programme was based those found to be most beneficial in promoting hypertrophy and improvements in strength in other patient groups with deconditioned muscles (Neder et al, 2002; Quittan et al,

2001; Harris et al, 2003; Dobšák et al, 2006a; Roig and Reid, 2009). The stimulation parameters were selected to favour gains in strength over endurance (frequency), minimise skin irritation by instigating contraction at low amplitudes (pulse width) and allow for sufficient recovery of the muscles between contractions to minimise muscular fatigue (duty cycle) (Baker et al, 2000; Vivodtzev et al, 2008; Dehail et al, 2008). Stimulation frequency and pulse width are important in determining the profile of change obtained with a NMES programme. The use of higher frequencies, i.e. ≥40Hz, has been suggested to preferentially target type II muscle fibres and lead to improvements in muscular strength rather than endurance as was the aim with the current programme (Bax et al, 2005; Dal Corso et al, 2007). Wider pulses were selected as these lead to greater force production and are most appropriate when attempting to achieve a visible tetanic contraction (estimated 20−30% maximum voluntary contraction) of larger muscle groups such as the quadriceps (Vivodtzev et al, 2008). The duty cycles were selected as a means to prevent muscular fatigue during and post-stimulation. Skeletal muscle fatigues more rapidly during NMES than during volitional exercise due to differences in motor unit recruitment order and imprecise control of motor unit recruitment and the level of muscular contraction (Delitto et al, 1990; Peckham and Knutson, 2005; Dehail et al, 2008). Therefore, relatively short active periods (11−25%) and long inactive periods were selected to allow sufficient recovery of the muscle following each contraction (Vivodtzev et al, 2008).

7.2.4 Protocol

All assessments, except free-living physical activity, were carried out in a human performance laboratory based in the Clinical Sciences Building (Nottingham University Hospitals NHS Trust, City Hospital Campus) at the same time of day (±1h). Patients were given written instructions to avoid caffeine for one hour, large meals for two hours, excess alcohol the night before the tests and to keep the times of any drug administration constant. Verbal encouragement was minimal and standardised. Patients were randomised 1:1 into NMES or control groups (no intervention) using randomised permuted blocks generated by an independent researcher and concealed using opaque envelopes.

Over a five-week period, all patients attended the hospital three times and received two home visits; those in the NMES group received two additional home visits. The initial home visit was to begin recording free-living physical activity. One week later, at hospital, patients undertook spirometry and two ISWT, 30 minutes apart, the first for familiarisation purposes. The maximal walking speed achieved in the second ISWT was used to determine the ESWT walking speed. The next day, an ESWT was undertaken followed, after 30 minutes rest, by assessment of quadriceps muscle strength. Those receiving NMES were taught how to use the stimulator and received two additional weekly home visits to facilitate optimal usage and adherence. After three weeks, all patients were visited at home to begin recording free-

living physical activity. One week later, at the final hospital visit, the ESWT, quadriceps muscle strength and spirometry were repeated and the evaluation form completed. Patients randomised into the control group were given the opportunity to use NMES for four-weeks following the formal study period as a method to optimise recruitment and retention (Figure 7.1).

Time point	NMES group	Control group
Initially	Home visit to consent and receive ActivPal™	Home visit to consent and receive ActivPal™
Baseline week	Wear ActivPal™ for 1 week Monday to Monday. First evaluation visit: • Questionnaires about health, medication and quality of life • height, weight, spirometry • first ISWT • 30 minutes rest • second ISWT Second evaluation visit: • ESWT • 30 minutes rest • Cybex dynamometry Receive stimulator and training protocol	Wear ActivPal™ for 1 week Monday to Monday First evaluation visit: • Questionnaires about health, medication and quality of life • height, weight, spirometry • first ISWT • 30 minutes rest • second ISWT Second evaluation visit: • ESWT • 30 minutes rest • Cybex dynamometry Control period
End of week 1	Home visit	
End of week 2	Home visit	
End of week 3	Home visit to receive ActivPal™ Wear ActivPal™ for 1 week Monday to Monday.	Home visit to receive ActivPal™ Wear ActivPal™ for 1 week Monday to Monday.
End of week 4	Third evaluation visit: • Questionnaires about health, medication and quality of life • height, weight, spirometry • ESWT • 30 minutes rest • Cybex dynamometry End of study	Third evaluation visit: • Questionnaires about health, medication and quality of life • height, weight, spirometry • ESWT • 30 minutes rest • Cybex dynamometry Receive stimulator and training protocol

Figure 7.1 Study overview

7.2.5 Statistical analysis

Normally distributed data were expressed as mean ± standard deviation. Age, body mass index, spirometric values and baseline values and changes in quadriceps muscle strength, exercise endurance, free-living physical activity and health-related quality of life were compared between the control and NMES groups using Student's t-test. Change between groups was compared by mean differences and their 95% confidence intervals. The use of change rather than absolute values was preferred in light of the exploratory nature of this study, the small sample size, which was only sufficient to detect differences of 2 standard deviations between groups, and the large degree of natural variability in many of the chosen outcomes. Calculations were performed using Statistical Package for the Social Sciences (SPSS) version 15.0. A p value of <0.05 was regarded as statistically significant.

7.3 Results

7.3.1 Participants

Of 53 patients approached over a two-year period commencing in January 2006, 16 completed the study (Figure 7.1; Table 7.1). All patients were able to complete all assessments. In the NMES group, due to equipment failure, quadriceps muscle strength and free-living physical activity data was lost in one patient each. Three patients, (two in the control group), reached the maximum duration (20 minute) of the ESWT at baseline; only one in the control group achieved this subsequently. There were no significant differences in age, body mass index or spirometry, nor baseline values of quadriceps muscle strength, exercise endurance and free-living physical activity between the control and NMES groups (Table 7.1). To date, thirteen patients have died with a median (range) survival of 40 (10–67) weeks.

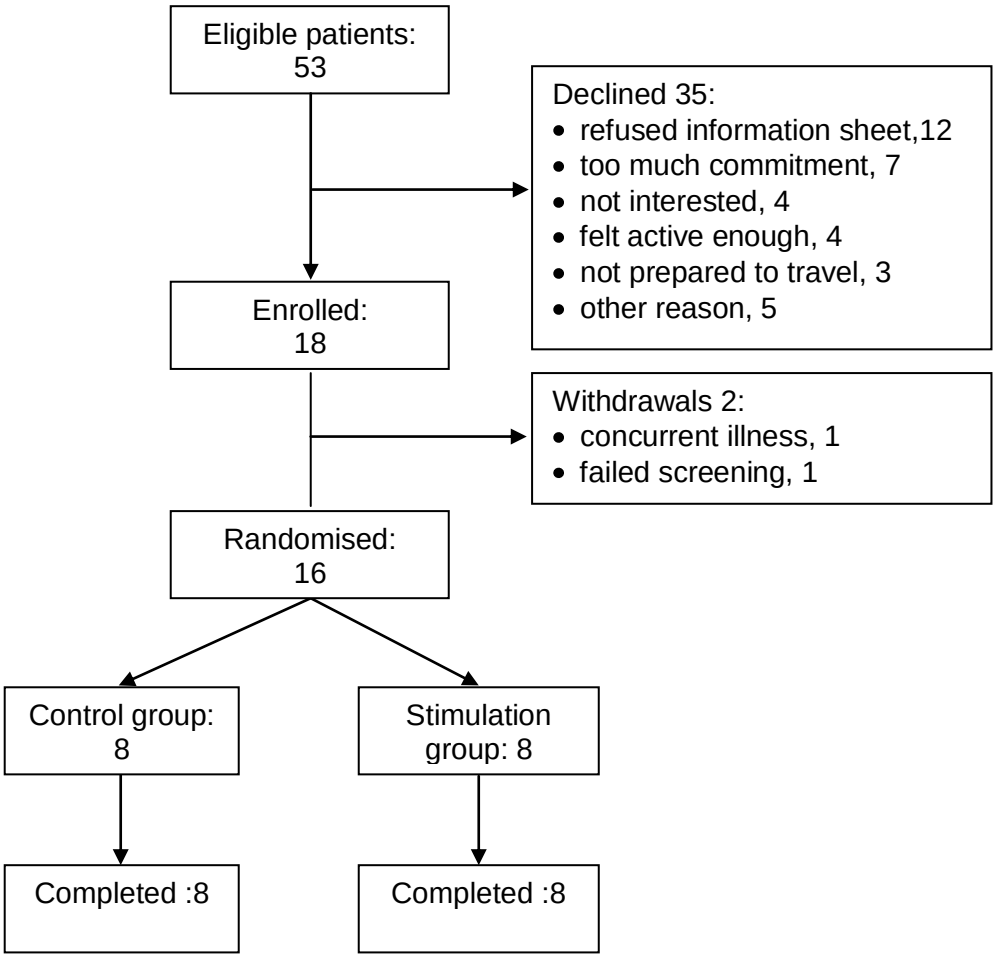


Figure 7.2 Study flow diagram.

Table 7.1 Patient details at baseline. Mean (SD) unless otherwise stated.

	Control (n=8)	*NMES (n=8)*	*p value*
Sex (m / f)	5 / 3	4 / 4	-
Age (years)	64 (5)	56 (9)	0.65
ECOG performance status (0 / 1)	2 / 6	2 / 6	-
Body mass index (kg/m^2)	26.2 (1.2)	27.2 (2.8)	0.39
Diagnosis			
adenocarcinoma	3	5	-
squamous	2	3	
large cell	1	0	
undifferentiated	2	0	
Stage (III / IV)	2 / 6	3 / 5	-
Treatment history			
surgery	1	2	-
chemotherapy	8	8	
radiation therapy	3	3	
Medication			
non-opioid analgesic	4	0	-
weak opioid analgesic	4	1	
inhaled bronchodilator	8	2	
inhaled corticosteroid	1	1	
oral bronchodilator	1	0	
hormone therapy	1	2	
β–blocker	0	1	
other	8	5	
Spirometry			
FEV_1 (L)	1.64 (0.78)	1.71 (0.69)	0.87
FVC (L)	2.56 (0.63)	2.63 (1.01)	0.87
FEV_1/FVC (%)	59 (21)	66 (11)	0.72
Quadriceps muscle strength (Nm)	57 (23)	46 (22)	0.34
Distance walked on ESWT (m)	845 (517)	660 (550)	0.50
Mean daily step count	5554 (4581)	5061 (1516)	0.78

7.3.2 Use of NMES

Patients reported undertaking NMES for a median (range) of 80% (69–100) of the overall recommended treatment time, often whilst carrying out activities such as watching television, or completing a crossword. The main reason for missing a treatment session was another activity taking priority. No serious adverse events were reported. Three patients reported minor muscle discomfort following the first day of use, lasting about one hour. One patient each commented that the treatment sessions sometimes felt long or restricted other activities. At the end of the study, all patients provided positive comments about the ease of use of the device, and three about its impact; "The stairs are easier now", "I am better at standing up after sitting around" and "My legs feel more solid when I am walking". All were prepared to use NMES again.

7.3.3 Physical performance

Quadriceps muscle strength and free-living physical activity levels improved by a mean of 7.4 Nm (22%) and 136 steps (11%) respectively in the NMES group whilst exercise endurance deteriorated by a mean of 20m (4%). This compared to essentially no change -2.0 Nm (0%), or a mean deterioration of 633 steps (3%) or 159m (12%) in quadriceps muscle strength, free-living physical activity levels and exercise endurance respectively in the control group (Table 7.2). The mean difference in outcomes between the two groups varied from 8 to 21% in favour of the NMES group; however the degree of difference was not statistically significant (Table 7.2). On an individual patient basis, for each of the outcome measures, consistently more patients improved in the NMES group than the control group (Figure 7.2).

Table 7.2. Mean (SD) absolute and percentage change in outcome measures.

	Baseline	*Post-intervention*	*Change*	*Difference in change [95% CI]*	*p value*
Quadriceps muscle strength					
absolute (Nm)					
control group	56.9 (22.9)	54.9 (18.9)	-2.0 (9.0)		
NMES group	45.8 (22.2)	55.1 (24.9)	7.4 (10.3)	9.4 [-1.3, 20.7]	0.08
percentage (%)					
control group	100	101 (26)	0 (26)		
NMES group	100	122 (31)	22 (31	21 [-10, 53]	0.17
Distance walked on ESWT					
absolute (m)					
control group	845 (517)	687 (499)	-159 (222)		
NMES group	660 (550)	640 (569)	-20 (254)	138 [-118, 394]	0.27
percentage (%)					
control group	100	88 (31)	-12 (31)		
NMES group	100	96 (51)	-4 (51)	8 [-37, 54]	0.70
Mean step count per day					
absolute (steps)					
control group	5554 (4581)	4922 (3512)	-633 (1335)		
NMES group	5016 (1515)	5301 (2077)	136 (2660)	768 [-1530, 3066]	0.48
percentage (%)					
control group	100	97 (26)	-3 (26)		
NMES group	100	111 (52)	11 (52)	15 [-35, 65]	0.49

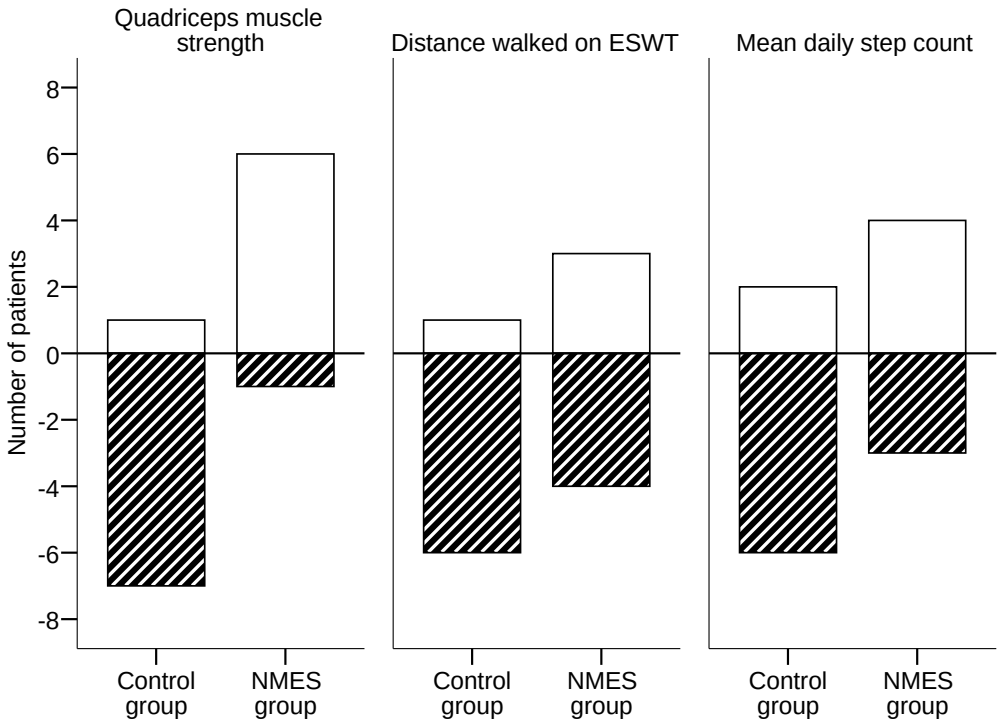


Figure 7.3 Number of patients improving or deteriorating in outcome.

