COMBINED AEROBIC AND RESISTANCE EXERCISE TRAINING INTERVENTION PROGRAMME (CARP)

FOR LYMPHOMA SURVIVORS FOLLOWING THERAPY

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ABSTRACT

There is abundant evidence supporting the health benefits physical activity in cancer survival. Exercise *per se* is associated with positive physical and psychosocial benefits for survivors of solid tumours. There are limited available research data on blood borne cancers. Lymphoma is one such haematological cancer where survivors often experience decrements in psychosocial, physical functioning and quality of life (QoL) domains. A minority (~25%) of lymphoma survivors meet the recommended public guidelines for exercise. Further to this, the work of Bellizzi and colleagues (2009) indicates that QoL decrements often persist for years following treatment. Conventional wisdom dictates that exercise is likely to be an effective means of alleviating some adverse outcomes from blood borne cancers but this hypothesis is largely untested to date. Further to this, the theory of planned behaviour (TPB) has been shown to provide effectual model for predicting exercise behaviour amongst cancer survivors but known to differ by tumour type. Therefore, the aims of the present thesis were to determine the effects of 12-weeks of a combined aerobic and resistance training programme (CARP) on QoL and health related outcomes in Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL) survivors. The thesis focused specifically on four main aims;

Aim 1 — the primary aim was to identify whether a 12-week CARP is effective at improving QoL in HL and NHL survivors.

Secondary Aims were to;

Aim 2 — to determine whether a 12-week CARP is effective at improving standard measures of muscle function and cardio-respiratory fitness in HL and NHL survivors.

Aim 3 — to examine whether a 12-week CARP affects inflammatory environment and/or immune function in HL and NHL survivors.

Aim 4 — to identify whether theory of planned behaviour (TPB) may be an effectual model to predict exercise intention in HL and NHL survivors.

In realising these aims, a parallel group randomised control exercise trial (RCT) was conducted with two components. Forty-one (n=41) HL and NHL survivors completed the trial at St George's hospital, London. Participants, who had completed chemotherapy or radiation treatment (<6 months), were stratified according to tumour type and randomly assigned to either control (CON; n=21) or intervention (INT; n=20). The intervention consisted of a combination of 12-weeks supervised aerobic and resistance training (CARP) whilst the control group received usual care. The first component consisted of three measurement phases; baseline (T0; n=41), post-intervention (T1; n=41) for all measurements, and 12 months follow-up (T2; n=15) for qualitative measures. A

representative sample (n=6) from the intervention group took part in a focus group to explore participant perception of the impact of the CARP.

QoL was assessed using the previously validated European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-30) questionnaire. Secondary outcome measures consisted of health-related quality of life (HRQoL) determined by Functional Assessment of Cancer Therapy in Lymphoma (FACT-Lym); Mood disturbance and fatigue were determined using Profile of Mood States (POMS) questionnaire; anxiety and depression were determined using Hospital Anxiety and Depression scale (HADS). Participant cardiorespiratory fitness was assessed using the Balke-ware treadmill test, muscle function assessed by grip strength and muscle endurance tests. Blood was sampled using the standard venepuncture method followed by radioimmunoassay to determine interleukin 6 (IL-6) and c-reactive protein (CRP) concentrations. In order to identify determinants of exercise intention and behaviour in HL and NHL survivors, a second component to the trial utilised a validated TPB questionnaire, assessed at baseline (T0; n=41), and post-intervention (T1; n=41). Data were analysed using SPSS version 18.0 using appropriate statistical functions. Statistical significance was set at $p<0.05$. Data are presented as means ± standard deviations (S.D.).

Results demonstrate that study adherence between T0 and T1 was 87.2% (41/47) with a large accession rates at 12 months follow up (15/41). Linear mixed models analysis was used to examine subjectively reported outcomes. Clinically relevant improvements in QoL were achieved in both groups at T1. HRQoL, a domain of QoL, increased with exercise; the improvements were both clinically relevant and statistically significant. Subscales of QoL and HRQoL that significantly improved with exercise are social function ($p=0.020$), emotional well-being ($p=0.029$), and functional well-being ($p=0.025$), as well as functional lymphoma specific concerns ($p=0.034$). Mood disturbance was unchanged in either group, physical function improved only in the control group ($p=0.049$). Both groups showed improved ($p<0.05$) physical well-being, vigour, reduced fatigue, and increase in subjectively reported amount of physical activity (IPAQ) as time passed from the end of treatment. At follow-up, HRQoL, lymphoma concerns, fatigue, and the trial outcome index significantly improved in both groups ($p<0.05$) from baseline; anxiety significantly increased in the intervention and anxiety, physical well-being, and functional well-being improved in the control group. Both groups reduced physical activity at follow-up.

Predicted aerobic capacity showed a trend towards an increase, whereas resting heart rate ($p=0.041$) abdominal muscle endurance ($p=0.018$) significantly improved in the INT group with a concomitant trend for a decrease in the CON group. However, this did not reach a level of significance. Although both groups experienced worsening of pulmonary function post intervention, this only reached a level of significance in the INT group. No significant changes in

either IL-6 or CRP were observed during the study. ANOVA and MANOVA were used to analyse physical outcomes.

Regression analysis was used to determine the predictive value of the TPB variables upon intention to exercise, and TPB variables and intention upon actual behaviour. Simultaneous Multiple Regressions were used first to determine the equation for each model. Stepwise Multiple Regressions were used to examine the impact of each variable on the dependent variable to find the best model of prediction. At baseline (both INT and CON groups collapsed to one) the model predicts intention (68.6%), but prediction of variation in actual behaviour is low (36.2%); self-efficacy (β=0.495) and social support (β=0.469) predict intention to exercise among lymphoma survivors and self-efficacy (β=0.609) alone predicts actual behaviour at T0. At T1, the model predicts 77.0% of the variation in intention amongst the CON group but only 14.7% of actual behaviour; attitude (β=0.864) predicted intention to behave. Amongst the exercising group, the model predicts 61.5% of the variation in intention, but only 19.2% of actual behaviour; social support (β=0.800) predicts intention to exercise. None of the determinants significantly predicted actual behaviour at T1.

The current thesis presents the first data in examination of the impact of a CARP amongst post-treatment lymphoma survivors. The exercise training intervention significantly improved HRQoL and psychosocial well-being. This is noteworthy as lymphoma survivors are often burdened with reduced HRQoL and psychosocial morbidity. Although predicted aerobic fitness levels were statistically unchanged in INT following the intervention, the trend towards an improvement indicates that either an increase in exercise programme length or intensity of exercise sessions may achieve statistical improvement in future studies.

The findings from this thesis indicate CARP to be effective in improving psychosocial outcomes in lymphoma survivors. At 12-month follow-up, reduced physical activity was associated with increased anxiety; functional and physical well-being did not improve despite increases seen in CON. Thus, future research should aim to increase long-term exercise behaviour in hopes to maintain the positive effects seen with exercise. Such interventions should focus on social support and self-efficacy as a means to encourage intention to exercise. Behaviour techniques should be designed to enhance self-efficacy and social support when devising an exercise programme for lymphoma survivors. Further to this, CARP is well tolerated and demonstrates high levels of adherence in HL and NHL survivors. However, the same participants display large accession rates in the 12 months following completion of the intervention. Results at 12 months follow up should cautiously owing to the risk of bias, particularly performance, detection, and attrition bias. As such, methods of promoting exercise adherence in the months following completion of an exercise intervention may be particularly important in HL and NHL survivors.

PEER REVIEWED PUBLICATION ARISING FROM THIS THESIS

In the course of this thesis, a summary of Chapter 2 was prepared and published in *Open Access Cancer* (https://www.oapublishinglondon.com/article/544). The idea for the manuscript was initially conceptualised by Professor A. Jewell. Mrs. Daroux-Cole was subsequently responsible for completing the submission under the guidance of Professor A. Jewell and Dr. R. Pettengell.