7.3.4 Health-related quality of life

Health-related quality of life deteriorated by a small and similar degree in both groups. Scores for global quality of life, physical functioning and lung cancer symptoms changed by 1, 4 and 3 points respectively in the NMES group compared to 0, 3 and 4 points in the control group. The mean difference between the two groups did not exceed one point and was not statistically significant for any of the outcomes (Table 7.3)

Table 7.3 Mean (SD) change in health-related quality of life scores.

	Baseline	*Post-intervention*	*Change*	*Difference between groups [95% CI]*	*p value*
Symptoms sub-scale					
control group	15 (8)	18 (8)	3 (4)		
NMES group	16 (5)	19 (7)	4 (9)	0 [-8,3]	0.94
Physical functioning subscale					
control group	77 (13)	72 (22)	-4 (12)		
NMES group	82 (9)	79 (14)	-3 (12)	-1 [-14,11]	0.85
Global Quality of Life					
control group	56 (13)	55 (17)	-1 (12)		
NMES group	59 (24)	59 (17)	0 (13)	0 [-13,6]	0.95

7.4 Discussion

The findings from this pilot study suggest that NMES is acceptable and tolerable to patients with NSCLC. Adherence over a longer period will need to be formally evaluated, and it may help to halve the overall treatment duration by stimulating both thighs simultaneously but on average patients reported undertaking NMES on five days of each week. Patients receiving NMES fared better than the control group with improvements in quadriceps muscle strength and free-living physical activity and less of a decline in exercise endurance. However, there were no significant differences between the NMES and control groups, health–related quality of life appeared relatively unchanged, and efficacy requires further exploration in adequately powered studies.

The use of therapeutic exercise to improve physical function and quality of life in patients with cancer has mostly involved those receiving curative treatment with limited experience in patients with incurable cancer (Conn et al, 2006; Maddocks et al, 2009). Nonetheless, programmes based on traditional types of exercise often experience difficulties with recruitment and retention due, in part, to their impractical nature (Maddocks et al, 2009). This was particularly apparent in a recent study by Temel et al (2009), in which patients with non-small cell lung cancer were offered an eight week mixed aerobic and resistance training programme based in a hospital setting. Of 25 patients who consented to the study and started the programme, only eleven completed it and achieved only a low level of attendance (Temel et al,

2009). The authors suggested that programmes should be offered in the home as a means to improve practicality providing rationale to explore more novel therapies. We first explored NMES by including it as one of six different types of exercise when determining the preferences of two-hundred patients with incurable cancer, mostly receiving chemotherapy (chapter 7; Maddocks et al, in press). When provided with videos of each type of exercise and full details of a programme likely to provide benefit, NMES was the most preferred type of exercise, mainly because of its perceived practicality and convenience (chapter 7; Maddocks et al, in press). Our completion and adherence rates (100% and 80% respectively) support this notion.

NMES has been used therapeutically for at least 20 years, mainly as an adjunct in the rehabilitation of patients with neurological conditions involving upper-motor neurone lesions, e.g. post-stroke, spinal cord injury (Sheffler and Chae, 2007). More recently, the use of NMES has been examined in patients with COPD (e.g. Bourjelly-Habr et al, 2002; Neder et al, 2002; Dal Corso et al, 2007) or chronic heart failure (e.g. Quittan et al, 2001; Nuhr et al, 2004; Dobšák et al, 2006a). Details on these studies have been described previously in chapter three. After several weeks of use, evidence suggests that NMES results in similar beneficial changes in muscle as with other types of exercise, such as improved oxidative capacity resulting from changes in fibre type and levels of oxidative enzymes (Nuhr et al, 2004; Dal Corso et al, 2007; Sillen et al, 2008). Improvements in muscle function and ability to

exercise are also comparable to those found from other types of exercise. A recent meta-analysis of data in patients with COPD demonstrated moderate improvements in muscle function and exercise performance from NMES programmes with mean [95%CI] improvements in peak torque and 6MWT distance of 9.7 [1.2−18.1]Nm and 48 [9−86]m respectively (Roig and Reid, 2009). Similarly, in patients with chronic heart failure, a median [IQR] improvement in muscle function following NMES programmes of 23 [17−43]% has been found and, where measured, maximal and sub-maximal exercise capacity has improved by 9 [5−32]%. In patients with cancer, the literature appears limited to a single case report of the beneficial effect of NMES in a patient with lung cancer and brain metastases (Crevanna et al, 2006).

The mean improvement in quadriceps muscle strength in the NMES group was 22%, in-keeping with the 10−40% gains reported by others (chapter 3). This is likely to be within the limits of measurement accuracy of the assessment protocol (Wilcock et al, 2008a) and is suggestive of a clinically meaningful change, although this would need to be validated against external criteria and by patient report. With similar magnitudes of change in quadriceps muscle strength, others have also reported improvements in exercise capacity/endurance assessed by various means, e.g. 6-minute walk test (Dal Corso et al, 2007; Neder et al, 2002; Bourjelly-Habr et al, 2002). By comparison, exercise endurance assessed by the ESWT deteriorated in the NMES

group. There are several possible explanations for this discrepancy, including differences in the patient groups and stimulation programme. All of our patients had advanced incurable disease and some were rapidly progressing whilst other studies were in patients with chronic disease which was more stable in nature. Outcomes were evaluated after 4 weeks of NMES compared to 6–10 weeks in other studies and perhaps this was too short for changes in exercise endurance to appear. Furthermore, we only stimulated the quadriceps whilst others have concurrently stimulated additional muscle groups such as the glutei (Zanotti et al, 2003), hamstrings (Quittan et al, 2001; Bourjelly-Habr et al, 2002) and calves (Harris et al, 2003; Nuhr et al, 2003). The quadriceps are usually targeted as they represent a large proportion of lower limb muscle mass and are important in many activities of daily living, e.g. sit-to-stand, ambulation. Targeting additional muscle groups may provide further benefit. However, this needs to be balanced against the increased demand on the patient with added stimulator channels and more electrodes to position, some of which may require external assistance and compromise the overall experience. Finally, we used the ESWT which may have created a potential mis-match between two of the outcome measures used. The high frequency (50Hz) of stimulation we used may favour improvements in muscle strength by producing a training effect biased towards type II muscle fibres (Baker et al, 2000; Vivodtzev et al, 2008). Although this will improve the contractile property of the muscle, as measured with the maximal strength test, it will only marginally increase the oxidative

capacity of the muscle as these fibre types are low in mitochondrial density and easily fatigued (Dal Corso et al, 2007).

Three of the 16 patients reached the maximum duration of the ESWT (20min) at baseline, suggesting that it is not an ideal assessment for the range of abilities found in this patient group due to a ceiling effect. Further, its inclusion limited the rate of recruitment, as many potential participants were excluded and not approached because of contra-indications to undertaking a maximal exercise test. Moreover, formal exercise tests are artificial and an assessment of a patient's capacity as opposed to what they actually do from day to day. For this reason, physical activity level was included as a potentially more meaningful outcome (Dahele et al, 2007). The mean daily step count, as measured by the ActivPAL™ monitor, improved in the NMES group and decreased in the control group. The experience of assessing physical activity level was promising. Unlike the walking tests, the use of physical activity monitors did not exclude any patients from entering. Those with significant comorbidities, including ischeamic heart disease, could be included the free-living assessment of this aspect of physical function does not place any additional stress on the patient. Anecdotally, all patients recognised the value of measuring and quantifying their physical activity and feedback around their use of chosen monitors was generally positive. Few patients experienced difficulties using them for one week and data were only lost on one occasion. Of the outcome measures used in the study, it is suggested

that this is one worth developing further. In the first instance, research questions should be based around formally assessing acceptability in a larger group of patients and deterring the optimal methodology, e.g. duration of monitoring and treatment of missing data.

In this study, NMES has been portrayed as a convenient and practical approach to exercise well-suited to those patients who are unable or unwilling to undertake more traditional types of exercise. However, some differences between NMES and other exercise, e.g. walking and stationary cycling, need to be noted. Programmes of NMES target a limited number of muscles whilst more traditional types of exercise can be used to train numerous muscle groups concurrently. NMES is undertaken whilst seated and has no direct training effect on the cardiorespiratory system whilst traditional exercises can incorporate aerobic and muscular training to provide added benefit. In addition, the use of a stimulator means the exercise being undertaken independently and family and friends are unable to join in and provide peer support. Therefore, whilst NMES may prove to be a useful clinical tool, it may best be offered in combination with other types of exercise or as a means to improve strength specifically so patients become capable of undertaking more active types of exercise. A better understand of how NMES compares to or compliments other types of exercise is required.

The data from this pilot study can be used to inform sample size calculations in the future, for example, a controlled study would require

25 patients per group to reliably detect the observed difference in peak torque of 9.4 Nm (α=0.80, β=0.05). Undertaking controlled studies of NMES is challenging because of the difficulties of blinding a treatment which produces a visible contraction of the muscle. We considered a no treatment control group sufficient for this pilot study, however, it is possible that our findings reflect that those in the NMES group derived greater psychological benefit from undertaking the intervention and/or the two additional visits from the physiotherapist. This could have enhanced their motivation to be more active and to perform better in the assessments. Future studies could include the use of a placebo or dummy stimulator, with no or minimal output, or an active control group offered a stimulation programme unlikely to be of physiological benefit, e.g. once weekly, but having similar contact time with professionals.

In conclusion, NMES appears an acceptable and tolerable exercise intervention and one worth pursuing in patients with lung cancer. If successful, it may be best offered as a proactive supportive care intervention soon after diagnosis, in order to preserve muscle mass and physical function as best as possible, rather than wait until the cachectic process is advanced.

CHAPTER 8:

PHYSICAL ACTIVITY LEVEL AS AN OUTCOME MEASURE FOR USE IN CANCER CACHEXIA TRIALS: A FEASIBILITY STUDY

8.1 Introduction

Cachexia is common in patients with cancer of the lung and upper gastro-intestinal tract causing weight loss, muscle wasting, fatigue and mood disturbance (Gordon et al, 2005). These consequences can limit treatment options, quality of life and survival. There are no satisfactory treatments and cachexia is a major unmet need in supportive and palliative care (Muscaritoli et al, 2006; Steer, 2003). Increasing understanding of the pathophysiology of cancer cachexia is allowing new treatments to emerge and the previous three chapters have been concerned with the use of therapeutic exercise in this group. However, these interventions need to be assessed using outcome measures which are meaningful to patients.

The assessment of physical activity may be one such measure; levels of physical activity relate to psychological well-being and quality of life (Rejeski and Mihalko, 2001; Netz and Wu, 2005) and patients with incurable cancer generally want to maintain their independence for as long as is possible. Subjective assessments of physical activity, e.g. by questionnaire or activity diary, can be inaccurate and unreliable (Dahele and Fearon, 2004; Prince et al, 2008). An objective assessment is possible from the use of activity monitors such as pedometers and accelerometers. Pedometers use spring-lever technology and are not sufficiently sensitive to detect stepping at walking speeds typical of older

people (~1.0m/s). More sensitive accelerometers such as the ActivPAL™ are therefore preferred in these groups (Mathie et al, 2004; Valanou et al, 2006). This small lightweight monitor is easily sited on the anterior thigh and can record several parameters of physical activity, e.g. sit to stand transitions, time spent upright, step count, over a one week period. The ActivPAL™ monitor has been used in small pilot studies and appears to be acceptable, but this has not been formally tested and the optimal duration of monitoring is unknown. Further, it is unclear if the more detailed information it provides has advantages over a simple step count, which can be measured more cheaply, and how the outcomes it produces compare to commonly-used functional assessment tools.

The primary aim of this study was to formally assess if the use of the ActivPAL™ monitor was acceptable to patients with lung or upper-gastrointestinal cancer, who are most likely to be offered interventions aimed at preventing or managing cancer cachexia. Secondary aims were to explore the optimal period of monitoring, the added value of the monitor's estimate of energy expenditure over a step count, and the extent to which physical activity reflects physician-rated performance status.

8.2 Methods

8.2.1 Subjects

Patients with lung or upper-gastrointestinal cancer and an ECOG performance status of 0–2 as judged by the treating physician were recruited from oncology clinics (Oken et al, 1982). Patients were excluded if they were receiving radio- or chemotherapy, had undergone surgery within the last four weeks or had severely restricted mobility, e.g. due to uncontrolled pain on movement. Patients gave written informed consent and the study was approved by Oxfordshire A Research Ethics Committee (ref. 07/Q1604/16) and registered with Current Controlled Trials (ISRCTN 32511542).

8.2.2 Instruments

8.2.2.1 Activity monitor

The ActivPAL™ monitor (PAL technologies Ltd, Glasgow, UK) was selected because its accuracy is well documented, it provides more detailed information than some other monitors, is easy to apply and our research group had prior experience of its use in people with cancer. It is a small, lightweight (20 x 30 x 5mm, 20g) uni-axial accelerometer that is applied to the anterior thigh using adhesive PALStickies™ and a layer of Tegaderm™ dressing. The ActivPAL™ records time spent sitting, standing and walking, sit-to-stand transitions, step count and rate of stepping (cadence) over a one week period. Accompanying software allows each of these outcomes to be displayed by hour, day or week (Figure 8.1).

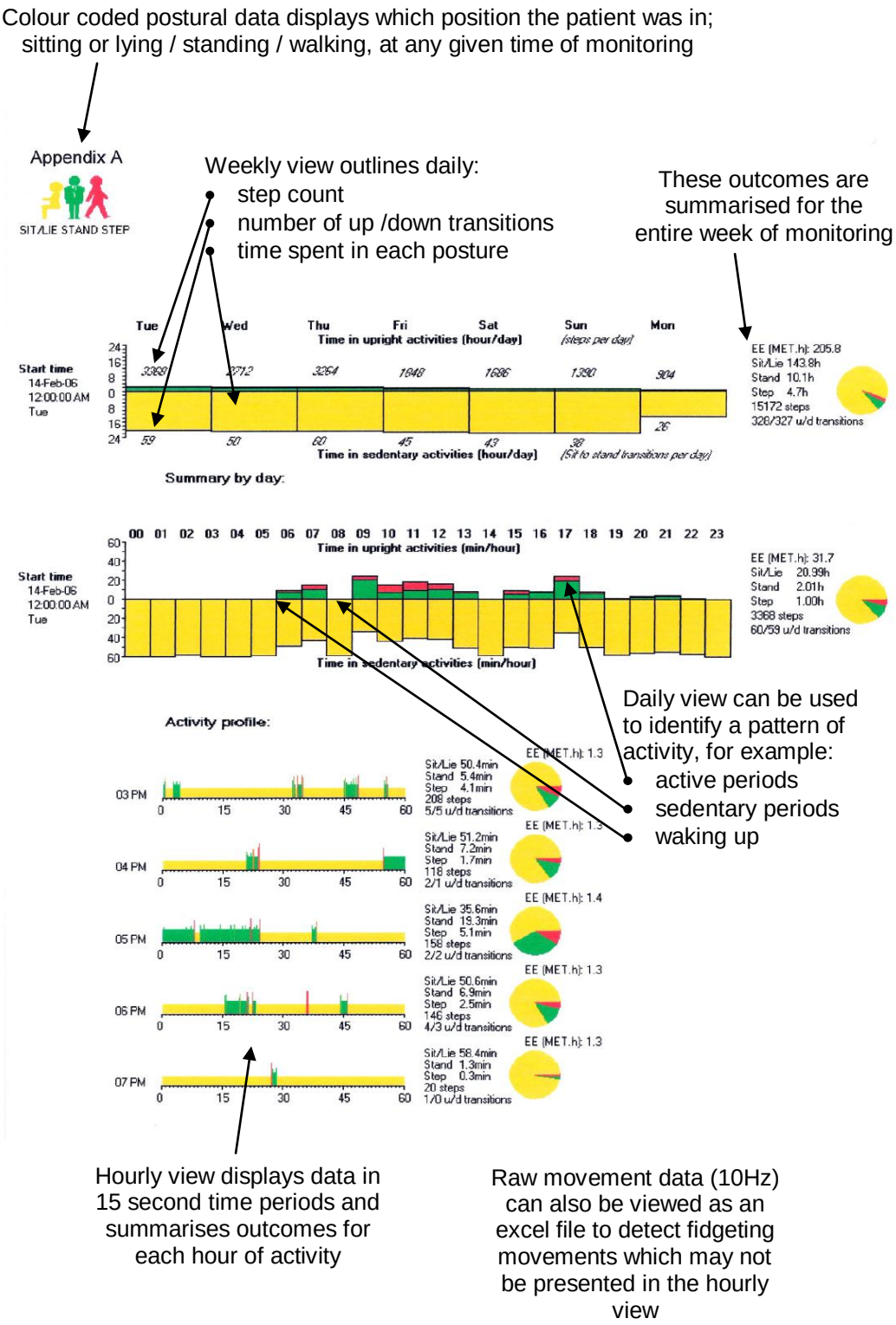


Figure 8.1 Display from the ActivPAL™ monitor software.

Measurement of time spent in a given posture has been validated using video analysis (Grant et al, 2006) and the step count has been shown to be accurate across a range of walking speeds (0.6-2.4m/s) with measurement error of <5% (Grant et al, 2006; Ryan et al, 2006; Maddocks et al, 2008). Despite its sensitivity during slow walking, the ActivPAL™ does not record erroneous steps during motor vehicle travel as can be a problem with other accelerometers (Gotshall et al 2003; Le Masurier & Tudor-Locke, 2003; Maddocks et al, 2008). The monitor also provides an estimate of energy expenditure in metabolic equivalent hours (METh), based on the time spent sitting, standing, walking and cadence, however, this outcome has not been validated.

8.2.2.2 Patient activity diary

Patients were asked to complete a paper diary daily for one week recording the time they got up, went to bed, slept during daytime hours and any period when they did not wear the activity monitor, providing a reason where possible. They were asked to note any problems experienced with the monitor, e.g. skin irritation, discomfort, and, at the end of the week, to indicate if they found wearing the monitor acceptable and if they would be prepared to repeat the experience (Appendix 1.9).

8.2.3 Protocol

Patients were provided with an ActivPAL™ monitor during a hospital or home visit on a Monday and taught how to apply, remove and reapply it. The monitor was positioned on the mid-third of the anterior thigh of their dominant leg. A helpline number was provided in case of a technical problem, e.g. low battery warning. Patients were instructed to wear the monitor at all times, except when submersed in water, e.g. bathing, showering, and swimming, and to complete the activity diary as above. The monitor and diary were retrieved at a second visit one week later. Data were uploaded to a computer using ActivPAL™ Professional software (version 5.8.2.2) and data from each Monday were omitted, leaving six full days of data, Tuesday (day 1) to Sunday (day 6), to be analysed. To assess compliance, each hour of data was visually inspected (up to10Hz) for signs of movement. If no movement was found, the hour was registered as non-compliant unless it corresponded to a period of sleep in the diary.

Acceptability, the primary endpoint, was defined as ≥80% of patients wearing the monitor for ≥80% of the time based on a consensus view of the Cachexia subgroup of the National Cancer Research Institute Palliative Care Clinical Studies Group. No specific sample size is necessary for the proposed method of analysis, but the intention was to recruit 60 patients based on the likely accrual given the duration of the study.

8.2.4 Statistical analysis

Normally distributed continuous data and other forms of data were expressed as mean (SD) or median [IQR] respectively.

Acceptability: The total period of non-compliance in hours was expressed as a percentage of the 6 day period of monitoring. The proportion of patients wearing the device ≥80% of the time was calculated with 95% confidence intervals using Wilson's method (Wilson, 1927). Content analysis of the diary determined factors contributing to non-compliance.

Optimal duration of monitoring: To examine for the effect of duration of measurement, the changes in step count and estimated energy expenditure between each two consecutive days, e.g. day 1–2, 2–3, were calculated. Difference in daily step count and daily estimated energy expenditure obtained over 2 or 4 and 6 days of monitoring were compared using a Wilcoxon signed rank test and Students t-test respectively.

Relationship between overall energy expenditure and step count: The monitor provides an estimate of energy expenditure (METh) based on the time spent sitting, standing, walking and cadence. If a close relationship exists between the estimated energy expenditure and the step count, i.e. step count is the primary determinant of the estimate, the energy expenditure may add little additional information over this outcome. Because step

count is a component of the estimated energy expenditure, a direct comparison was not possible. Thus, daily overall energy expenditure was separated into expenditure due to stepping and non-stepping activity, i.e. sitting and standing. Non-stepping energy expenditure was correlated with daily step count using a Pearson's correlation coefficient and the square of the correlation was used to estimate the proportion of the variance in the non-stepping energy expenditure which could be explained by stepping energy expenditure. To allow comparison with stepping energy expenditure, daily step count was multiplied by the mean energy per step for the entire sample to provide an arbitrary but comparable value, and agreement was examined using Bland and Altman's approach (Bland and Altman, 1999).

Physical activity according to performance status: Mean daily number of sit-to-stand transitions, time spent upright (standing or stepping), step count and estimated energy expenditure across the 6 days of monitoring were compared between groups according to ECOG performance status using a one-way ANOVA and post-hoc comparisons with a Bonferroni correction.

All calculations were performed using Statistical Package for the Social Sciences (SPSS) version 14.0 and a p value of <0.05 was regarded as statistically significant.

8.3 Results

8.3.1 Participants

Of 78 patients approached over a one-year period commencing in July 2007, 62 were enrolled into the study. Two patients withdrew, one as a result of a fractured femur following a fall and another due to monitor failure leading to loss of data (Figure 8.2). Of the 60 participants, most had lung cancer, around a third had concurrent co-morbidities and a wide range of physical activity levels were represented within the group (Table 8.1).

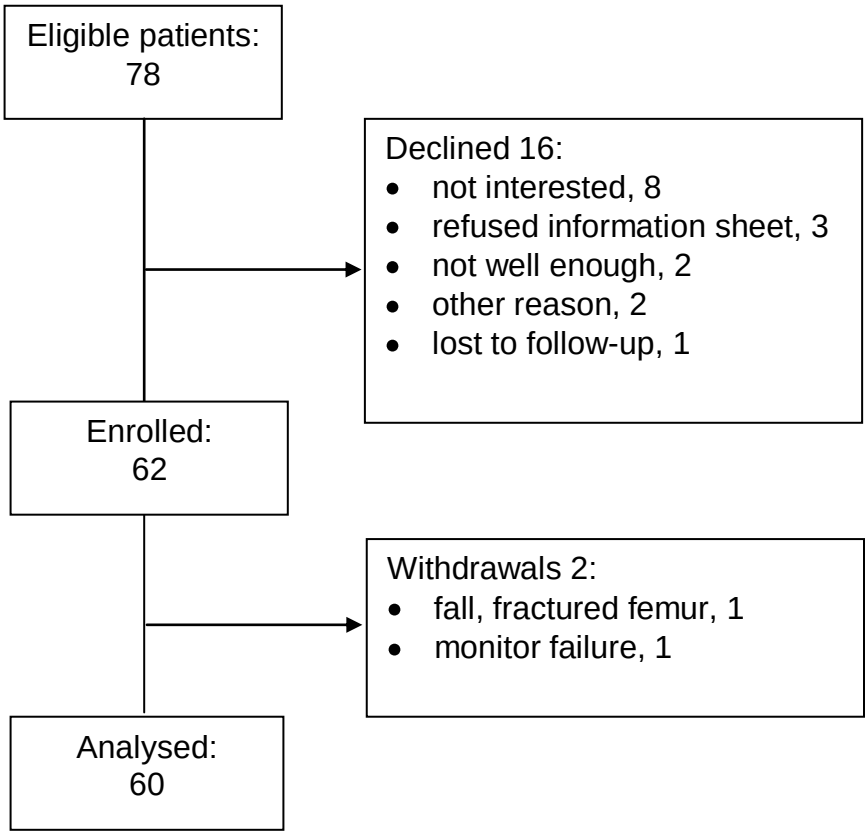


Figure 8.2 Study flow diagram.

Table 8.1 Patient details. Mean (SD) unless otherwise stated.

Sex (m / f)	40 / 20
Age (years)	68 (9)
Diagnosis and histology	
lung / upper-gastrointestinal cancer	58 / 2
squamous	25
adenocarcinoma	16
small cell	9
undifferentiated	5
mesothelioma	5
Disease extent	
local / advanced	35 / 25
Metastases	
bone	11
lung	10
liver	4
pancreas	2
adrenal	2
brain	2
breast	1
Co-morbidities	
Ischemic heart disease	15
COPD	9
Arthritis	7
Diabetes	4
Other	3
Medications	
β-blockers	13
ACE inhibitors	11
strong opiods	9
NSAIDS	9
weak opiods	6
corticosteroids	3
ECOG Performance status	
0	8
1	34
2	18
Daily physical activity	
up/down transitions	45 (16)
time spent upright (h.min)	4.20 (2.10)
step count	4244 (2939)
estimated energy expenditure (METh)	32.1 (1.3)
stepping activity	29.2 (0.7)
non-stepping activity	2.9 (1.9)

8.3.2 Acceptability

Fifty-nine of the 60 patients (98%) wore the monitor ≥80% of the time, giving a 95% confidence interval for the proportion of patients wearing the device the minimum required time in a large population of 91–100%. Thus, the ActivPAL™ monitor fulfilled the definition of acceptability. The mean level of non-compliance was 2% of the total duration of monitoring, equating to 55 minutes per day.

All patients indicated that they found the device acceptable, with 55 (92%) prepared to repeat the experience. Nine patients reported minor skin irritation which settled on removal of the self-adhesive dressing. Other problems, reported by one patient each, were the monitor being an annoyance in bed, or when leaning on their thigh to stand from sitting, and the monitor falling off and having to be re-applied.

8.3.3 Optimal duration of monitoring

Between-day variation in median [IQR] step count was high throughout the six days of monitoring ranging from 24% [15–45] to 35% [15–63]. Change in mean (SD) estimated energy expenditure was proportionally less and more consistent at 2 (2)% (Table 8.2).

Table 8.2. Percentage change in daily step count and energy expenditure.

Day	*Step count*		*Energy expenditure (METh)*	
	median	*IQR.*	*mean*	*SD*
1 to 2	24.2	14.7 – 45.3	*1.8*	*1.5*
2 to 3	35.2	14.5 – 63.3	*2.2*	*2.1*
3 to 4	29.5	15.7 – 47.4	*2.0*	*2.1*
4 to 5	31.5	16.2 – 48.0	*1.8*	*1.5*
5 to 6	34.2	17.0 – 63.0	*2.0*	*1.8*

Median [IQR] daily step counts obtained over 2 (3669 [2226–6131]) and 4 (3563 [2216–6165]) days of monitoring were significantly different to that obtained over 6 days (3317 [2164–5676]), p=0.01 and <0.01 respectively (Table 7.3). Mean (SD) daily energy expenditure measured over 2 days (32.3 (1.6) METh) and 4 (32.2 (1.3) days were significantly different to that obtained over 6 days (32.1 (1.3) METh), p<0.01 and *p*=0.01 respectively (Table 8.3).

Table 8.3. Change in average daily values according to duration of monitoring.

Day	*Median [IQR] step count*		*Mean (SD) energy expenditure (METh)*	
	Daily	*Over 2,4 and 6 days*	*Daily*	*Over 2,4 and 6 days*
1 / Tue	3536 [2314–6130]		32.3 (1.7)	
2 / Wed	3702 [2062–6336]	3669 [2226–6131]	32.3 (1.5)	32.3 (1.6)
3 / Thu	3490 [1934–6762]		32.4 (1.6)	
4 / Fri	3252 [1826–6236]	3563 [2216–6165]	32.1 (1.4)	32.2 (1.3)
5 / Sat	3334 [1630–5594]		32.1 (1.5)	
6 / Sun	2770 [1652–4402]	3317 [2164–5676]	31.8 (1.2)	32.1 (1.3)

8.3.4 Relationship between energy expenditure and step count

The mean (SD) overall daily energy expenditure was 32.1 (1.3) METh, with non-stepping activity (29.2 (0.7) METh) and stepping activity (2.9 (1.9) METh) accounting for 91 (5) and 9 (5)% of overall energy expenditure respectively. The correlation between non-stepping energy expenditure and daily step count was negative and strong ($r=-0.91$, $p<0.01$), thus 85% of the variance in the non-stepping energy expenditure could be explained by the stepping component. The Bland and Altman plot revealed a mean (2SD) difference of 0.02 (0.42) METh between the step count (expressed in METh units) and stepping energy expenditure (Figure 8.3).