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LIST OF ABBREVIATIONS, SYMBOLS, and NOMENCLATURE

ABVD	Adriamycin, Bleomycin, Vinblastine and Dacarbazine
ACSM	American College of Sports Medicine
ADL	Activities of Daily Living
AH	Attitude
BPM	Beats per Minute
CARP	Combined Aerobic and Resistance Exercise Training Intervention Programme
CF	Cognitive Function
CPAFLA	Canadian Physical Activity, Fitness and Lifestyle Appraisal
CRF	Cancer-Related Fatigue
CSEP	Canadian Society of Exercise Physiology
CV	Cardiovascular
ECOG	Eastern Cooperative Oncology Group
EF	Emotional Function
EORTC-QLQ-30	European Organisation for Research and Treatment of Cancer - Quality of Life
EWB	Emotional Well-being
FACIT	Functional Assessment of Chronic Illness Therapy - Measurement System
FACT-Lym	Functional Assessment of Chronic Illness Therapy - Lymphoma
FEV1	Forced Exploratory Volume in 1 second
FITT	Frequency, Intensity, Time, Type
FVC	Forced Vital Capacity
FWB	Functional Well-being
HADS	Hospital Anxiety & Depression Scale
HL	Hodgkin's Lymphoma
HRQoL	Health-Related Quality of Life
IPAQ	International Physical Activity Questionnaire
LymS	Lymphoma related symptoms/concerns
MCID	Minimal Clinical Important Difference
MHR	Maximum Heart Rate
MID	Minimal Important Difference
MSE	Muscular Strength and Endurance
NHL	Non-Hodgkin's Lymphoma
PBC	Perceived behavioral control

PF	Physical Function
POMS	Profile of Mood States
PWB	Physical Well-being
QoL	Quality of Life
RCT	Randomized Controlled Trial
REC	Research Ethics Committee
RF	Role Function
RHR	Resting Heart Rate
RPE	Rating of Perceived Exertion
SCT	Social cognitive theory
SET	Self efficacy theory
SF	Social Function
SN	Subjective norm
SWB	Social Well-being
TPB	Theory of Planned Behaviour
TRA	Theory of reasoned action
WB	Well-being

Chapter 1.
INTRODUCTION

There is considerable evidence that physical activity can have a significantly positive impact in a person's psychological well-being, physical health, and overall quality of life (QoL) (Lox *et al.,* 2010). Systematic reviews have shown that exercise can be effective in improving physical and psychosocial outcomes in cancer survivors (Courneya, 2003; Knols *et al.,* 2005; Galvao & Newton, 2005). However, studies in this field have mainly focused on breast and prostate cancer (Winters-Stone *et al.,* 2013). There is limited available information on haematologically derived cancers.

Lymphomas are haematological cancers that develop in the lymph nodes and tissues of the body's immune system (Roman and Smith, 2011). Following a bimodal age distribution primarily affecting young adults (with Hodgkin's lymphoma) and older adults (with Hodgkin's lymphoma and non-Hodgkin's lymphoma), both Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL) accounts for approximately 5% of newly diagnosed cancers (Roman & Smith, 2011). The advent of monoclonal antibody therapy, which directly target molecules on the cell surface of NHL cells, has been a significant clinical advance in lymphoma treatment (Weiner, 2007). As a result, lymphomas are one of the most curable of all non-cutaneous malignancies (CanceresearchUK, 2012). In these circumstances, effective therapy for lymphoma survivors should involve measures to assist long term coping in addition to treatment of the disease.

Commonly cited side and late-effects of lymphoma and lymphoma treatment cause reduced psychological and physical functioning (Bellizzi *et al.,* 2009; Reeve *et al.,* 2009), leading to lower QoL scores. This is of Particular significance to lymphoma as lymphoma survivors score remarkably low on QoL scales (Stein *et al.,* 2008), often lower than other cancer types (Ahles *et al.,* 2005). Reduced QoL often persists years post-treatment (Bellizzi *et al.,* 2009). Importantly, QoL may even deteriorate with time (Mols *et al.,* 2007; Smith *et al.,* 2013), post treatment. Recent literature shows that QoL scores can be dramatically affected by physical activity (Ferrer *et al.,* 2011). The current thesis hypothesises that methods of improving physical activity levels in lymphoma survivors will produce concomitantly improved subjective QoL scores. It also examines psychological indices of fatigue and mood disturbance which affect QoL; the primary outcome in the current thesis.

Lymphoma survivors regularly present with significant declines in physical function (Reeve *et al.,* 2009), particularly loss of musculo-skeletal function (Lee *et al.,* 2003), and increased cardiopulmonary toxicity (Czuczman *et al.,* 2010; Roper *et al.,* 2009). Reduced PF and subsequent loss (or sense of loss) of independence is further associated with low QoL scores (Khimani *et al.,* 2012). Health-related quality of life (HRQoL), a sub-component of QoL that examines satisfaction with health and health-related activities (Center for Disease Control and Prevention, 2000) is particularly low in lymphoma survivors (Mishra *et al.,* 2012); it is expected that these will be improved as a result of improved PF.

Exercise may be one effective method for preventing and/or treating the side effects of treatment amongst solid tumour survivors (Courneya, 2003; Knols *et al.,* 2005; Galvao & Newton, 2005; McNeely *et al.,* 2006; Schmitz *et al.,* 2005). Exercise has been widely shown to improve self-reported QoL and provides various physical and psychosocial benefits, while positively impacting rate of recurrence and overall survival (Courneya *et al.,* 2003; Meyerhardt *et al.,* 2006; Belizzi *et al.,* 2009; Elter *et al.,* 2009). At a recent American College of Sports Medicine (ACSM) roundtable it was suggested that *exercise* training is safe during and after *cancer* treatments and may result in improved PF, QoL, and *cancer*-related fatigue (CRF) in many *cancer* survivor groups (Schmitz *et al.,* 2010). However, the majority of evidence supporting these conclusions were primarily from breast and prostate cancer studies (Winters-Stone *et al.,* 2013). Recent literature highlights the importance of examining the impact of exercise by tumour type independently rather than extrapolating from findings from other tumour types (Winters-Stone *et al.,* 2013; Vallance *et al.,* 2013), as treatment, side effects, and the tumours themselves differ.

Currently, there is considerably little available literature that centres on the impact of physical exercise interventions in lymphoma cancers. Indeed, at the time of writing this thesis, approximately 75-79% of lymphoma survivors are not achieving the government guidelines for maintaining or improving cardiovascular health and are further failing to return to pre-disease level of physical activity and functioning (Vallance *et al.,* 2005). As such, lymphoma survivors are at an increased risk for the development of cardiovascular disease (Miller *et al.,* 2008), in addition to their already increased risk for treatment induced cardiotoxicity (Roper *et al*;(2009). A single high quality randomized controlled trial (RCT) has examined the impact of exercise on lymphoma survivors (Courneya *et al.,* 2009). Courneya and colleagues (2009) examined the impact of a 12 week supervised aerobic exercise programme and reported overall QoL and PF depression, happiness, fatigue, general health, cardiovascular fitness, and lean body mass improved amongst those receiving the exercise intervention. In addition, one small pilot study reported improved aerobic capacity, PF, and fatigue scores amongst HL survivors with CRF (Oldervoll *et al.,* 2003). A second small pilot study reported improved QoL scores after 12 weeks of mixed exercise, but little detail was given regarding the exercise programme, and only 6 participants took part in the intervention (Hayes *et al.,* 2004). The remainder of lymphoma specific exercise studies published prior to writing this thesis have focused on exercise behaviour (Vallance *et al.,* 2005; Habermann *et al.,* 2005; Oldervoll *et al*;. 2007;), and maximal physical capacity (Lee *et al.,* 2003; Eilb *et al.,* 2006); combined aerobic and resistance training remains unstudied, to date, in lymphoma.

Further, recent evidence shows that exercise may provide beneficial changes in inflammation (Kasapis & Thompson, 2005), and, possibly, immunity in cancer survivors (Ballard-Barbash *et al.,* 2012). Biomarkers that have recently been examined in exercise and immune function literature include Interleukin -6 (IL-6) and C-reactive protein (CRP). Interleukin 6 (IL-6) is commonly classified as a pro-inflammatory cytokine, but during exercise it decreases

inflammation by blocking the production of tumour necrosis factor alpha (TNF-α) (Starkie *et al.*, 2003, Petersen & Pedersen, 2006). IL-6 not only shows a unique response to exercise, but it is also a biomarker of interest because of the role of elevated IL-6 in lymphoma (Fayad *et al.*, 1998). C-reactive protein (CRP) has also been examined in recent exercise and cancer related research, although the effects of exercise remain inconsistent to date (Fairey *et al.*, 2005; Galvao *et al.*, 2009; Kohut *et al*; 2006; Ballard-Barbash *et al*; 2012). CRP is an acute phase protein that provides a convenient marker of global inflammation and infection and shows value as a prognostic marker in lymphoma (Legouffe *et al.*, 1998). The current thesis hypothesises that exercise- induced changes in QoL will be supported with concomitant improvement in biochemical markers of inflammation in lymphoma survivors.

The optimal exercise training modality for cancer survivors remains to be elucidated (Irwin, 2011; Winters-Stone *et al.*, 2013). In cancer survivors, aerobic exercise has provided favourable physical and psychosocial benefits particularly cardiopulmonary function (Courneya *et al.*, 2009), improved fatigue and QoL scores (McNeely *et al.*, 2006), and has produced mixed results with serum CRP (Kohut *et al*; 2006). Resistance training has been shown to provide improvements in both physical (muscle function, reduced muscle wasting, and improved body composition) (De Backer *et al.*, 2009; Segal *et al.*, 2009) and psychological indices, as well as significant improvements in QoL (Segal *et al.*, 2009), and reductions in CRP levels (Donges *et al.*, 2010). Since beginning the writing of this thesis, a handful of studies using combined aerobic and resistance training with cancer survivors have shown improvements in cardiovascular fitness and muscle strength without adverse effects (DeBacker *et al.*, 2009). The effects of combined exercise in lymphoma survivors remain unstudied to date. The present thesis hypothesises that a combined aerobic and resistance training intervention programme (CARP) will provide the benefits exhibited from both types of training.

While the current literature often refers to all patients as cancer survivors from diagnosis onwards, this trial makes a distinction between cancer patients and cancer survivors. For the purpose of this trial, 'cancer patients' will refer to patients on active treatment, and 'cancer survivors' will refer to survivors who have completed treatment. A person is considered a "cancer survivor" through the balance of his or her life, which highlights that the effects of cancer do not disappear when the cancer is in remission or potentially cured (Center for Disease Control and Prevention and the Lance Armstrong Foundation, 2004).

Further to the impact of CARP on QoL, immune function, and cardio-respiratory fitness amongst cancer survivors, the current thesis set out to examine whether the Theory of Planned Behaviour (TPB) may be an effectual model for predicting exercise behaviour amongst lymphoma survivors. Indeed, should the TPB be found to be an effectual model to predict exercise behaviour, these determinants of exercise may potentially be used to increase exercise adoption and adherence

amongst survivors of lymphoma, by providing insight into the appropriate behavioural techniques to use when devising an exercise programme. Recently, Michie and colleagues devised an outline of behavioural techniques to improve specific determinants of exercise (including the determinants examined using the TPB) (Michie *et al*; 2008). This is discussed further in Chapter 7 of the current thesis. The present thesis hypothesised that TBP would be an effective model for the prediction of exercise behaviour amongst lymphoma survivors.

With this information in mind, the present thesis set out to achieve outcomes respective to the following four aims;

> Primary Aim 1 Identify whether a 12-week combined aerobic and resistance exercise training programme (CARP) is effective at improving quality of life (QoL) in Hodgkin's and Non-Hodgkin's lymphoma survivors.
>
> Secondary Aims
>
> Aim 2 Determine whether a 12-week combined aerobic and resistance exercise training programme (CARP) is effective at improving standard measures of muscle function and cardio-respiratory fitness in Hodgkin's and Non-Hodgkin's lymphoma survivors.
>
> Aim 3 Examine whether a 12-week combined aerobic and resistance exercise training programme (CARP) affects inflammatory environment and/or immune function in Hodgkin's and Non-Hodgkin's lymphoma survivors.
>
> Aim 4 Examine whether Theory of Planned Behaviour (TPB) may be an effectual model to predict exercise behaviour in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Further to the four main aims of the thesis, an additional component was added. The objective of this auxiliary qualitative exploratory component was to further explore response to exercise, with the intention of gaining a greater understanding of how a convenient sample of participants perceived the CARP may have impacted their lives and what they perceived the benefits of this programme to be.

Additional exploratory outcomes were also assessed and reported. Tertiary exploratory outcomes include well-being and functional subscales of QoL (physical, emotional, social, and role function) and HRQoL (physical, emotional, social, functional well-being), symptoms of cancer (pain, insomnia, dyspnea, constipation, vomiting, nausea, appetite loss, and financial difficulty),

mood states including anxiety, depression, vigour, confusion, and anger. Body composition, blood pressure, body mass index and flexibility were also examined as tertiary outcomes.

HYPOTHESES

In addressing these thesis aims, the following hypotheses were tested;

Hypothesis 1 12-weeks of combined aerobic and resistance exercise training (CARP) will positively affect quality of life (QoL) and QoL subscales in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Hypothesis 2 12-weeks of combined aerobic and resistance exercise training (CARP) will produce measurable improvements in musculo-skeletal and cardiovascular fitness in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Hypothesis 3 12-weeks of combined aerobic and resistance exercise training (CARP) will demonstrate beneficial effects on the inflammatory environment and immune function in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Hypothesis 4 Theory of Planned Behaviour (TPB) will be an effectual model in the predication of exercise behaviour in Hodgkin's and Non-Hodgkin's lymphoma survivors.

SIGNIFICANCE

The current trial provides unique contributions to the exercise and cancer field of study. The benefits of exercise for lymphoma survivors are only beginning to emerge. If exercise is beneficial in improving QoL in this group who currently exhibit low QoL scores, then exercise can be promoted as an optional post-treatment care intervention for this cohort. If it is found that immune function improves with exercise, positive outcome non-pharmacological interventions may be promoted. A majority of previous studies in the exercise and cancer field have used either aerobic or resistance modes of exercise. The CARP utilizes both aerobic and resistive components so there is an argument for combining exercise modes for greater improvements from exercise.

New knowledge with respect to methods of maximizing the benefits of exercise in lymphoma survivors will be a significant addition to the small body of available literature. The intervention takes place during the transition period from the end of treatment into survivorship, thus providing new information regarding the usefulness of exercise during this time. Furthermore,

new information will be useful in the exercise industry for prescribing exercise regimens for cancer survivors, specifically, HL and NHL survivors. The current trial will potentially provide an opportunity to help lymphoma survivors improve QoL, while additional late effects of treatment pertaining to physical and immune function may be improved. In conjunction with previous literature as well as future research, exercise may offer health-care professionals an alternative to traditional means of dealing with negative long term and late treatment effects.

The following thesis is organised as follows:

Chapter 1 introduces the study and how it came about, as well as introduces the aims and hypotheses of the trial.

Chapter 2 provides a review of relevant literature to give the reader a thorough background of what is currently known in the field, and to highlight what is missing in the literature. The chapter begins with an overview of research examining exercise for cancer survivors which is intended to identify how exercise has been useful in reducing side effects of solid tumour or heterogeneous groups of cancer survivors. All available lymphoma specific exercise research is also presented to highlight what is currently known, and to highlight any gaps in the literature, along with an explanation of lymphoma and associated side effects. An introduction to the Theory of Planned Behaviour (TPB) is presented to provide the reader a view of how this theory has previously been used to predict behaviour and adherence in other cancer groups. Finally, a summary of cancer specific exercise prescription is provided to explain the rationale for the current intervention design. A short summary of this chapter was published in *Open Access Cancer.*

Chapter 3 provides a detailed description of the methodology followed for the randomised controlled trial (RCT). Study design, outcomes, data collection and analysis procedures are described following the CONSORT guidelines for parallel nonpharmacoligical trials. (Schultz *et al.,* 2010; Moher *et al.,* 2010; Boutron *et al.,* 2008).