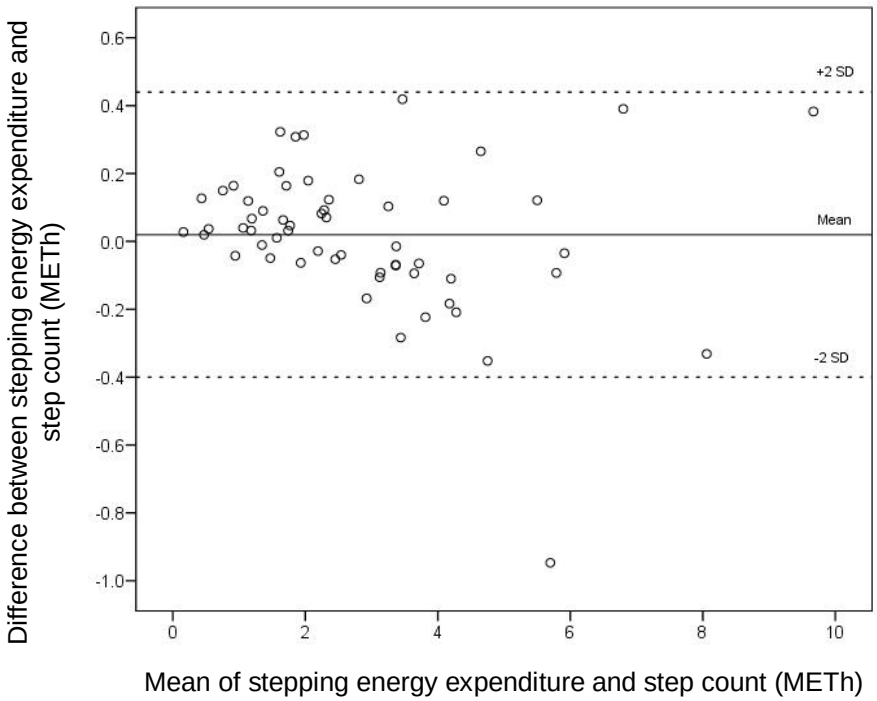


Figure 8.3. Bland and Altman plot of the mean and difference between daily stepping energy expenditure and step count expressed in METh.

8.3.5 Physical activity according to performance status

With the exception of up-down transitions, each component of mean daily physical activity measured by the monitor declined as performance status worsened (Table 8.4). The differences for time spent upright, step count and estimated energy expenditure were statistically significant ($p<0.01$ to 0.03) and the decline in mean daily step count was particularly apparent (Figure 8.4).

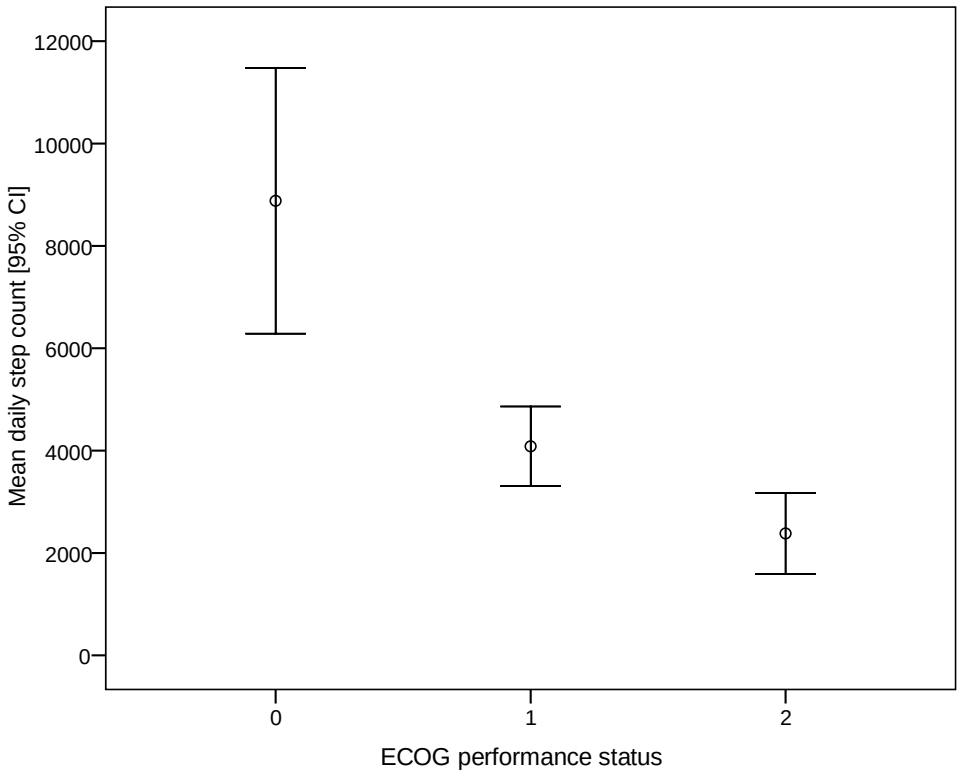


Figure 8.4 Mean daily step count according to ECOG performance status.

Table 8.4 Mean (SD) daily physical activity according to ECOG performance status.

	Performance status 0	*Mean difference [95% CI]*	*Performance status 1*	*Mean difference [95% CI]*	*Performance status 2*
Up-down transitions	46 (7)	1 [11, -13]	47 (16)	-7 [-17, 2]	40 (19)
Time spent upright (h)	7.5 (1.8)*	-3.2 [-4.6, 1.8]	4.3 (1.7)*	-1.3 [-2.3, 0.3]	3.0 (1.5)*
Step count	8880 (3104)*	-4796 [-6705, 2886]	4084 (2228)*	-1703 [-2914, 492]	2382 (1540)*
Energy expenditure (METh)	34.2 (1.4)*	-2.1 [-3.0, 1.2]	32.1 (1.0)*	-0.8 [-1.4, 0.3]	31.3 (0.8)*

* significantly different to others ($p<0.05$)

8.4 Discussion

This is the first study to formally assess the acceptability of the use of the ActivPAL™ physical activity monitor over a one week period in patients with cancer. Compliance in the group was high, exceeding the set standard, and the majority of patients were prepared to repeat the experience suggesting it is feasible to use the monitors in future studies. There is no gold standard for assessing compliance, and it is generally based on patient self-report of achieving an arbitrarily set standard (Ward et al, 2005; Paul et al, 2008). The inclusion of analysis of movement data will have increased the accuracy of the assessment and the standard we for a minimum level of compliance was relatively high, with others suggesting minimum compliance of 60% (Ward et al, 2005).

Patients' physical activity levels were lower than those reported in healthy volunteers and other patient groups (Tudor-Locke et al, 2009). Most took <5000 steps a day and spent two-thirds or more of their waking time either sitting or lying underscoring physical activity as a key therapeutic target for this patient group. There is a lack of directly comparable data but this level of activity is similar to that seen in patients with upper-gastrointestinal cancer receiving palliative chemotherapy (Dahele et al, 2007). Levels of physical activity will naturally vary from day to day, and can be influenced by factors such as the day (weekends generally lower) and in response to being monitored (generally an initial increase). They will also be affected by fluctuations

in external factors, such as the weather or social events, and the patient's mood. Therefore, the longer the period of monitoring, the more accurate an assessment is likely to be, but this has to be balanced against the practicality of wearing a monitor for an extended period of time. We considered one week a pragmatic period to examine and standardised the start day so that the six complete days of monitoring consisted of four weekdays followed by two weekend days. Both daily step count and estimated energy expenditure reduced over the period of monitoring, which could relate to a monitoring effect or a habitual reduction in activity on a weekend. Based on the variability seen in step count, we do not recommend less than six full days of monitoring, which is in general agreement with the recommendations for monitoring activity in other patient groups (Ward et al, 2005; Paul et al, 2008). This limits the strength of findings from previous cancer cachexia studies, which have only monitored physical activity for a few days or less (Fouladiun et al, 2007).

Components of physical activity measured by the ActivPAL™ were compared across patients according to their performance status as determined by their oncologist. Although the inter-rater reliability of the ECOG performance scale is only modest (Sorensen et al, 1993), it is a widely used in clinical tool and this comparison allowed insight into how physical activity patterns may change as global physical function deteriorates. In our participants as performance status worsened, the number of up-down transitions, time spent upright and amount of

energy expended declined. Conversely, the number or bouts of physical activity, indicated by up-down transitions, remained relatively unchanged suggesting that function becomes limited by the capacity to work for prolonged periods of time rather than the ability to stand. This is in agreement with Dahele et al (2007), who observed a tendency for patients with upper-gastrointestinal cancer and a poor performance status to spend less time upright as more active patients despite standing a similar number of times. There was wide variation in physical activity within each performance score and overlap between adjacent scores. Therefore, although the discriminate ability of the ECOG performance scale is supported, physical activity level measured with the ActivPAL™ should be more sensitive to change. Thus, this may be a useful method to help detect small but important effects of interventions that may not amount to a change in performance score.

The assessment of physical activity levels as an outcome measure for cachexia studies is attractive, offering a patient-centred outcome concerned with functional status and independence. The responsiveness of this outcome requires further exploration, but physical activity declines as cachexia progresses (Fouladiun et al, 2007) and improvements have been seen following a pilot intervention study of neuromuscular electrical stimulation of proximal leg muscles in patients with lung cancer (Chapter 7; Maddocks et al, 2009). On the other hand, the not insignificant cost of monitors, time to process physical activity data and potential for missing data all need to be borne

in mind. In this study patients with a reasonable performance status were selected as this reflects the population we aim to target with proactive supportive therapies designed to maintain function. Future studies may examine the relationship between physical activity and quality of life in patients with a wider range of performance status and to determine what level of physical activity is generally required to allow patients to remain independent at home in different social circumstances, e.g. living alone or with a carer, in a house or a flat, etc. The relationship between physical activity levels and commonly used performance scales, e.g. ECOG, Karnofsky, could also be explored.

The estimate of energy expenditure provided by the monitor has not been validated and should be treated with appropriate caution. Comparison with the current gold standard measure of energy expenditure, i.e. doubly labelled water, is required. We found that step count was strongly related to both stepping and non-stepping energy expenditure suggesting that these estimates added little additional information about a patient's physical activity level. This raises the possibility that a step count could be a reasonable proxy for energy expenditure, and as such, could be obtained using a cheaper accelerometer or pedometer. Nonetheless, this would have to be balanced against the loss of the other supplementary information the ActivPAL™ monitor provides, e.g. up/down transitions, time spent upright. Further, in a recent comparison of the ActivPAL™ monitor (PAL Technologies, UK, £600), a cheaper PALlite™ accelerometer (PAL

Technologies, UK, £200) and a high-end SW−401 Yamax Digi-Walker™ pedometer (New lifestyles Inc, Missouri, USA, £30), we found the pedometer to become progressively less accurate as walking speeds slowed to those typical of older patients, and all but the ActivPAL™ recorded erroneous steps during motor vehicle travel (Maddocks et al, 2008).

In conclusion, the ActivPAL™ monitor worn for one week is an acceptable method of providing an assessment of free-living physical activity in patients with cancer. A mean daily step count obtained over 6 days appears to be an appropriate outcome to use in future studies. Although it is of particular relevance to assessing the impact of a cachexia intervention, this outcome has the potential to be a useful outcome across the whole spectrum of health research.

CHAPTER 9.

GENERAL CONCLUSIONS AND SUGGESTIONS FOR FUTURE WORK

9.1 Introduction

This chapter revisits the original aims and objectives and reflects on the work in this thesis. The background chapters and four original studies are retraced and the main strengths and limitations are outlined before general conclusions are drawn. Suggestions for further work and potential clinical implications of the findings are then outlined before closing remarks are made.

9.2 Aims and objectives revisited

The overall aim of this thesis was to examine the role of therapeutic exercise in patients with or at risk of cancer cachexia to help maintain physical function and independence for as long as possible.

Objectives set out in the first chapter were to:

- review the use of exercise in patients with cancer to determine if it is an acceptable and practical therapy
- identify and pilot the most acceptable type(s) of exercise in patients with incurable cancer most risk of cachexia
- identify and examine outcome measures suitable for use in studies aimed at maintaining physical function in this group.

The first objective was achieved by reviewing the use of exercise in patients with curable or incurable cancer (chapter 3), rates of uptake, adherence and completion to exercise programmes and common reasons for patients declining or withdrawing from an exercise study

(chapter 5). These components of the thesis considered the prior use of therapeutic exercise to help identify how exercise could be optimally used in those with or at risk of cancer cachexia. Although the evidence base suggested exercise to be of benefit, multiple barriers to exercise were identified and issues with acceptability and practicality were uncovered. Highlighting challenges of using exercise as a therapy prompted the exploration of alternative approaches, e.g. NMES.

The second objective was achieved through chapters 2, 6 and 7 in which NMES was identified as a potential therapy, found to be popular among patients and piloted in those with incurable lung cancer. Asking patients for their preferences was a useful way to identify types of exercise that were in-keeping with their interests and needs. Their answers supported our assumption that novel therapies such as NMES may be preferred over more traditional types of exercise because of their practicality and convenience. In the pilot study we selected patients with lung cancer at high risk of cachexia and potentially able to gain the most from therapeutic exercise. Although this was a difficult group to examine, all patients completed the study and allowed the research aims to be met.

The third aim was achieved by the undertaking of a background review into the assessment of physical function (chapter 4) and preliminary and more focused examinations of an activity monitor in chapters seven and eight respectively. Among other outcomes used to

assess aspects of physical function, physical activity level was identified as having high face validity and reflecting patients' desire to remain active and independent. The use of lightweight monitors to objectively assess physical activity level was considered and one, the ActivPAL™, was chosen for use in the NMES study (chapter 7). On the basis of our experience with the monitor and patient feedback, we highlighted its potential role in future studies and formally examined its acceptability in chapter 8.

9.3 Main strengths and limitations

A number of strengths and some important limitations to this thesis should be considered.

9.3.1 Strengths

Despite exercise having been studied in patients with cancer for over twenty years, this has been the first time that more novel approaches, e.g. NMES and whole-body vibration, have been considered in this group. These may help improve the acceptability and practicality of therapeutic exercise by overcoming many of the issues with impracticality demonstrated in chapter 5.

The exercise preferences study presented in chapter 6 used an innovative methodology to overcome many of the pitfalls of previous studies, which used a reductionist approach and compartmentalised exercise programmes befroe asking about each separate element, e.g.

session length, frequency, duration etc.. The use of looping video clips and clear descriptions of exercise programmes likely to provide benefit helped better inform patients about the type of exercise in question and contextualised it within a real-world setting. This is likely to have improved patients' comprehension and understanding of what they were asked, potentially leading to more valid and relevant findings.

The sample size for each study was appropriate to the research design and aims. For example, the aim of chapter 6 was to *determine* the acceptability of six programmes based on different types of exercise. Therefore, the large sample size (n=200) was based on the precision to which the preferences of a larger group could be estimated; two-sided 95% CIs would not exceed ±7%. In contrast, the pilot study in chapter 7 aimed to *explore* if NMES was a feasible and tolerable intervention. Therefore a smaller sample size (n=16) was used, which was adequate to pilot the use of NMES, but was only sufficient to detect differences of two standard deviations between groups.

Where possible, study aims were grounded within clinical practice and lead to conclusions that could immediately be utilised by others. For example, chapter 8 examined the use of the ActivPAL™ to answer questions such as 'if patients are asked to wear the monitor for one week do they?' and 'how many days monitoring are required?' By designing studies around meaningful research questions such as these, findings can immediately be utilised researchers and clinicians alike.

A further strength is the undertaking of one of a limited number of intervention studies in chapter 7. Only a handful of research groups have successfully completed an exercise study in patients with incurable disease. Where they have, this has taken considerable time and effort, for example Temel et al took three years to accrue 25 patients with advanced NSCLC to their hospital-based programme (Temel et al, 2009). Exploratory work to determine the most appropriate types of exercise to study is important, but interventions must be offered and examined if advances are to be made in a timely manner.

9.3.2 Limitations

The omission of more qualitative data is unfortunate. The use of patient interviews and focus groups would have been an equally valid means of examining the role of therapeutic exercise in this setting and would have complimented the findings of each piece of work. When exploring issues around acceptability, preferences and experiences in chapters 5, 6 and 7 respectively some more open questioning would have enhanced the richness of the data obtained from the patient diaries and feedback forms.

In some of the studies, the large sample size targets meant that in order to recruit within the restraints of time and resource, reasonably broad eligibility criteria were used. On occasions this resulted in a degree of heterogeneity in terms of cancer diagnosis, particularly in chapter 6. The result was that some patients had cancers in which

cachexia is not particularly prevalent, e.g. breast or urological cancers, which reduces the external validity of findings.

More detail on the nutritional status of participants, i.e. previous weight loss or body mass index, would have been useful to help determine their degree of cachexia, malnutrition and anorexia. As many studies lack this information, the reader is left to make assumptions about whether the groups have or are at risk of cachexia based on their diagnosis, disease stage and treatment status. More transparency with regards to these parameters is required in the future.

A further limitation, which was more of a missed opportunity, relates to chapter 8 in which physical activity level was assessed in patients with incurable lung or upper-gastrointestinal cancer. Although the specified research aims were achieved, this sample provided an excellent opportunity to examine how physical activity level related to other factors, e.g. quality of life, fatigue, symptomology. Information on these relationships could have easily been achieved with the inclusion of relevant self-report questionnaires, completed the patient's convenience, and would have further enhanced the findings.

9.4 General conclusions

Findings of individual studies have been discussed in the relevant chapters and should be considered in light of the main strengths and limitations, but can be summarised as follows:

- Only half of all patients with or cured of cancer offered an exercise programme complete one, mainly due to a lack of interest or the impractical and demanding nature of the exercise offered. There is a need to modify existing programmes or explore more practical alternatives if exercise is to be acceptable and practical for the majority of patients.
- When presented with a range of exercise programmes, two-thirds of a group of patients with incurable cancer felt capable and prepared to undertake at least one programme. Neuromuscular electrical stimulation was the most popular therapy and patients cited the practicality and convenience of this therapy as the main reason for their choice, in keeping with a clear preference for exercise to be undertaken at home and unsupervised.
- Neuromuscular electrical stimulation appears to be an acceptable and tolerable exercise intervention for patients with non-small cell lung cancer. In the pilot study patients who received stimulation generally fared better than those in the control group, with improvements in quadriceps muscle strength and physical activity and less of a decline in exercise endurance. Further studies to

formally examine the longer term acceptability and efficacy of this therapy in patients with lung cancer are warranted.

- The wearing of an ActivPAL™ monitor for one week is an acceptable method of assessing free-living physical activity level in patients with incurable upper-gastrointestinal or lung cancer. A mean daily step count measured over 6 days appears to be an appropriate outcome to use in future studies.

Collectively, this work supports the use of therapeutic exercise in patients with or at risk of cancer cachexia. It highlights a particular role for novel approaches, e.g. NMES, which may require lower levels of motivation and less of a change in lifestyle than traditional types of exercise and thus be more acceptable to patients

9.5 Suggestions for further work

As well making a unique contribution to the evidence base, this thesis provides rationale for further study to examine the acceptability of exercise, neuromuscular electrical stimulation as a novel exercise therapy and physical activity level as an outcome of physical function.

9.5.1 Acceptability of exercise

The systematic review and exercise preferences study helped identify a need to make exercise programmes more practical and convenient. Further work into the acceptability of therapeutic exercise could examine in more detail factors influencing uptake. Possible approaches

include the use of qualitative interviews to explore levels of motivation and self-efficacy at different time points, applying behavioural models to explore patient readiness to change, or conducting focus groups to determine whether modifying or tailoring exercise programmes would alter patients' preparedness to undertake them. A useful development of the exercise preferences study would be to provide patients with an opportunity to perform a typical session of the various types of exercise, especially given that more novel therapies, e.g. neuromuscular electrical stimulation, were popular choices.

9.5.2 Neuromuscular electrical stimulation

In the pilot study, neuromuscular electrical stimulation was acceptable, tolerable and appeared to provide benefit to some patients. NMES potentially has multiple applications as a supportive therapy across a number of patient groups, e.g. incurable upper-gastrointestinal, and clinical scenarios, e.g. patients prescribed corticosteroids or on bed rest with spinal cord compression. In patients with incurable cancer, success is more likely if NMES can be offered proactively soon after diagnosis rather than reactively once significant loss in function has occurred. In practice this would necessitate offering it alongside first-line palliative chemotherapy, the standard treatment following a diagnosis of incurable NSCLC. This is appropriate given that chemotherapy can lead to deterioration in muscle strength and physical activity levels (Ancoli-Israel et al, 2001; Kasymjanova et al, 2007).

Our group have recently secured funding for a Phase II study of NMES in this setting with the overall aim to formally examine if NMES is an acceptable supportive therapy. This will help determine the justification for a definitive phase III trial. We are offering a longer programme of NMES, timing assessments to the administration of chemotherapy, and including measures of muscle strength, mass and physical activity level. In two sub-studies, patient experiences of NMES will be explored with semi-structured interviews and the molecular events underlying the regulation of muscle mass will be examined using muscle biopsy techniques.

9.5.3 Physical activity level

The final study demonstrated the feasibility of using an ActivPAL™ monitor to assess physical activity level in patients with cancer. A step count remains a suitable outcome for use in future studies but the added value of additional outcomes, e.g. time spent upright, is worth determining. Another aim would be to determine, and if necessary improve, the accuracy of the monitor's energy expenditure estimate. Such studies would require doubly-labelled water so would be costly, but by computing algorithms to adjust the overall energy estimate according to a patient's resting energy expenditure, there is potential to develop an outcome of use to all researchers interested in cachexia, e.g. nutritionists, pharmacologists, physiologists etc. It would also be useful to begin to examine the relationships between physical activity level, independence and quality of life with a large-scale cross-sectional

study. This would seek to determine the strength of any relationships and identify ‘thresholds’ of physical activity relating to various social circumstances, e.g. to remain independent at home alone or with spouse. This knowledge would help indentify if interventions aimed at maintaining physical activity have the potential to reduce or delay the need for additional home care or admission to hospital.

9.6 Clinical implications

The ultimate purpose of research is to improve the quality of routine patient care. Although this work is unlikely to bring about change in isolation, the findings may lead to developments in local clinical practice and inform others who influence teams providing care.

In the United Kingdom, an increasing number of multidisciplinary teams use exercise to help people diagnosed with incurable cancer stay as active and independent as possible for as long as possible. A number of these are known to the research team and have been kept abreast of our findings through regular meetings, seminars and publications. Interest in this work has grown and some teams have begun to make changes to their practice in line with our recommendations. For example, more clinicians are measuring physical activity level objectively and use outcomes with their patients as motivational and education tools. Some teams have also introduced NMES to their clinical ‘toolkit’ and offer it to patients they feel would benefit from strength training but who are unable or unwilling to

undertake more traditional types of exercise. Evidence supporting the wider use is of course lacking but this initial interest is encouraging.

9.7 Closing remarks

Conducting research into exercise in the supportive and palliative care setting is challenging but fulfilling. Supportive care is an emerging field of research and initial efforts were directed towards developing strong links with the oncologists from whom patients would be recruited. Each study took considerable time to complete and during the recruitment process the role of exercise in light of a diagnosis of incurable cancer was questioned by some patients. However, those who enrolled onto a study engaged with the research process, developed an insight into the potential role of exercise and hopefully found personal reward from taking part. In light of the general conclusions, they also contributed to the generation new knowledge around therapeutic exercise, which should help improve care for others in the future.

This work makes a small but important contribution to the field by informing the direction and design of future work examining therapeutic exercise in those with or at risk of cachexia. In the longer term, therapeutic exercise will likely be supplemented by nutritional support and immunomodulatory agents to form part of a multimodal approach to cancer cachexia. The continued development and careful matching of each component offers the best hope for patients to remain active and independent for as long as possible.

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APPENDIX 1:

QUESTIONNAIRES

1.1 ECOG Performance Status scale

Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

1.2 Karnofsky Performance Status scale

Grade	KPS description
100	Normal no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead

1.3 EORTC core questionnaire

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _ _ _

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

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

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

1.4 EORTC lung cancer module

Patient Trial No					

Patient initials:
Date Of Birth (dd,mm,yyyy):
Visit Date (dd,mm,yyyy):

NMES

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

1.5 Exercise preferences study patient demographics questionnaire

Exercise Therapy Questionnaire - Participant Demographics

Participant ID number: ☐

Age: ☐ **Gender:** ☐ Male ☐ Female

Cancer diagnosis: ☐

Previous treatment: [Tick all that apply]

- ☐ None
- ☐ Surgery
- ☐ Chemotherapy
- ☐ Radiotherapy
- ☐ Concurrent chemotherapy and radiotherapy

Current treatment: [Tick all that apply]

- ☐ None
- ☐ Surgery
- ☐ Chemotherapy
- ☐ Radiotherapy
- ☐ Concurrent chemotherapy and radiotherapy

Past medical history:

☐

Performance status:

- ☐ 0
- ☐ 1
- ☐ 2

1.6 Exercise preferences study main patient questionnaire

Exercise Therapy Questionnaire

ID No *[researcher to complete]*:

Q1. Considering a typical one week period before you were diagnosed with your current illness, how many times on average did you do the following kinds of exercise for more than 15 minutes during your free time?

Strenuous exercise (heart beats rapidly)	
Moderate exercise (not exhausting)	
Mild exercise (minimal effort)	

Q2. Considering a typical one week period over the last month, how many times on average do you do the following kinds of exercise for more than 15 minutes during your free time?

Strenuous exercise (heart beats rapidly)	
Moderate exercise (not exhausting)	
Mild exercise (minimal effort)	

Exercise therapy programmes: Introduction

Exercise has been used as a therapy to improve peoples' physical condition, mood and quality of life.

We are going to show you a selection of exercise therapies that may provide benefit.

When repeated on a regular basis these are called programmes.

We want to find out how acceptable they are to you.

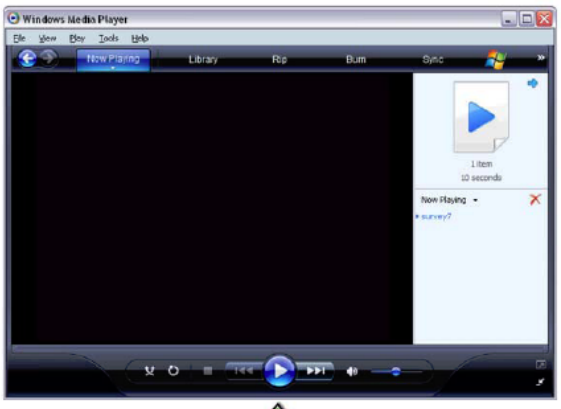
We will ask you if you feel capable of doing them and if you would be prepared to undertake them at this moment in time.

Walking programme

Please click here to view a short video demonstrating the walking programme

Once you have viewed the clip, close Windows Media Player by clicking on the cross in the top right corner, as shown below.

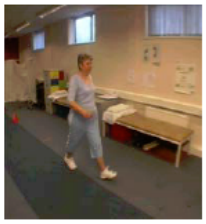
Then click on **next** below to go to the questions about this programme.



Click on the cross to close the Windows Media Player once you have finished viewing the film

To view the film again, click the play button

Walking programme



You would be asked to walk at a moderate but not exhausting pace (i.e. brisk walking) on the flat.

Each day would consist of ***three walks*** with rest periods in between. The duration of each walk would initially be ***3 minutes*** building up to ***10 minutes***.

This would be for ***three days a week*** for ***six weeks***.

Q3a. At this moment in time do you think you are physically capable of undertaking this type of exercise therapy programme?

- ☐ Yes
- ☐ No

Q3b. If no, why not?

Q4a. At this moment in time, would you be prepared to undertake an exercise therapy programme similar to this?

- ☐ Yes
- ☐ No

Q4b. If no, why not?

Treadmill walking programme

You would be asked to walk on a treadmill at a moderate but not exhausting pace (i.e. brisk walking).

Each day would consist of ***three walks*** with rest periods in between. The duration of each walk would initially be ***3 minutes*** building up to ***10 minutes***.

This would be for ***three days a week*** for ***six weeks***.

Q5a. At this moment in time do you think you are physically capable of undertaking this type of exercise therapy programme?

- ☐ Yes
- ☐ No

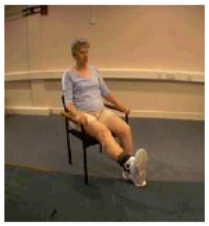
Q5b. If no, why not?

Q6a. At this moment in time, would you be prepared to undertake an exercise therapy programme similar to this?

- ☐ Yes
- ☐ No

Q6b. If no, why not?

Weight training



You would be asked to sit on a chair and straighten your leg whilst wearing a small ankle weight.

Each day would consist of ***two sets*** of repetitions with rest periods in between. Each set would initially be ***2 lifts*** building up to ***8 lifts***.

This would be for ***three days a week*** for ***six weeks***.

Q7a. At this moment in time do you think you are physically capable of undertaking this type of exercise therapy programme?

- ☐ Yes
- ☐ No

Q7b. If no, why not?

Q8a. At this moment in time, would you be prepared to undertake an exercise therapy programme similar to this?

- ☐ Yes
- ☐ No

Q8b. If no, why not?

Cycling programme

You would be asked to cycle at moderate speed on an exercise bike set at a low level. This should represent moderate but not exhausting exercise.

Each day would initially consist of ***20 minutes*** building up to ***30 minutes.***

This would be for ***five days a week*** for ***ten weeks***.

Q9a. At this moment in time do you think you are physically capable of undertaking this type of exercise therapy programme?

- ☐ Yes
- ☐ No

Q9b. If no, why not?

Q10a. At this moment in time, would you be prepared to undertake an exercise therapy programme similar to this?

- ☐ Yes
- ☐ No

Q10b. If no, why not?

Whole-body vibration programme

You would be asked to stand on a vibrating platform and bend your knees slightly. You would feel a fine buzzing sensation in your legs.

Each day would consist of ***three stands*** with rest periods in between. The duration of each stand would be ***3 minutes.***

This would be for ***three days a week*** for ***ten weeks***.

Q11a. At this moment in time do you think you are physically capable of undertaking this type of exercise therapy programme?

- ☐ Yes
- ☐ No

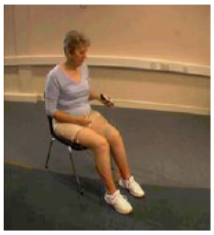
Q11b. If no, why not?

Q12a. At this moment in time, would you be prepared to undertake an exercise therapy programme similar to this?

- ☐ Yes
- ☐ No

Q12b. If no, why not?

Muscle stimulation programme



You would be asked to use a muscle stimulation machine to allow you to exercise your thigh muscles whilst sitting. You would feel a fine tingling sensation and your muscles will slowly contract and relax.