Chapter 4 begins with a flow diagram for the RCT, followed by a description of the participants, by group (demographics table). Therefore, the results from the first three aims of the RC, the primary aim and outcomes associated with QoL, then psychological indices, followed lastly by physical variables and immune markers.

The TPB was given its own chapter. The methods followed for the TPB are in the methodology section, but the results along with a short discussion of the findings are presented in Chapter 5.

Chapter 6 describes an added component to the current study; the qualitative exploratory component. This chapter provides a brief introduction and description of methodology. Results and interpretation are combined, followed by a concise summary of findings.

The discussion, Chapter 7, summarises and integrates the research findings from the previous chapters, providing limitations of the current trial and future directions.

Finally, Chapter 8, the conclusion, provides a summary of the thesis and discusses broader implications of the findings. References and appendices follow.

Chapter 2.
LITERATURE SUMMARY

2.0 INTRODUCTION

This chapter reviews the available literature relating to the known effects and potential impact of exercise *per se* as an adjunct to improving quality of life in Hodgkin's (HL) and non-Hodgkin's lymphoma survivors. In order to rationalise the research objectives of the present thesis, this summary firstly reviews relevant exercise and cancer literature. There follows an outline of the main associated consequences of haematologically centred cancers, particularly lymphomas; there is a concomitant critique of relevant exercise and cancer literature, highlighting the known and the conceivable effects of exercise for lymphoma survivors. The Theory of Planned Behaviour (TPB) is explained, and its use in the cancer and exercise field is briefly reviewed. The current review explores the modes of exercise commonly used in cancer related studies and subsequently ascertains gaps in the current literature, paying particular attention to the effects of exercise on the main secondary medical effects particular to lymphoma survivors.

Sources of Information. The following databases were identified and searched from 1976 to March 2013: PsycINFO, PubMed Medline, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and SportsDiscus. The initial reporting of exercise for cancer in humans began in 1985 and therefore, the literature search date was set from this date. An exhaustive list of search terms were used relating to the topic of the current thesis, including: lymphoma, cancer survivors, exercise, quality of life, health-related quality of life, aerobic capacity, muscle function, endurance, inflammation, transition period, qualitative, theory of planned behaviour, exercise prescription, combined resistance and aerobic exercise.

Studies that met the following criteria were included in this literature review: (1) published as a full-text manuscript; (2) participants included adult cancer survivors; (3) included a measure of physical activity. This review included randomised controlled trials (RCTs), non-randomised control trials (NRCTs), and uncontrolled trials (UCTs) as well as relevant cross-sectional studies.

2.1 EXERCISE FOR CANCER SURVIVORS

Many pharmacological agents and psychosocial therapies are used to minimise the short and long term psychological effects of cancer treatment (Meyer and Mark, 1995), but reduced QoL and physical functioning prevalent in cancer survivors may be better addressed by exercise-based interventions which reportedly improve both physical and psychological outcomes (Courneya and Friedenreich, 1997; Vallance *et al.,* 2005). Exercise has recently become a popular supportive therapy for cancer survivors as research has shown positive effects within several cancer groups on various physical (Courneya *et al,* 2003; Segal *et al,* 2001; Belizzi *et al.,* 2009), and psychological outcomes (Courneya *et al* 2003, Segal *et al,* 2001, 2003; Holmes *et al.* 2005; Meyerhardt *et al.* 2006) and has been found to improve QoL scores (Knobf *et al.,* 2007; Burnham and Wilcox, 2002). Emerging observational and clinical data suggest the importance of physical activity in solid

tumour survivors and provide increasing evidence that exercise positively impacts major clinical endpoints such as rate of infection, rate of recurrence, and overall survival (Meyerhardt *et al.*, 2006; Holmes *et al.*, 2005; Elter *et al.*, 2009; Belizzi *et al.*, 2009).

After the current research study began in 2008, the first formal consensus suggesting the safety and usefulness of exercise for cancer survivors was produced by a panel of experts at an American College of Sports Medicine (ACSM) roundtable in 2010. They deduced from the current literature that exercise training improved physical functioning (PF), QoL, and cancer-related fatigue (CRF) in cancer survivors, and that it was safe to perform both during and after cancer treatment (Schmitz *et al.*, 2010). Although a plethora of research was considered in this decision, this field of research is saturated with breast and prostate cancer studies (Speck *et al.*, 2010; Galvao *et al.*, 2005). Authors reported that much of the literature informing the roundtable decision was from limited tumour types (Schmitz *et al.*, 2010). In the circumstances, caution should be exercised when applying these findings across all tumour types, as many different forms of cancer have not yet been examined in the current literature. Indeed, other researchers in this field have recognised that, because each type of cancer comes with its own unique symptoms, and treatment modalities differ between tumour types (let alone each individual tumour), examination of the impact of exercise by tumour type is needed (Winters-Stone *et al.*, 2013; Vallance *et al.*, 2013). A unique concern with haematological cancers, particularly lymphomas, for example, is that immunity is often compromised in these survivors both from intensive treatment but also the disease itself (Grulich *et al.*, 2007) as a result of Lymphomas targeting the lymphatic system and impairing immunity (Roman & Smith, 2011). At the time the current trial began, few studies had examined the impact of exercise in survivors of haematological cancers.

The limited research examining exercise for haematological cancer survivors has almost exclusively focused on ameliorating side effects of intensive treatment (Dimeo *et al.*, 1996). Medical treatment used in blood-borne cancers result in significant reductions in cardiorespiratory fitness and muscle strength and increased fatigue, all which impact daily functioning (Felder-Puig *et al.*, 2006). Low levels of physical activity observed in haematological cancer survivors further aggravate these effects (Hacker *et al.*, 2006).

At the time of commencing this thesis, six intervention-based haematological survivorship studies were published in this area, but none were of high methodological quality (Mello *et al.*, 2003; Oldervoll *et al.*, 2003; Hayes *et al.*, 2004; Carlson *et al.*, 2006; Dimeo *et al.*, 1996, Wilson *et al.*, 2005). The studies examined, walking and stretching (Mello *et al.*, 2003), combined exercise (Hayes *et al.*, 2004), and the remaining four employed aerobic exercise intervention (Oldervoll *et al.*, 2003; Carlson *et al.*, 2006; Dimeo *et al.*, 1996, Wilson *et al.*, 2005). Studies were all limited by sample size; ranging from 6 to 18 subjects randomized, some studies including solid tumour survivors in those samples. Strength improved with walking and stretching (Mello *et al.*, 2003),

aerobic capacity and strength with combined exercise (Hayes *et al.*, 2004). The remaining studies showed improvements in aerobic capacity, PF, and fatigue with aerobic activity (Oldervoll *et al.*, 2003; Carlson *et al.*, 2006; Dimeo *et al.*, 1996, Wilson *et al.*, 2005). Thus, with an insufficient number of studies in this area further investigation is needed, particularly randomized controlled trials (RCTs) with adequate sample size in order to evaluate benefits and risk of exercise in this immune-compromised population. Although cancer differs in each patient, there are more similarities within tumour types than in cancer as a whole, and treatments are often similar within tumour type (Vallance *et al.*, 2013). Thus, it may be beneficial to separate haematological cancers by tumour type as treatment and side effects may differ (Wolin *et al.*, 2010).

Exercise for lymphoma survivors has received little attention in the academic literature to date. Despite the debilitating side effects associated with treatment and significantly reduced QoL amongst survivors of lymphoma (Stein *et al.*, 2008). These are exacerbated by the low percentage (less than 25%) of lymphoma survivors performing even the minimum recommended amount of exercise for health benefits (Vallance *et al.*, 2006).