Each day would initially consist of ***30 minutes*** on both legs building up to ***45 minutes.***

This would be for ***five days a week*** for ***six weeks***.

Q13a. At this moment in time do you think you are physically capable of undertaking this type of exercise therapy programme?

- ☐ Yes
- ☐ No

Q13b. If no, why not?

Q14a. At this moment in time, would you be prepared to undertake an exercise therapy programme similar to this?

- ☐ Yes
- ☐ No

Q14b. If no, why not?

Q15. Which type of exercise therapy programme would you be most prepared to undertake at this moment in time?

- ☐ Walking programme
- ☐ Treadmill walking programme
- ☐ Weight training programme
- ☐ Cycling programme
- ☐ Whole-body vibration programme
- ☐ Muscle stimulation programme
- ☐ I would not be prepared to undertake any of these programmes

Q16. Can you give one or more reasons why you preferred this type of exercise programme over the others?

We also want to find out the conditions under which you would be prepared to undertake your preferred exercise therapy programme and your preferences for **how**, **where** and **when** it takes place.

Q17a. Following initial instruction on how to use the various equipments required, would you be prepared to undertake the subsequent exercise therapy sessions under these conditions?

	Yes	No
Alone, unsupervised	☐	☐
Alone, supervised	☐	☐
In a group, unsupervised	☐	☐
In a group, supervised	☐	☐

Q17b. How would you most prefer to undertake the exercise therapy programme?

☐ Alone, unsupervised

☐ Alone, supervised

☐ In a group, unsupervised

☐ In a group, supervised

Q18a. Following initial instruction would you be prepared to undertake subsequent exercise therapy sessions at these places?

	Yes	No
Home	☐	☐
Hospital	☐	☐
Community centre	☐	☐
Gym	☐	☐

Q18b. Where would you most prefer to undertake an exercise therapy programme?

☐ Home

☐ Hospital

☐ Community centre

☐ Gym

Q19. For each of the treatments you have received, would you be prepared to undertake an exercise therapy programme at these times?

	Yes	No	I have not received this treatment
During chemotherapy	☐	☐	☐
Immediately after chemotherapy	☐	☐	☐
During radiotherapy	☐	☐	☐
Immediately after radiotherapy	☐	☐	☐
During combined chemotherapy and radiotherapy	☐	☐	☐
Immediately after combined chemotherapy and radiotherapy	☐	☐	☐

Thank you for answering these questions.
Now please click submit at the bottom of the page.

How to use the ActivPal Monitor

The ActivPal monitor is a small device. It weighs 20 grams (about the weight of a small box of matches) and is only 5 x 3.5 x 0.7 cm in size (about the size of a small battery)

Applying
The monitor is stuck to your thigh with specially made 'stickies'. These are a bit like Post-It notes in that they can be taken off and repositioned easily. They don't stick to your clothes and do not harm your skin. However, some people find that after a few days they lose their stickiness. In this case you can either use new 'stickies' or you can use a special type of tape we will provide. Again this won't harm your skin, is easily removed and won't damage your clothes.

The ActivPal is positioned on the front of your thigh about midway between your hip and your knee. We will show you where to put it and how to look after it.

Removing
We would like you to wear it for as long as possible during the monitoring period. It does take a little getting used to, as most of us don't wear things around our legs. But there will be times when you need to take it off.

Taking the ActivPal off is easy. All you need to do is peel it off the 'stickies' or tape which will easily come off your thigh and either leave it to one side or put it back in the box we will give you.

Caring for
The ActivPal is robust but you should avoid getting it wet or banging it. So please remove it when you have a bath or a shower. It can easily be stuck on again afterwards. It should be perfectly Ok if you wear it under your clothes if you go out in the rain or damp.

You will need to get used to wearing it, as it feels a bit odd at first. A few minor knocks shouldn't be too much of a problem but please be careful.

Nottingham City Hospital NHS
NHS Trust

Neuromuscular electrical stimulation (NMES) diary card

Patient No | | Patient Initials | | |

Date (DD/MON/YYYY) | | | | | | | | | |

Below is a reminder of how to use the stimulation device.

Each time you apply the device, please fill in the corresponding part of the diary card so that we have a record of how often and for how long you have used the stimulator.

Please make a note of any problems that you may be having and contact the research team at Nottingham City Hospital for further advice.

Mon-Fri 9am-5pm	0115 840 4880/1
Out of hours	0115 962 7619

1. Connect all the leads to the stimulator as you have been shown.
2. Apply the electrodes to your thigh as you have been shown.
3. Connect the leads to the electrodes.
4. Once all connections are secure and the intensity is set to zero, check the other settings are as we have shown you.
5. Turn the stimulator on and gradually increase the intensity until it is as high as you can reasonably tolerate. Use for as long as you need to (or can tolerate) for the week of the study (up to 15 minutes per day in week 1 or up to 30 minutes in any other week.)
6. When you have used it for the set time or have decided that you want to stop (whichever is the sooner), turn the intensity to zero. Switch off the stimulator and then disconnect the leads. Remove the electrodes from your thigh. Clean up and put stimulator, leads and electrodes away until next time.

DIARY

Day	Date	Duration of stimulation (15 mins)	
Week 1	DD/MM/YY	Right leg	Left leg
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day	Date	Duration of stimulation (30 mins)	
Week 2	DD/MM/YY	Right leg	Left leg
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

DIARY

Day	Date	Duration of stimulation (30 mins)	
Week 3	DD/MM/YY	Right leg	Left leg
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day	Date	Duration of stimulation (30 mins)	
Week 4	DD/MM/YY	Right leg	Left leg
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

1.8 Neuromuscular electrical stimulation study patient evaluation questionnaire

Nottingham City Hospital NHS
NHS Trust

EVALUATION FORM

Thank you for helping us with the neuromuscular electrical stimulation study.

We would like to ask you a few final questions about your experiences of participating in the study. Please take your time to answer the following questions.

Neuromuscular electrical stimulation device	
Do you have any good or bad comments about the device e.g. any difficulties with its use?	
Would you be prepared to use this in the future?	Yes / No
If No, why not?	
ActivPal monitor	
Do you have any good or bad comments about the device e.g. any difficulties with its use?	
Would you be prepared to use this in the future?	Yes / No
If No, why not?	
Cybex (leg exercise) machine	
Do you have any good or bad comments about this test?	
Would you be prepared to do this test again?	Yes / No
If No, why not?	
Shuttle Walking Test	
Do you have any good or bad comments about this test?	
Would you be prepared to do this test again?	Yes / No
If No, why not?	

1.9 Physical activity level study patient diary and evaluation questionnaire

ActivPAL Diary

Thank you for agreeing to participate in this study.
Please fill out in the diary ***each day***:

- time you ***got up***
- time you ***went to bed***
- periods when you ***slept during the day***
- periods when you ***did not wear the monitor*** (giving a reason where possible).

Participant study ID:
☐ / ☐☐
Centre no. / patient no.

	Morning	Afternoon	Evening	Night
Example	*Got up 7.15 am*	*Slept 1 hour*	*Monitor off 30 min (bath)*	*Went to bed 9 pm*
Monday				*Went to bed_____*
Tuesday	*Got up _____*			*Went to bed_____*
Wednesday	*Got up _____*			*Went to bed_____*
Thursday	*Got up _____*			*Went to bed_____*
Friday	*Got up _____*			*Went to bed_____*
Saturday	*Got up _____*			*Went to bed_____*
Sunday	*Got up _____*			*Went to bed_____*
Monday	*Got up _____*			

Patient Dairy July 2006 Version 1.0

ActivPAL Diary

To be completed during the week

Please write down any problems you have with the monitor (e.g. skin irritation, device falling off, discomfort).

e.g. Tuesday afternoon, dressing came off, new one applied

To be completed at the end of the week.

Overall have you found this device acceptable?	Yes / No
Would you be prepared to wear it again?	Yes / No

If *no,* please give reason(s).

APPENDIX 2:

PATIENT INFORMATION SHEETS, CONSENT FORMS

AND ETHICAL APPROVAL LETTERS

2.1 Patient information sheets

2.1.1 Exercise preferences study

Nottingham University Hospitals NHS
NHS Trust

Physical activity as a therapy for people with cancer: the how, where and when?

Patient Information Sheet

Please read this information carefully and feel free to ask any questions or to request further information.

Principle Investigator: **Dr Andrew Wilcock**
Reader/Consultant in Palliative Medicine and Medical Oncology

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

What is the purpose of the study?

Physical activity has been used as a treatment. This has involved undertaking exercises such as walking on a regular basis for a prolonged period of time. Reported benefits in people treated for cancer have been improved physical and mental well-being, leading to a better overall quality of life. However, for people with cancer there are difficulties undertaking and completing such programmes therefore to realise the potential benefits, we need to tailor exercise options to make them more acceptable. The purpose of this study is to identify the most acceptable forms of physical activity used as a therapy to people with cancer. The results will help to inform the development of future studies both locally and nationally and may be used as part of a Ph.D. project being completed by Mr Matthew Maddocks, a qualified physiotherapist, who is part of the team undertaking this research.

Why have I been invited to participate?

You have been chosen because of your diagnosis.

Do I have to take part?

You are under no obligation at all to take part in this study. It is up to you to decide whether or not you take part. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form, which you will be given a copy of. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to

withdraw at any time, or a decision not to take part, will not affect the standard of care you receive either at home or in hospital.

What will happen to me if I take part?

The study involves completing a computer-based questionnaire that first asks about your current level of physical activity. You would then be shown videos of various types of physical activity and asked if you feel able and willing to complete the activity being shown as part of a therapy programme. No physical activity will be completed as part of this research study and you will not be offered any supervision to complete any of the exercise programmes detailed in the questionnaire.

What do I have to do?

Completing the questionnaire will take approximately 15-30 minutes of your time and can take place in a room close to the clinic. It can be done before or after your clinic appointment. We can ensure that should your appointment come up whilst you are completing the questionnaire, you can attend and return later to complete it if you wish.

What are the side effects of taking part?

There should not be any side effects of taking part in this research.

What are the possible disadvantages and risks of taking part?

There should not be any disadvantages or risks of taking part in this research. If you find any aspect of the study distressing, please speak to one of the researchers for advice on further support.

What are the possible benefits of taking part?

There are no direct benefits to you by taking part in this study. However, you will be helping us to identify the most acceptable types of physical activity that we may offer to people with cancer in the future.

What happens when the research study stops?

You will continue with your current care. If you wish to try any of the exercises you are shown at home or a local centre, or want any further advice on physical activity and exercise, please speak to your doctor.

What if something goes wrong?

If taking part in this research harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds for legal action but as in other cases in civil law you would need to employ a lawyer and pay for their services in the usual way. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, you may wish to contact the Trust's Patient Advice and Liaison Service (PALS), Hospital Headquarters, Nottingham City Hospital, FREEPOST MID21426, Nottingham, NG5 1BR.

Will my taking part in this study be kept confidential?

All information that is collected about you during the study will be kept strictly confidential.

What will happen to the results of the research study?

The information that the research team obtains or receives about you will be entered onto a database controlled by the research team. It will be kept in an anonymised form (e.g. you will be identified by a number not by your name). Access to the database containing the data is restricted to authorised personnel and is password protected. Results from the study will be published in medical journals and presented at major research meetings. You will not be referred to by name or be identified in any presentation or report of the study results. If you withdraw your consent to participate in the study, no new data will be collected or processed. However, you may be asked to agree to some of the data already collected about you being used. During this study, you have the right to access the data relating to your taking part in the study, and, in the event of any inaccuracies about you being recorded, you have the right to request that such data be corrected. Please talk to the research team about this.

Who is organising and funding the research?

The study is organised by Dr Andrew Wilcock of the University of Nottingham. Funding for the study has been awarded by the Dimbleby Cancer Care Trust. The study has been granted ethical approval by Nottingham 1 Research Ethics Committee and this study has the reference number 07/H0403/116.

Contact for further information

Please keep this sheet to think about the study and to discuss with your family or friends. We will happily see you and your relatives or friends together to answer any questions about the study. After completing the questionnaire, if you have any additional questions, please contact one of the research team on 0115 9691169 ext 56842.

2.1.2 Neuromuscular electrical stimulation study

Nottingham City Hospital NHS
NHS Trust

Does neuromuscular electrical stimulation of the proximal leg muscles improve leg muscle endurance, exercise endurance and activity levels in people with lung cancer?

Patient Information Sheet

Please read this form carefully and feel free to ask any questions or to request further information.

Lead Investigators: **Dr Andrew Wilcock (Nottingham City Hospital)**
Mr Simon Mockett (Nottingham City Hospital)
Dr Vincent Crosby (Queens Medical Centre)
Mrs Ruth Feakes (Nottingham Primary Care Trust)
Dr Joanna Hocknell (Derby Royal Infirmary)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. You should take time, at least 24 hours, to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

People with lung cancer often experience increasing muscle weakness that can interfere with their ability to carry out daily activities. Currently, there are no specific treatments that prevent or delay this. One of the aims of our research is to help people with lung cancer remain as independent as possible for as long as possible. This requires new approaches to be tried and assessed using appropriate and meaningful outcome measures.

Undertaking regular exercise such as walking or weight training to strengthen the leg muscles could be beneficial. However, this may not always be practical for people with lung cancer due to other factors such as fatigue. A suitable alternative could be neuromuscular electrical stimulation (NMES) of the muscles in the top of the legs. In people with severe chronic bronchitis this has been shown to improve muscle strength, muscle endurance, ability to exercise and quality of life. Our study will be the first to examine if NMES could be of similar benefit to people with lung cancer.

Why have I been invited to participate?

You have been chosen because of your diagnosis.

Do I have to take part?

You are under no obligation at all to take part in this study. It is up to you to decide whether or not you take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form, which you will be given a copy of. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive either at home or in hospital.

What will happen to me if I take part?

You will be allocated randomly (by chance, like the toss of a coin) to one of two groups. Group 1 will receive the neuromuscular electrical stimulation device (NMES) immediately and group 2 will receive the NMES device after a period of four weeks. The diagram at the end of this leaflet summarises what will happen. We will ask people in group 1 to make three visits to the Clinical Sciences Building at Nottingham City Hospital over a four-week period and people in group 2 to make four visits to Nottingham City Hospital over an eight-week period. Each visit will last for about 2 hours. One week prior to each visit a member of the research team will visit you at home in order to provide you with an ActivPal activity monitor to wear until your hospital visit. The ActivPal is a small, lightweight (20g) device that attaches to the front of the thigh using an adhesive gel pad and a light bandage. It measures the amount of time that you spend standing, walking or sitting/lying. We will teach you how to apply, remove and reapply the monitor (it is removed when bathing etc).

We will either pay for a taxi to bring you to and from the hospital or we can reimburse your petrol costs if you choose to use your own transport.

First visit (Groups 1 and 2)

We will ask you some questions about your medication and ask you to complete a health questionnaire and some simple breathing tests by blowing through a tube. We will also record your height and weight.

After sitting resting for at least 5 minutes we will ask you to carry out a shuttle walking test. This involves you walking up and down a 10-metre course around two marker cones. The

speed at which you will walk is dictated by a beeping noise from a tape cassette. To start with you will only need to walk very slowly but after every minute the speed of walking will increase and we will ask you to continue until you are unable to carry on for whatever reason. At regular intervals we will ask you to point to a scale to tell us how breathless you are feeling and how tired your legs are. After a rest of 30 minutes we will ask you to carry out the same walking test again.

Second visit (Groups 1 and 2)

On the following day we will ask you to do another shuttle walking test. This time however, following a slower warm-up period, the speed at which you walk will remain constant. We will ask you to continue until you are unable to carry on for whatever reason. At regular intervals we will ask you to point to a scale to tell us how breathless you are feeling and how tired your legs are.

After a rest of 30 minutes we will assess the strength of your leg muscles using a Cybex exercise machine. This involves you sitting on the seat of the Cybex machine and having the lever arm of the machine strapped to the ankle of your dominant leg, the one you tend to kick a ball with. To stabilize your body, straps like a seatbelt will be used. You will then be asked to move your leg up and down 25 times as quickly as possible using all your strength.

Group 1 will then be given the neuromuscular electrical stimulation (NMES) device and taught how to apply and use it correctly. The device is about the size of a pack of playing cards, which you can attach to your belt or let rest beside you. You attach the leads to your thigh using sticky tape and turn the stimulator on. People generally feel a gradual tingling sensation, which will rise to a peak and then fade away. You can control how strong the sensation is and we ask that during the first week you gradually turn up the intensity as you get used to it.

You will be asked to apply the NMES device at home to each leg for 15 minutes five times a week in the first week, increasing to 30 minutes five times a week in the second, third and fourth weeks. The research team will visit you once a week to see how you are getting on. You will also be asked to keep a diary of the number and duration of treatments that you have given yourself at home.

Third visit (Groups 1 and 2)

After four weeks you will be asked to return to Nottingham City Hospital where we will ask you to repeat the questionnaire and the simple breathing tests. We will also record

your height and weight again. We will ask you to repeat the shuttle walking test and after a rest of 30 minutes we will assess the strength of your leg muscles on the Cybex machine.

Group 1 will return the NMES device, as they will now have finished the study.

Group 2 will now receive the NMES device and be taught how to apply and use the device correctly as described above.

Fourth visit (Group 2 only)

After a further four weeks, group 2 will be asked to return to Nottingham City Hospital where we will ask you to repeat the questionnaire and the simple breathing tests. We will also record your height and weight again. We will ask you to repeat the shuttle walking test and after a rest of 30 minutes we will assess the strength of your leg muscles on the Cybex machine. Group 2 will return the NMES device, as they will now have finished the study.

What do I have to do?

Before the visits to the hospital, we will ask you to avoid caffeine drinks within one hour, large meals within 2 hours and excess alcohol the night before the test. You will be allowed to take all your normal medication but it is important that you take it at the same time each day ± 15 minutes. Once you have been trained how to use the NMES machine you will have a training protocol to follow at home.

What is the procedure that is being tested?

We are testing if neuromuscular electrical stimulation device will improve muscle strength and endurance in people who have lung cancer.

What are the side effects of taking part?

Both the shuttle walking test and Cybex machine have been used in people with lung cancer. Apart from possibly making you feel tired or breathless, there should be no side effects from doing the shuttle walking test. The Cybex machine has also been used in people following recent hip operations and apart from possibly making your leg muscles feel tired, there should be no side effects. The NMES device has been used in a wide range of medical conditions and there should be no side effects. Occasionally the

stimulation may feel uncomfortable and that is why it will be set up and monitored by the research team and the duration of stimulation built up from 15 minutes to 30 minutes after the first week. If you experience any unusual symptoms between the regular visits then you should report these to the research team.

You may find some of the questions in the health questionnaire upsetting. You are not obliged to answer all of the questions although it would help the research team if you can answer as many as possible. If you find the questions particularly upsetting please let a member of the research team know so that we can provide you with appropriate support.

What are the possible disadvantages and risks of taking part?

This treatment has not been used in this way before. It is possible that you will not gain any benefits from using the neuromuscular electrical stimulation device.

What are the possible benefits of taking part?

The study will help us to direct future research into ways of trying to improve muscle strength and endurance, exercise endurance and physical activity levels in people with lung and other types of cancer.

What if new information becomes available?

Sometimes during the course of a study, new information becomes available. If this happens, your research doctor will tell you about it and discuss whether you want to continue in the study or not. If you decide to withdraw, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What happens when the research study stops?

The neuromuscular electrical stimulation device is only available for the duration of the study. We are not able to continue using it once the study stops.

What if something goes wrong?

If taking part in this research harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds

for a legal action but as in other cases in civil law you would need to employ a lawyer and pay for their services in the usual way. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, you may wish to contact the Trust's Patient Advice and Liaison Service (PALS), Hospital Headquarters, Nottingham City Hospital, FREEPOST MID21426, Nottingham, NG5 1BR

Will my taking part in this study be kept confidential?

All information that is collected about you during the study will be kept strictly confidential. We would inform your GP of your participation.

What will happen to the results of the research study?

The information that the research team obtains or receives about you will be entered onto a database controlled by the research team. The data will be entered onto the database in an anonymised form (e.g. you will be identified by a number not by your name). Access to the database containing the data is restricted to authorised personnel and is password protected.

Results from the study will be published in medical journals and presented at major national and international research meetings. You will not be referred to by name or be identified in any presentation or report of the study results.

If you withdraw your consent to participate in the study, no new data will be collected or processed. However, you may be asked to agree to some of the data already collected about you being used.

During this study, you have the right to access the data relating to your taking part in the study, and, in the event of any inaccuracies about you being recorded in the study data, you have the right to request that such data be corrected. Please talk to the research team about this.

Who is organising and funding the research?

The study is co-ordinated by Dr Wilcock and Mr Mockett of the University of Nottingham. The Nottinghamshire, Derbyshire and Lincolnshire Research Alliance are funding it.

Contact for further information

Please keep this sheet to think about the study and to discuss with your family or friends. We will happily see you and your relatives or friends together to answer any questions about the study.

Whilst on the study, if you (or your own family doctor) have any additional questions, please contact one of the research team on 0115 962 7619 or Matt Maddocks directly on 0115 8231801

Dr Andrew Wilcock	- Reader/Consultant
Dr Mary Lewis	- Research Registrar
Sr Cathann Manderson	- Research Sister
Sn Lani Patterson	- Research Nurse
Mr Matthew Maddocks	- Research Physiotherapist

If outside of normal working hours, please phone Hayward House, Nottingham City Hospital (0115 962 7619) and ask for the doctor on call.

Study Summary

1. Consent obtained.
2. Randomised to one of two groups.
3. **First Evaluation Visit:** Questionnaires about health and medication, height, weight, spirometry
   First incremental shuttle walking test (ISWT)
   30 minutes rest
   Second ISWT
4. **Second Evaluation Visit:** Endurance shuttle walking test (calculated from ISWT)
   30 minutes rest
   Cybex – to assess leg muscle strength

	Group 1	Group 2
Initially	Home visit to receive ActivPal device and teach participant how to use correctly.	Home visit to receive ActivPal device and teach participant how to use correctly.
Baseline week	Wear ActivPal device for 1 week. Monday-Monday starting at midday.	Wear ActivPal device for 1 week. Monday-Monday starting at midday.
Beginning week 1	**First evaluation visit** **Second evaluation visit** Receive NMES device and training protocol	**First evaluation visit** **Second evaluation visit** Control period
End of week 1	Home Visit	
End of week 2	Home Visit	
End of week 3	Home Visit Apply ActivPal	Home Visit Apply ActivPal
End of week 4 **(Third Visit)**	Questionnaires Weight, spirometry Endurance shuttle walking test 30 minutes rest Cybex – leg muscle strength Return ActivPal and NMES devices **FINISH**	Questionnaires Weight, spirometry Endurance shuttle walking test 30 minutes rest Cybex – leg muscle strength Receive NMES device and training protocol Receive ActivPal device and remind how to use correctly
End of week 5		Home Visit
End of week 6		Home Visit
End of week 7		Home Visit Apply ActivPal
End of week 8 **(Fourth Visit)**		Questionnaires Weight Spirometry Endurance shuttle walking test 30 minutes rest Cybex – leg muscle strength Return ActivPal and NMES devices **FINISH**

2.1.3 Physical activity level study

Nottingham University Hospitals NHS
NHS Trust

Physical activity level as an outcome measure for use in future cancer trials: a feasibility study

Patient Information Sheet

Please read this information carefully and feel free to ask any questions or to request further information.

Chief Investigator:

Dr Andrew Wilcock (Reader/Consultant in Palliative Medicine and Medical Oncology)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. You should take time, at least 24 hours, to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

In general, the more physically active a person is, the better their quality of life is. Thus, looking for changes in a person's physical activity level may be a useful way of identifying if various anticancer or palliative treatments are providing meaningful benefit or not. Simple methods of assessing physical activity, such as a questionnaire are inaccurate. A more accurate assessment can be obtained by the use of an ActivPAL monitor, which is small (2 x 4 x 0.5cm) and lightweight (20g). It is worn on the thigh and can record physical activity for up to one week. It has been used by people with a wide range of diagnoses, including cancer. The purpose of this study is to examine in more detail the use of the ActivPAL monitor in people with cancer in order to assess:

- how acceptable it is to use an ActivPAL monitor over one week
- if the detailed activity information the ActivPAL monitor provides has any advantage over a simpler measure of activity, e.g. the number of steps a person takes
- the shortest period of time a person needs to wear the monitor for in order to provide useful information.

The results of this study will help to inform the development of future studies both locally and nationally and may be used as part of a Ph.D. project.

Why have I been invited to participate?

You have been chosen because of your diagnosis.

Do I have to take part?

You are under no obligation at all to take part in this study. It is up to you to decide whether or not you take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form, which you will be given a copy of. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive either at home or in hospital.

What will happen to me if I take part?

The study involves two visits to hospital. On the first visit a member of the research team will show you the ActivPAL monitor and teach you how to attach and remove it using sticky tape and dressing. During this visit you will be asked to secure the ActivPAL monitor to the front of your thigh and to wear it for a full week, apart from when you shower or bathe, whilst it records your physical activity level. You will also be given a diary for the week, to complete on a daily basis, to record periods when you sleep as well as any difficulties you have with the monitor. On the second visit you will return the ActivPAL monitor and your completed diary to the research team. They will then send the information about your activity during the past week to the coordinating centre and you will have finished the study.

What do I have to do?

You will have to visit the hospital on two occasions (one week apart) to collect and return the monitor to the research team. Taxis are available to you should you require transport for these journeys. Alternatively we can reimburse any costs of alternative transport such as petrol expenses or public transport fares.

What is the procedure that is being tested?

The procedure being tested is the wearing of an activity monitor on the front of the thigh for a period of one week.

What are the side effects of taking part?

There is the potential that you may have an allergic reaction to the adhesive pads and sticky tape used to secure the ActivPAL Monitor to the front of your thigh. Please inform the researcher if you have a known skin allergy.

What are the possible disadvantages and risks of taking part?

The two extra visits to the hospital and filling out the daily diary for one week.

What are the possible benefits of taking part?

There are no direct benefits to you by taking part in this study. However, you will be helping us to identify if the measurement of physical activity level is a good way of identifying if new approaches provide meaningful benefit to people with cancer.

What if new information becomes available?

Sometimes during the course of a study, new information becomes available. If this happens, your research doctor will tell you about it and discuss whether you want to continue in the study or not. If you decide to withdraw, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What happens when the research study stops?

You will continue with your current care.

What if something goes wrong?

If taking part in this research harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds for legal action but as in other cases in civil law you would need to employ a lawyer and pay for their services in the usual way. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, you may wish to contact the Trust's Patient Advice and Liaison Service (PALS), Hospital Headquarters, Nottingham City Hospital, FREEPOST MID21426, Nottingham, NG5 1BR.

Will my taking part in this study be kept confidential?

All information that is collected about you during the study will be kept strictly confidential. We would inform your GP of your participation.

What will happen to the results of the research study?

The information that the research team obtains or receives about you will be entered onto a database controlled by the research team. It will be kept in an anonymised form (e.g. you will be identified by a number not by your name). Access to the database containing the data is restricted to authorised personnel and is password protected.

Results from the study will be published in medical journals and presented at major national and international research meetings. You will not be referred to by name or be identified in any presentation or report of the study results. If you withdraw your consent to participate in the study, no new data will be collected or processed. However, you may be asked to agree to some of the data already collected about you being used.

During this study, you have the right to access the data relating to your taking part in the study, and, in the event of any inaccuracies about you being recorded in the study data, you have the right to request that such data be corrected. Please talk to the research team about this.

Who is organising and funding the research?

The study, involving six other centres in the United Kingdom, is organised by Dr Andrew Wilcock of the University of Nottingham, which will act as the co-ordinating centre. Funding for the study has been awarded by The Population and Behavioural Sciences Committee, Cancer Research UK. The study has been granted ethical approval by Oxfordshire Research Ethics Committee 'A' and this study has the reference number 07/Q1604/16.

Contact for further information

Please keep this sheet to think about the study and to discuss with your family or friends. We will happily see you and your relatives or friends together to answer any questions about the study. After completing the questionnaire, if you have any additional questions, please contact one of the research team on 0115 9691169 ext 56842.

2.2 Consent forms

2.2.1 Exercise preferences study

Nottingham University Hospitals NHS
NHS Trust

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: **Physical activity as a therapy for people with cancer: the how, where and when?**

Principle Investigator: **Dr Andrew Wilcock**
Reader/Consultant in Palliative Medicine and Oncology

The patient should complete the whole of this sheet himself/herself.

Please initial box

1. I confirm that I have read and understood the patient information sheet version 1.2 dated 20th August 2007 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that anonymised quotes taken during the course of this research may be used in the publication of this research ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals or the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I agree to take part in the above study. ☐

Name of patient	Date	Signature
Name of Person taking consent (If different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes.

Consent form patient Page 1of 1 20th August 2007
Version 1.2
Nottingham 1 Research Ethics Committee Study reference number: 07/H0403/116

2.2.2 Neuromuscular electrical stimulation study

Nottingham City Hospital NHS
NHS Trust

Centre Number:

Study Number:

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: **Does neuromuscular electrical stimulation of the proximal leg muscles improve leg muscle endurance, exercise endurance and activity levels in people with lung cancer ?**

Lead Investigators: **Dr Andrew Wilcock (Nottingham City Hospital)**
Mr Simon Mockett (Nottingham City Hospital)
Dr Vincent Crosby (Queens Medical Centre)
Mrs Ruth Feakes (Nottingham Primary Care Trust)
Dr Joanna Hocknell (Derby Royal Infirmary)

Please initial box

1. I confirm that I have read and understand the information sheet version 1.2, dated August 2005 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent (If different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Consent Form
Version 1.2

August 2005

2.2.3 Physical activity level study

Nottingham University Hospitals NHS
NHS Trust

Centre Number:
Study Number:
Patient Identification Number for this trial:

CONSENT FORM

Title of Project: **Physical activity level as an outcome measure for use in cancer trials: a feasibility study.**

Chief Investigator: **Dr Andrew Wilcock (Reader/Consultant in Palliative Medicine and Oncology)**

The patient should complete the whole of this sheet himself/herself.