This highlights the lack of available information and requirement for haematological cancer focused exercise studies. The next section will indentify specifics of lymphoma and outline the potential for exercise in the treatment of associated side effects.

2.2 HAEMATOLOGICAL CANCERS

Haematological cancers are blood-borne and affect the production and function of blood cells (Smith *et al.*, 2011). In 2008, haematological malignancies comprised 7% of the 12.68 million cancer diagnoses estimated to have occurred around the world (GLOBOCAN 2008: Ferlay *et al.*, 2010). The International Classification of Diseases for Oncology (ICD-10) (www.who.int/classifications/icd/en/) classifies blood related cancers via the broad anatomy-based categories of non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), myeloma and leukaemia. NHL and HL make up approximately 74.9% of all haematological malignancies in the United Kingdom, and specifically target the lymphatic system thus impairing immunity (Horner *et al.*, 2009; Smith *et al.*, 2011). Hodgkin's lymphomas account for one-sixth of all lymphomas (Marcus *et al.*, 2007).

2.2.1 LYMPHOMAS

Lymphomas are a heterogeneous group of immune-based haematological malignancies whereby uncontrolled abnormal lymphocyte proliferation produces a mass of cells (tumour) which aggregate in lymphoid tissues (Roman and Smith, 2011). Lymphomas are divided into two categories: Hodgkin lymphoma (HL) is predominantly B cell in origin and is distinguished by the presence of Reed-Sternberg lymphoid cells (Roman and Smith, 2011) whereas non-Hodgkin

lymphoma (NHL) is derived from either abnormal B or T cells, and is classified into 30 subtypes (Roman and Smith, 2011).

Lymphoma incidence follows a bimodal age distribution primarily affecting young adults (HL) and older adults (HL and NHL). Incidence increases with age for NHL, and becomes markedly higher in males than females as age increases (Roman and Smith, 2011; Smith *et al.*, 2011), whereas HL incidence distribution peaks both in young adults (ages 15-34) and in seniors (aged 60+) (Marcus *et al.*, 2007; Roman and Smith, 2011) with a mean age for HL diagnosis is 38 years (Altekruse *et al.*, 2010).

Over the past two decades the incidence of lymphoma has plateaued and long-term survival from lymphoma has increased substantially during the past 30 years (Yung and Linch, 2003). NHL is the sixth most common cancer in the United Kingdom (Marcos-Gragera *et.al*, 2010) and has a 5 year survival rate of 61-66% in England which is among the highest of the most common cancers (Office for National Statistics, 2011). HL is now one of the most curable of all non-cutaneous malignancies with a 5-year relative survival rate of 83.3% in England; the third highest 5 year survival rate of the most common cancers (Office for National Statistics, 2011; Cancer Research UK, 2012). Younger patients have a very high survival rate of approximately 93%, whereas the average 5-year survival rate of survivors aged 70-79 years is unsurprisingly lower at approximately 46% (Office for National Statistics, 2011; Altekruse *et al.*, 2010).

Lymphomas are often treated with intense multi-agent chemotherapy regimens with or without radiation, and/or bone marrow/stem-cell transplantation (BMT/SCT) (Sehn & Connors, 2005). Treatment often results in debilitating long term side effects for the survivor which lead to reduced quality of life (QoL) (Bellizzi *et al.*, 2009; Jerkeman *et al.* 2001; Bellizzi *et al.* 2007; Demierre *et al.*, 2006), which may continue to worsen over subsequent years (Mols *et al.*, 2007; Smith *et al.*, 2013). Non-pharmacological strategies, such as exercise have been an underappreciated yet potentially effective method for improving QoL in lymphoma survivors.

Lymphoma was chosen for the present thesis due to increased number of survival years, severity of treatment-related side effects, a need for of non-pharmacological interventions post-treatment, lack of exercise-related research and finally the reduction in immune function specific to this cohort. Firstly, the number of lymphoma survivors is growing as detection and treatment modalities improve (Cramp & Daniel, 2008; Marcus *et al.*, 2007). The treatment modalities for lymphoma are intensive, arguably more so than many other tumour types, and cause a number of physical and psychosocial side effects that reduce QoL and functioning (Aleman *et al.*, 2003; De Bruin *et al.*, 2009; Hjermstad *et al.*, 2005). Treatment induced cardiopulmonary toxicities place lymphoma survivors at high risk for cardiovascular disease, while muscle-wasting resulting in loss of muscle strength lead to reduced physical function (Al-Majid and Waters, 2008). These, in

combination with the reportedly low levels of physical activity specifically reported amongst lymphoma survivors result in reduced QoL scores and likely increase risk for co-morbidities (Vallance *et al.,* 2005). From a medical perspective, QoL is associated with reduced illness; therefore improving QoL amongst those who have reportedly low QoL scores can reduce the burden on the healthcare system (Tengs, 2004). In addition to the lack of literature in this area, another reason to examine this particular tumour type is to offer non-pharmacological post-treatment care to help lymphoma survivors cope with the deleterious side effects of treatment. As the impact of exercise is not reported, it is worthwhile to explore whether exercise may be useful, as it has been found in solid tumours, in combating the many side effects of lymphoma. Finally, this population is often immune-compromised, which may remain for years after treatment ends (Dr Ruth Pettengell, personal communication, July 2012; Grulich *et al.,* 2007). Reduced immunity increases risk of co-morbidities (Miller *et al.,* 2008) and impairs QoL scores (Segerstrom *et al.,* 2003. This research addresses the long term and late effects of lymphoma-related treatment.

2.2.2 SUMMARY OF EXERCISE STUDIES FOR LYMPHOMA

The number of studies examining the impact of exercise on lymphoma patients and survivors is very limited, but has been increasing over the past few years. At the time the current trial began, only two small intervention based studies had examined the impact of exercise amongst lymphoma survivors alone (Oldervoll *et al.,* 2003). One pilot study examined the impact of a 20-week home based aerobic exercise programme for n=9 chronically fatigued (symptoms for 6 months or more) HL survivors as compared to a control group (n=15) of lymphoma survivors without fatigue (Oldervoll *et al.,* 2003), the other similarly small (n=12) study examined combined exercise amongst survivors of haematological malignancies (with few (4/12) lymphoma survivors) after having peripheral blood stem cell transplantation, (Hayes *et al.,* 2004). The aerobic intervention revealed improvements in fatigue, PF, and maximal aerobic capacity compared to baseline scores, but changes in aerobic capacity were not significantly different from the control group (Oldervoll *et al.,* 2003); whereas the combined intervention showed significant improvements in QoL scores and reported positive association between aerobic capacity and QoL (Hayes *et al.,* 2004). The studies differed in many ways, which may explain differences in results. The type of exercise, supervision of exercise (the aerobic programme was performed at home), characteristics of participants, and timing of the intervention (combined exercise was performed immediately after transplant whereas participants in the aerobic intervention ranged in time (0-10+ years) from end of treatment. Results from both studies should be taken with caution because of the low sample size. Adittionally, in the study by Oldervoll and colleagues (2003) the differences may be prevalent amongst participants as the range of years since treatment is so large, and also the control group did not suffer from chronic fatigue, so changes are not necessarily attributed to the exercise intervention alone, but may be due to differences between HL survivors with or without chronic fatigue.

Prior to the initiation of this thesis, all other studies that examined exercise in lymphoma patients and survivors had focused on exercise behaviour (Vallance *et al.*, 2005; Vallance *et al.*, 2006; Oldervoll *et al.*, 2007) and exercise capacity (Elbl *et al.*, 2006); none of which included an intervention. One cross-sectional study published after the current trial began also reported exercise behaviour in lymphoma survivors (Bellizzi *et al.*, 2009). From all the studies performed to date, it has been found that only 21-25% lymphoma survivors are meeting the American College of Sports Medicine (ACSM) recommended exercise guidelines for cancer survivors (a minimum of 150 minutes of moderate to vigorous exercise is recommended per week) (Vallance *et al.*, 2005; Bellizzi *et al.*, 2009), whereas 53% reported some activity (a weekly average of 60 minutes) and 20% reported no physical activity (Bellizzi *et al.*, 2009). Those meeting the ACSM exercise guidelines exhibited significantly higher scores in QoL and HRQoL (Vallance *et al.*, 2005), which is important for survivors of lymphoma as they experience lower QoL (Stein *et al.*, 2008) and physical HRQoL when compared to general population (Loge *et al.*, 1999).

Interestingly, Bellizzi and colleagues (2009) found a significant positive association between HRQoL of NHL survivors and at least *some* exercise (even exercise below the suggested health guidelines). This is very encouraging as seeing benefits from exercise at a lower threshold can improve exercise initiation and assist with adherence (they don't have to work as hard to experience positive results) (Lox *et al.*, 2010), as the guideline of 150 minutes per week may be daunting to some. Bellizzi and colleagues (2009) also found that as activity increased, decreases were seen amongst anxiety and depression scores and mental and physical health scores improved (in a dose-response pattern).

To date, only one high quality RCT has examined the impact of aerobic exercise training for lymphoma patients and survivors (Courneya *et al.*, 2009). Courneya and colleagues (2009) examined the impact of a 12-week supervised aerobic based exercise intervention on a number of psychological and physical measures; 122 lymphoma patients and survivors were stratified by disease type and treatment status (n=60 intervention, n=62 usual care control). In addition to their original publication, they continued to publish follow-up results from this study reporting predictors of exercise behaviour, exercise motivation, and adherence (Courneya *et al.*, 2011; Courneya *et al.*, 2012). In the original trial, both QoL and physical functioning significantly improved amongst the intervention group, and mean change scores were significantly better for the intervention group compared to the control group on cardiovascular fitness, lean body mass, percent body fat, fatigue, happiness, depression, and general health (Courneya *et al.*, 2009). The present thesis explores similar outcomes, but uses a different mode of exercise intervention (made up of two exercise components, aerobic and resistance training), a different means of instruction (exercise is performed one-to-one with the trainer), and examines survivors within six months from the end of treatment. In addition, this thesis examines inflammatory immune function as it would

be useful to know whether exercise can help improve immunity. To the author's knowledge, this is the first trial to explore lymphoma survivors' immunological response to exercise.

2.3 IMPACT OF REDUCED QUALITY OF LIFE (QoL)

QoL is a subjective evaluation of life satisfaction and overall sense of well-being, and describes the goodness of all the domains that make up one's life (Lox *et al.*, 2010; Courneya and Fredenrich, 1997b). Lymphoma is unique in that survivors experience differing symptom patterns that seem to have a profound negative impact on QoL (Stein *et al.*, 2008; Vallance *et al.*, 2005) which persists for months or even year's post-treatment (Bellizzi *et al.*, 2009; Jerkeman *et al.* 2001; Bellizzi *et al.* 2007; Demierre *et al.*, 2006). HL survivors reported low QoL which continues to worsen over subsequent years (Mols *et al.*, 2007). At 5 years post treatment 42% of NHL reported low or worsening QoL scores compared to 3-5 years earlier (Smith *et al.*, 2013). Low QoL scores have important implications for survivors. QoL is associated with ability to perform daily activities and many enhance capacity to return to pre-cancer lifestyle (Courneya *et al.*, 2000a). Reduced QoL is indicative of reduced satisfaction in well-being or function in one or more domains of one's life (Knobf *et al.*, 2007). Reduced QoL, particularly psychosocial factors, are associated with poorer survival in people with lymphoid cancers (Chida *et al.*, 2008).

2.3.1 EXERCISE AND QUALITY OF LIFE (QoL) IN CANCER SURVIVORS

Effectively designed exercise interventions have generally been found to have a positive effect on overall QoL and many of the QoL domains in cancer survivors (Keogh & MacLeod, 2012; Hayes *et al.*, 2012; Ferrer *et al.*, 2011; Knobf *et al.*, 2007), but most of the research to date is on solid tumours. Systematic reviews have reported significantly higher QoL scores amongst cancer survivors who exercise compared to those who did not (Conn *et al.*, 2006; Knolls *et al.*, 2005; Knobf *et al.*, 2007). Amongst those survivors who exercised, QoL scores were higher when compared to their baseline levels and these elevated scores remained at follow-up (Ferrer *et al.*, 2011). One systematic review reporting exercise to be a useful intervention for cancer patients and survivors (although only one study included in the review was specificially on lymphoma), suggests further research is needed to examine how the domains of QoL contribute to overall QoL scores.

At the start of the current trial, a majority of the studies examining the impact of exercise on QoL scores were aerobic-based and many examined primarily breast cancer (Knobf *et al.*, 2007) although, two studies reported improved QoL scores with combined aerobic and resistance training programme for breast cancer survivors (Herrero *et al.*, 2006; Milne *et al.*, 2008). One of these studies was a small controlled pilot study of only 16 subjects (8 per group) and the intervention was only 8 weeks long (Herrero *et al.*, 2006), whereas the other study was more robust, Milne and colleagues (2008) examined 58 breast cancer survivors (who had completed treatment in the past

two years) in a two-armed complete cross-over RCT where the intervention was 12-weeks in duration. Both studies reported significant improvements in QoL, although Milne and colleagues (2008) used the Functional Assessment of Cancer Therapy (FACT) questionnaire which provides an overall health-related QoL score (Webster *et al.*, 2003), whereas Herrero used the European Organization for Research and Treatment of Cancer (EORTC-QLQ-C30) questionnaire which provides an overall QoL score (Bjordal and Kassa, 1992). Although both studies lacked long term follow-up of QoL scores they do offer some promising information on the combined mode of exercise effective for the treatment of breast cancer and potentially other cancer types.

One cross sectional study of NHL survivors reported that those who met current public health exercise guidelines had significantly and meaningfully higher QoL scores than survivors who did not meet these guidelines (Vallance *et al.*, 2005). The authors of that study suggest that these findings need to be explored using an intervention based trial (Vallance *et al.*, 2005).The RCT conducted by Courneya and colleagues (2009) (mentioned previously) reported improved QoL in lymphoma survivors after an aerobic exercise intervention. It is not known whether other forms of exercise would impact QoL scores of lymphoma survivors.

Domains of QoL. The examination of domains of QoL will demonstrate how they contribute to overall QoL. Standard domains of QoL include physical, social, role, cognitive and emotional function (Lox *et al.*, 2010). Lymphoma survivors often experience problems with many of the functional QoL domains (Oerlemans *et al.*, 2011; Roper *et al.*, 2009). Reduced role functioning is prevalent; forty-one percent of NHL survivors reported ability and capacity to work is reduced; and amongst both NHL and HL, some had reported stopping work entirely (Mols *et al.*, 2007; Roper *et al.*, 2009). Physical function was reported as one of their lowest scores (Lee *et al.*, 2003) and an area of greatest concern for lymphoma survivors (Oerlemans *et al.*, 2011), which may be related to the cardiotoxic effects of medical treatment or other side effects, such as fatigue. Reduced social functioning is common of cancer survivor populations including lymphoma survivors (Luoma and Hakamies-Blomqvist, 2004; Stanton *et al*, 2005).

Research has shown that participant rated social (Alfano *et al.*, 2009), physical (Knobf *et al.*, 2007) and emotional function (Burnham and Wilcox, 2002) improves amongst cancer survivors who are physically active. Role function is reported to improve amongst exercising cancer patients receiving treatment (Adamsen *et al.*, 2003), but changes amongst survivors have not been reported. At the time of writing this review, the impact of exercise on the cognitive function amongst cancer survivors remains unreported despite demonstrating improvements amongst older adults (Colcombe & Kramer, 2003).