Please initial box

1. I confirm that I have read and understood the patient information sheet version 1.2 dated February 2007 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that anonymised quotes taken during the course of this research may be used in the publication of this research ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals or the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I agree to my GP being informed of my participation in the study. ☐
6. I agree to take part in the above study. ☐

Name of patient	Date	Signature
Name of Person taking consent (If different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

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2.3 Research ethics committee approval letters

2.3.1 Exercise preferences study

Nottingham Research Ethics Committee 1
1 Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 0115 9123344 ext 68575
Facsimile: 0115 9123300

6th September 2007

Dr Andrew Wilcock
Macmillan Reader in Palliative Medicine and Medical Oncology
The University of Nottingham
Hayward House Macmillan Specialist Palliative Cancer Care Unit
Nottingham University Hospitals NHS Trust
Nottingham
NG5 1PB

Dear Dr Wilcock

Full title of study: **Physical activity as a therapy for people with incurable cancer: the how, where and when?**
REC reference number: **07/H0403/116**

Thank you for your letter of 20th August 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Committee held on 7th August 2007. A list of the members who were present at the meeting is attached.

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.

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA. There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

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

Document	*Version*	*Date*
Application		17 July 2007
Investigator CV		01 July 2007
Protocol	1.1	01 July 2007
Letter from Sponsor		13 July 2007
Statistician Comments		10 July 2007
Questionnaire: Exercise Questionnaire	1.1	01 July 2007
Letter of invitation to participant	1.1	01 June 2007
Participant Information Sheet	1.2	20 August 2007
Participant Consent Form	1.2	20 August 2007
Response to Request for Further Information		20 August 2007
Letter from Funding Organisation		16 May 2007
Programme parameters	1.1	01 July 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nresform.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

07/H0403/116: Please quote this number on all correspondence

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

Yours sincerely

Dr K Pointon/Ms L Ellis
Chair/Coordinator

Email: linda.ellis@nottinghamshirecounty-tpct.nhs.uk

Enclosures: Standard approval conditions

Copy to: Mr P Cartledge

R&D office for NHS care organisation at lead site - NUH

2.3.2 Neuromuscular electrical stimulation study

North Nottinghamshire Local Research Ethics Committee
1 Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 0115 9123344 ext 49368
Facsimile: 0115 9123300

19 September 2005

Dr Andrew Wilcock
Reader/Honorary Consultant in Palliative Medicine and Medical Oncology
University of Nottingham/Nottingham City Hospital NHS Trust
Department of Oncology
Nottingham City Hospital NHS Trust
Nottingham
NG5 1PB

Dear Dr Wilcock

Full title of study: **Does neuromuscular electrical stimulation of the proximal leg muscles improve leg muscle endurance, exercise endurance and activity levels in people with lung cancer?**

REC reference number: **05/Q2402/62**

Thank you for your letter of 30 August 2005, 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.

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.

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

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

Document	*Version*	*Date*
Application		16 June 2005
Investigator CV		
Protocol	1	16 June 2005
Summary/Synopsis Protocol Flowchart	1	16 June 2005
Letter from Sponsor		26 January 2005
Questionnaire EORT QLQ-C30		
Advertisement Poster	1	16 June 2005
Letter of invitation to participant	1	16 June 2005

Participant Information Sheet	1.2	31 August 2005
Participant Consent Form	1.2	31 August 2005
Response to Request for Further Information		30 August 2005
Instructions for walking and strength tests	1	16 June 2005
GP Recruitment letter	1	16 June 2005
GP confirmation of participation letter	1	16 June 2005
Proforma for Shuttle Walking Tests and Cybex Machine Measurements	1	16 June 2005
Cybex Machine Test Sheet	1	16 June 2005
Incremental Shuttle Test Walking Test Scoring Sheet	1	16 June 2005
Endurance Shuttle Test Scoring Sheet	1	16 June 2005
ActivPal Monitor Information Sheet	1	16 June 2005
Patient Diary Card	1	16 June 2005
Evaluation Form	1	16 June 2005
Confirmation letter (time of meeting)	1	16 June 2005
EORTC QLQ-C30 User's Agreement		09 October 2003

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Notification of other bodies

The Committee Administrator will notify the research sponsor and the R&D Department for NHS care organisation(s) that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/Q2402/62	**Please quote this number on all correspondence**

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

Yours sincerely

P. Walsh

pp **Dr David Walsh**
Chair

Enclosures:

Standard approval conditions
Site approval form (SF1)

cc Research Sponsor
Trusts R & D - Nottingham City Hospital
- QMC
- Broxtowe/Hucknall PCT
- Derbyshire RI

SF1 list of approved sites

North Nottinghamshire Local Research Ethics Committee

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	05/Q2402/62	**Issue number:**	1	**Date of issue:**	19 September 2005
Chief Investigator:	Dr Andrew Wilcock				
Full title of study:	Does neuromuscular electrical stimulation of the proximal leg muscles improve leg muscle endurance, exercise endurance and activity levels in people with lung cancer?				

This study was given a favourable ethical opinion by North Nottinghamshire Local Research Ethics Committee on 10 September 2005. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* [1]
Dr Joanna Hocknell	Consultant Palliative Medicine	Nightingale Macmillan Unit Derbyshire Royal Infirmary London Road Derby DE1 2QS	Derbyshire Research Ethics Committee	19/09/2005	

Miss Ruth Creed	Community Macmillan Nurse	Broxtowe & Hucknall PCT Curtis Street Hucknall Nottingham NG15 5JE	Nottingham Research Ethics Committee 2	19/09/2005	
Dr Andrew Wilcock	Reader in Palliative Medicine and Medical Oncology/Honorary Consultant	Nottingham City Hospital	Nottingham Research Ethics Committee 2	19/09/2005	
Dr Vincent Crosby	Consultant in Palliative Medicine	Queens Medical Centre	Nottingham Research Ethics Committee 2	19/09/2005	

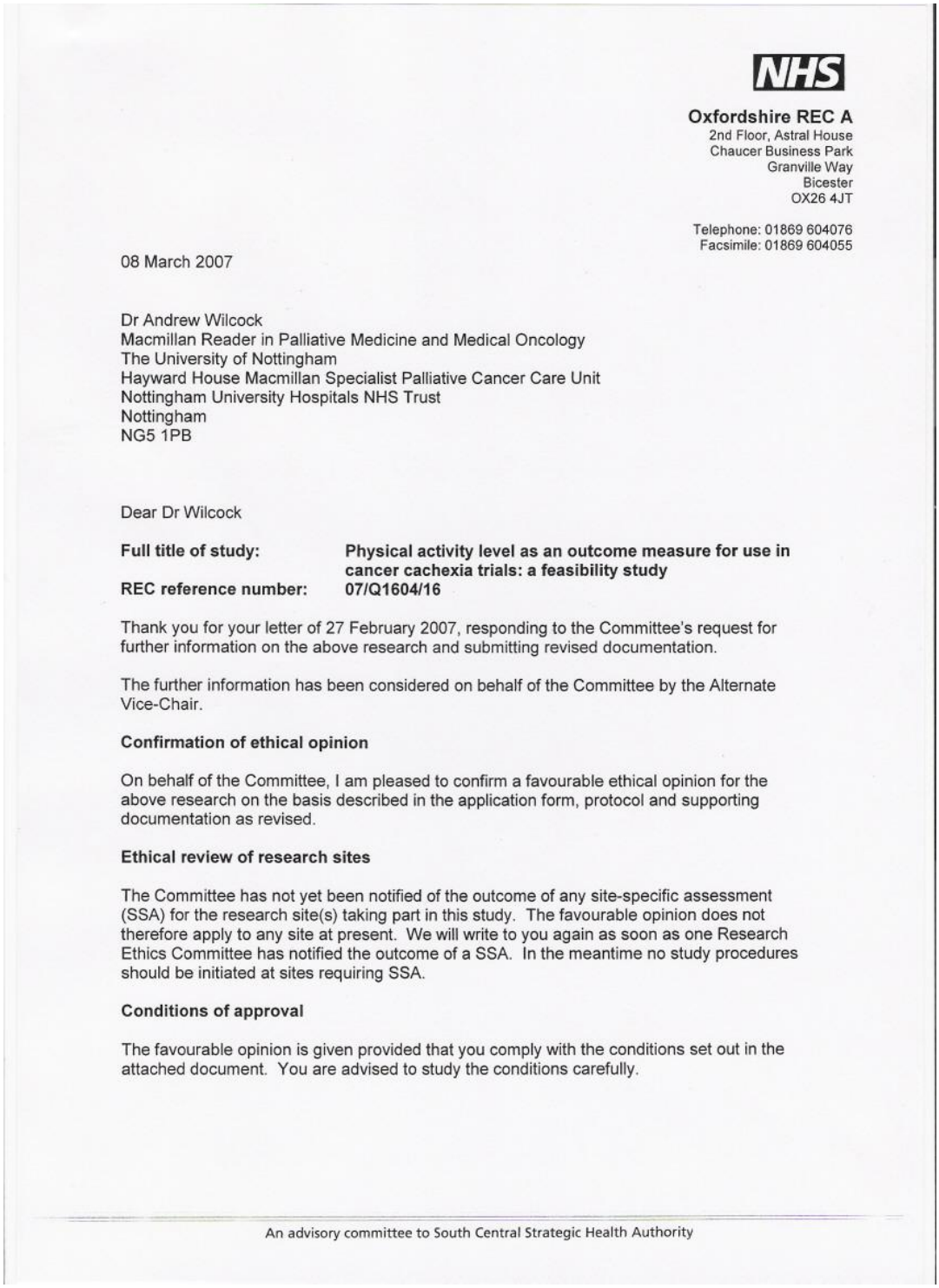
Approved by the Chair on behalf of the REC:

P. Wheat ..... (Signature of ~~Chair~~/Administrator)
(delete as applicable)

TRISH WHEAT ..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

2.3.3 Physical activity level study



NHS

Oxfordshire REC A
2nd Floor, Astral House
Chaucer Business Park
Granville Way
Bicester
OX26 4JT

Telephone: 01869 604076
Facsimile: 01869 604055

08 March 2007

Dr Andrew Wilcock
Macmillan Reader in Palliative Medicine and Medical Oncology
The University of Nottingham
Hayward House Macmillan Specialist Palliative Cancer Care Unit
Nottingham University Hospitals NHS Trust
Nottingham
NG5 1PB

Dear Dr Wilcock

Full title of study: **Physical activity level as an outcome measure for use in cancer cachexia trials: a feasibility study**
REC reference number: **07/Q1604/16**

Thank you for your letter of 27 February 2007, 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 Alternate Vice-Chair.

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.

Ethical review of research sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

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

Document	*Version*	*Date*
Application		04 January 2007
Investigator CV	Andrew Wilcock	01 January 2007
Protocol	1.1	01 December 2006
Covering Letter		05 January 2007
Summary/Synopsis	1.1 (Flowchart)	01 December 2006
Letter from Sponsor	University of Nottingham	04 January 2007
Peer Review	From Funder	13 November 2006
Statistician Comments	Paul Silcocks	04 December 2006
GP/Consultant Information Sheets	1.2	01 February 2007
Participant Information Sheet	1.2	01 February 2007
Participant Consent Form	1.2	01 February 2007
Response to Request for Further Information		27 February 2007
Initial Invitation Letter / Reply Slip	1.1	01 February 2007
Follow-up Invitation Letter	1.2	01 February 2007
Indemnity	PAL technologies	13 December 2006

R&D approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final approval from the R&D office for the relevant NHS care organisation.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

07/Q1604/16 **Please quote this number on all correspondence**

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

Yours sincerely

Sara Owen
Alternate Vice Chair

Email: m.ethicscommittee@nhs.net

Enclosures: *Standard approval conditions SL-AC2*
Site approval form
Copy to: The University of Nottingham

Oxfordshire REC A
2nd Floor, Astral House
Chaucer Business Park
Granville Way
Bicester
OX26 4JT

Telephone: 01869 604 062
Facsimile: 01869 604 055
Email: scsha.OxfordRECA@nhs.net

05 October 2007

Dr Andrew Wilcock
Macmillan Reader in Palliative Medicine and Medical Oncology
The University of Nottingham
Hayward House Macmillan Specialist Palliative Cancer Care Unit
Nottingham University Hospitals NHS Trust
Nottingham
NG5 1PB

Dear Dr Wilcock

Full title of study: **Physical activity level as an outcome measure for use in cancer cachexia trials: a feasibility study**
REC reference number: **07/Q1604/16**

The REC gave a favourable ethical opinion to this study on 05 March 2007.

Further notification(s) have been received from local site assessor(s) following site-specific assessment. On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s). I attach an updated version of the site approval form, listing all sites with a favourable ethical opinion to conduct the research.

R&D approval

The Chief Investigator or sponsor should inform the local Principal Investigator at each site of the favourable opinion by sending a copy of this letter and the attached form. The research should not commence at any NHS site until approval from the R&D office for the relevant NHS care organisation has been confirmed.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

07/Q1604/16	**Please quote this number on all correspondence**

Yours sincerely

MBrasseur

Muriel Brasseur
Assistant Co-ordinator

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England.

Oxfordshire REC A

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	07/Q1604/16	**Issue number:**	6	**Date of issue:**	05 October 2007
Chief Investigator:	Dr Andrew Wilcock				
Full title of study:	Physical activity level as an outcome measure for use in cancer cachexia trials: a feasibility study				

This study was given a favourable ethical opinion by Oxfordshire REC A on 05 March 2007. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* [1]
Dr Richard Wilson		Belfast City Hospital	Belfast City Hospital	13/09/2007	
Mr Colin Johnson	Reader in Surgery, Honorary Consultant Surgeon	Southampton University Hospitals NHS Trust	Southampton & South West Hampshire LREC (B)	04/09/2007	
Dr Andrew Wilcock	Macmillan Reader in Palliative Medicine and Medical Oncology	NUH Nottingham University Hospitals NHS Trust Nottingham	Nottingham Research Ethics Committee 2	22/05/2007	
Dr Patrick Stone	Senior Lecturer and Honarary Consultant in Palliative Medicine	St George's Hospital NHS Trust	Wandsworth Research Ethics Committee	03/05/2007	
Dr Anthony Byrne	**Marie Curie consultant in Palliative Medicine**	**Velindre NHS Trust**	**South East Wales Research Ethics Committee - Panel D**	**05/10/2007**	

Dr Anthony Byrne	**Marie Curie Consultant in Palliative Medicine**	**Cardiff and Vale NHS Trust**	**South East Wales Research Ethics Committee - Panel D**	**05/10/2007**	

Approved by the Chair on behalf of the REC:

M Brasseur ..... (Signature of ~~Chair~~/Co-ordinator)

(delete as applicable)

Maria Brasseur ..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*