Only the domain of physical functioning has been found to improve amongst lymphoma survivors who took part in a 12-week aerobic exercise intervention (Courneya *et al.*, 2009).

Combined exercise has positively improved physical function of cancer patients on treatment (including haematological patients) (Adamsen *et al.*, 2003), but no known studies have reported functional improvements amongst lymphoma survivors (post treatment) taking part in a combined aerobic and resistance programme.

Measurement of QoL. Multiple instruments are available for assessing QoL but they reflect varying conceptualizations and therefore differ in what they measure (Mast, 1995; Haas, 1999). The domains of QoL (physical, social, role, cognitive and emotional aspects of life) are measured in terms of functional ability, while some scales examine these areas of life as dimensions of well-being (Haas, 1999). Two instruments often used in this field of research are the Functional Assessment of Cancer Therapy (FACT), which have well-being subscales, and the European Organization for Research and Treatment of Cancer quality of life scale (EORTC-QLQ-30) which includes both functional scales and physical symptom scales (Bjordal and Kassa, 1992). Previous literature suggests that the two questionnaires measure markedly different aspects of QoL (Kemmler *et al.*, 1999, Luckett *et al.*, 2011). The EORTC-QLQ-30 is relatively objective in its measure of function, whereas the FACIT is more reflective and focuses on thoughts and feelings (Luckett *et al.*, 2011). The FACIT is commonly used to measure HRQoL (Fong *et al.*, 2012), as it is reportedly more precise (lower standard error of the mean) in measuring HRQoL amongst cancer participants (Cella, 1997).

2.3.2 HEALTH-RELATED QUALITY OF LIFE (HRQoL)

Health-related quality of life (HRQoL) is a subcomponent of QoL that reflects ones satisfaction in emotional, physical, mental and social well-being as related to health and healthful activities (Center for Disease Control and Prevention, 2000). As it relates specifically to health related well-being, HRQoL is frequently measured in exercise-related research, and is a valuable source of information in terms of efficacy of treatment and related therapies in cancer groups (Efficace *et al.*, 2003; Dr. Nicole Culos-Reed personal communication, 2012). Although health is one of the domains of overall QoL other domains are also key components that add to the complexity of its measurement, whereas HRQoL specifically examines satisfaction with life from a health-related perspective (The WHOQoL Group, 1998).

Even years after treatment has ended, cancer survivors present with low HRQoL scores (Bellizzi *et al.*, 2009; Bellizzi *et al.* 2007; Demierre *et al.*, 2006). Lymphoma survivors exhibit lower HRQoL scores than disease-free adults (Loge *et al.*, 1999; Oerlemans *et al.*, 2013) and have a lower perception of their health status (Mols *et al.*, 2007), which is not surprising in that health is often defined as absence of disease.

HRQoL is largely impacted by physical well-being. Medical management of HL can cause cardiac and lung toxicity, infertility and various secondary malignancies in survivors (Roper *et al.*,

2009), which can affect HRQoL for many years after treatment (Fernsler and Fanuele, 1998). Amongst NHL survivors, chemotherapy was associated with reduced HRQoL (Oerlemans *et al.*, 2011). Lymphoma survivors reported particularly low HRQoL 'physical health' scores (Loge *et al.*, 1999), which may be due to the severe treatment modalities used to treat lymphoma and these associated physical late effects of treatment. It is hypothesised that a CARP will prevent reductions and/or improve physical functioning in lymphoma survivors.

2.3.3 EXERCISE AND HEALTH-RELATED QUALITY OF LIFE (HRQoL) IN CANCER SURVIVORS

A review of the impact of exercise interventions on HRQoL published in 2012 reported exercise may provide improvements in HRQoL and domains of emotional well-being (EWB), social function (SF), role function (RF), and physical function (PF) for cancer survivors (Mishra *et al.*, 2012). Due to the heterogeneity of interventions and the different instruments used to measure HRQoL and domains, future research is necessary to understand which type of cancers are most impacted by exercise (Mishra *et al.*, 2012). A recent study showed that exercise has been associated with improved HRQoL scores amongst lymphoma survivors with a significant dose-response pattern in which more exercise resulted in better mental and physical health (Bellizzi *et al.*, 2009). The cross-sectional study explored physical activity and HRQoL amongst NHL survivors and reported that improvements were seen amongst survivors who exercised, even when exercise was below the public health guidelines (Bellizzi *et al.*, 2009). A limitation of the study was that phsycial activity levels were subjectively measured, and therefore could be somewhat inaccurately reported. Details of the type of exercises performed were not provided, only intensity was reported. Although this recent research (published after this trial began) has suggested that exercise may be useful for improving HRQoL of lymphoma survivors (Bellizzi *et al.*, 2009), further examination using an intervention-based RCT would be useful to see how specific exercise modalities impact HRQoL and an objective measure of activity would provide more accuracy.

The subscales of HRQoL measured using the FACIT (Functional Assessment of Chronic Illness Therapy) guestionnaire include EWB, physical well-being (PWB), functional well-being (FWB) and social well-being (SWB). Exercise has been found to enhance SWB, PWB, FWB (Courneya, 2003), and EWB in cancer survivors (Knobf *et al.*, 2007; Fong *et al.*, 2012), although the majority of research has examined solid tumour cancer survivors and most studies have used aerobic exercise as the intervent ion. For example, the meta-analysis by Fong and colleagues was conducted using 34 RCTs of which 22 were breast cancer, and 22 were based on aerobic exercise whilst only 4 examined combined exercise programmes (Fong *et al.*, 2012).

2.4 OTHER SUBJECTIVE OUTCOME MEASUREMENTS THAT MAY IMPACT QoL

2.4.1 MOOD DISTURBANCE

Psychosocial morbidity is prevalent in a large proportion of adult HL survivors (Ford *et al.*, 2008; Smith *et al.*, 2009) and NHL survivors (Zabora *et al.*, 2001; Demierre *et al.*, 2006; Devlen, *et al.*, 1987; Smith *et al.*, 2009). Lymphoma can progress slowly and often patients undergo treatment on and off for many years, which can cause extensive psychological distress or mood disturbance (Courneya *et al.*, 2009; Deng & Cassileth, 2005). Fatigue and reduced PF can reduce mood state, which can decreas overall QoL (Pinto *et al.*, 2002; Chang *et al.*, 2008; Myers, 2012). Higher levels of mood disturbance are associated with higher occurrence of cancer-related symptoms and adverse effects (Lee *et al.*, 2004); a retrospective study showed that mood disturbance was positively correlated with adverse effects of treatment amongst lymphoma survivors (Devlen *et al.*, 1987), but this study is dated and is having participants recall mood and symptoms from approximately 3 years before. Therefore, new research is necessary to explore this relationship amongst lymphoma survivors.

Two measurable components of mood disturbance are anxiety and depression, both of which can impact overall QoL (Lox *et al.*, 2010). Anxiety is reported as a significant concern amongst lymphoma survivors (Thompson *et al.*, 2010; Roper *et al.*, 2009); symptoms were seen in 14.5% of lymphoma survivors (3% higher than the general population scores at the time the study was conducted) (Loge *et al.*, 1997). Depression is moderately associated with lymphoma; 8-19% of lymphoma survivors report experiencing depression (Massie, 2004). When compared to their siblings who had not had cancer, survivors of haematological malignancy (including HL) were 1.6 to 1.7 times more likely to report somatic distress and symptoms of depression (Zebrack *et al.*, 2002). This finding is especially interesting because siblings would have experienced, to some level, the effects of cancer, (even if only second hand), as cancer impacts the family as well as the patient. It is possible that these heightened symptoms of depression may be directly related to cancer and treatment, and not just the 'experience' of cancer.

2.4.2 EXERCISE AND MOOD DISTURBANCE IN CANCER SURVIVORS

Cancer survivors who exercise report decreased levels of mood disturbance, as seen both from quantitative (Segar *et al.*1998; Pinto *et al.*, 2002; Pinto & Trunzo, 2004; Mutrie *et al.*, 2012, Culos-Reed *et al.*, 2004), and qualitative research (Stevinson & Fox, 2006; Spence *et al.*, 2011). Research indicates that amongst cancer survivors, anxiety (anxiety symptoms) (Burnham and Wilcox, 2002; Schneider *et al.*, 2003; Blanchard, *et al.*, 2001; Mock *et al.*, 2001) and depression (depressive symptoms) (Brown *et al.*, 2011; Mutrie *et al.*, 2007; Midtgaard *et al.*, 2005) decrease with regular aerobic exercise, and thus positively impact QoL (Courneya *et al.*, 2000).

Although the majority of studies in the field show exercise improves depression scores, some studies show no change in depression scores (although no adverse effects) amongst exercising cancer survivors (Ohira *et al.*, 2006; Courneya *et al.*, 2007; Dimeo *et al.*, 2008).

Resistance training, on the other hand, has shown conflicting results with regards to anxiety. Anxiety scores have been found to increase (or stay the same) after vigorous resistance exercise (Raglin, *et al.,* 1993; Cassilhas *et al.,* 2007) whereas mild to moderate resistance training (i.e. 50% 1 repetition maximum) reduced anxiety scores (Focht *et al.,* 1999; Bartholomew & Linder, 1998). To date, no known study has reported significant changes in anxiety scores amongst cancer survivors after taking part in a combined aerobic and resistance interval training exercise programme.

In the only RCT examining the impact of aerobic exercise amongst lymphoma patients and survivors, depression significantly improved after taking part in an aerobic exercise intervention, whereas anxiety scores decreased amongst exercisers, but the improvements were not significantly different from the control group (Courneya *et al.,* 2009). A cross sectional study showed a dose response relationship between exercise and anxiety and depression scores of NHL survivors: the higher the amount of activity reported, the lower the anxiety and depression scores (Bellizzi *et al.,* 2009), but the actual amount of exercise performed was not specified, nor was type of exercise. As the reporting was subjective, it could be possible that external factors may have impacted participant responses. Without an objective measure of activity level or physical fitness, it is difficult to determine whether reduced anxiety and depression was related to exercise, or whether the survivor had a more positive outlook in general, thus raises the question as to whether physical activity had any impact. It is not known if the survivors with lower depression and anxiety scores were more motivated (experienced less barriers) to exercise, or if the exercise itself reduced the feelings of anxiety and depression.

Although the single RCT examining the impact of aerobic exercise showed improvement in depression and anxiety scores amongst people with lymphoma (Courneya *et al.,* 2009), it remains worthwhile to examine the impact of other modes of exercise amongst this population, as mood disturbance can negatively impact lymphoma survivors, reducing QoL scores.

2.4.3 FATIGUE

Fatigue, which can be both a symptom of cancer and side effect of treatment, is the most commonly reported cancer related complaint that remains well into survivorship (Prue *et al.,* 2006; Blaney *et al.,* 2010; Baker *et al.,* 2005). Fatigue is associated with reduced QoL scores (Mock *et al.,* 2001). A common and distressing problem for people with lymphoma (Ruffer *et al.,* 2003; Hjermstad *et al.,* 2005), fatigue is more prevalent amongst HL survivors than survivors of other cancer types (Hjermstad *et al.,* 2005; Loge *et al.,* 1999, Ruffer *et al.,* 2003) and is one of the most prevalent long-term functional complications for people with NHL (Oerlemans *et al.,* 2010). High levels of fatigue may result from the strenuous treatment used to treat lymphoma. Approximately 60% of NHL survivors had higher fatigue scores when compared to the general population;

approximately 50% report constant fatigue which may remain high up to 10 years after diagnosis (Oerlemans *et al.*, 2013; Ruffer *et al.*, 2003). Twenty to 30% of HL survivors reported that elevated fatigue lasting longer than 6 months did not subside over time (Loge *et al.*, 1999; Bloom *et al.*, 1993). Vallance and colleagues (2005) believe this fatigue may result, in part, from survivors not returning to pre-diagnosis levels of physical activity (Vallance, *et al.*, 2005).

2.4.4 EXERCISE AND FATIGUE IN CANCER SURVIVORS

In the past, patients and survivors experiencing fatigue were traditionally advised to avoid physical activity and exertion (MacVicar *et al.*, 1989) which likely aggravated their fatigue. It is now understood that exercise can help to reduce fatigue amongst cancer survivors (Dimeo *et al.*, 2004; Fairey *et al.*, 2005; Courneya *et al.*, 2007; Mock *et al.*, 2005); recent literature suggests that moderate intensity resistance exercise reduces fatigue (Brown *et al.*, 2011). A cross sectional descriptive study reported that fatigue may limit survivor's ability to improve their health behaviours, but if they can perform exercise they are likely to experience less fatigue (Alfano *et al.*, 2009). Although these findings are promising, it is important to note that data were collected via survey and it is possible that the subjective values are affected by participant interpretation.

A minority of the few available lymphoma studies have examined the relationship between exercise, lymphoma, and fatigue. A small pilot study examining the impact of a 20-week aerobic exercise programme reported significantly reduced fatigue scores amongst HL survivors with cancer-related fatigue (CRF) (Oldervoll *et al.*, 2003). In addition to the small sample size of only 9 participants performing the home based intervention, these findings are also specific to a group of individuals experiencing a very distressing level of fatigue above and beyond every day fatigue (CRF), thus participants would have a higher baseline of fatigue than other survivors, therefore generalising these findings to all lymphoma survivors is not advised.

The impact of resistance training on fatigue has only recently been examined in this field. It was recently reported that although both resistance and aerobic exercise reduced fatigue scores in the short term, resistance exercise generated longer term improvements in fatigue scores (as well as increased QoL and physical strength) amongst men with prostate cancer (Segal *et al.*, 2009). A newer meta-analysis examining the effects of exercise on fatigue scores reported that moderate intensity resistance training was most useful in reducing fatigue (Brown *et al.*, 2011). Subgroup analyses showed that amongst lymphoma survivors fatigue was not significantly impacted by exercise (Brown *et al.*, 2011), but the four studies included in the subgroup were quite diverse and one was considered to be of low methodological quality. Only one study included in the lymphoma subgroup, (Courneya's RCT), examined aerobic exercise (Courneya *et al.*, 2009). One study included in the subgroup was specific to patients undergoing treatment for multiple myeloma (Coleman *et al.*, 2003), another examined the effects of Tibetan yoga amongst lymphoma patients

(Cohen *et al.*, 2004), and the final study was specific to patients undergoing allogeneic stem cell transplant (Jarden *et al.*, 2009). As only one of the studies in this subgroup examined survivors, this sub group analysis does not provide a strong case either way for impact of exercise on fatigue amongst lymphoma survivors, therefore further examination is useful. As is apparent, very little research has been conducted on the impact of exercise on fatigue scores of lymphoma survivors; to date, no studies have examined the impact of a combined aerobic and resistance training programme on fatigue scores of lymphoma survivors.

2.5 OTHER OBJECTIVE MEASUREMENT OUTCOMES THAT MAY IMPACT QoL

QoL is impacted by psychological and physical health, thus QoL should ideally be supported with clinically relevant markers of physical function, including aerobic capacity, muscle function and static lung volumes. Lymphoma survivors present with significant physical late effects (Ng *et al.*,2011); when compared to other cancer survivors, NHL survivors had one of the largest declines in physical function (Reeve *et al.*, 2009), particularly loss of musculo-skeletal function (Lee *et al.*, 2003) and increased cardiopulmonary toxicity (Czuczman *et al.*, 2010; Roper *et al.*, 2009). Reduced physical functioning decreases independence and is associated with low QoL scores (Khimani *et al.*, 2012). Improvement in these physical outcomes makes it easier to perform daily activities (Demark-Wahnefried *et al.*, 2006), increasing independence and therefore should improve QoL scores. Therefore, cardiovascular fitness and muscle function are secondary outcomes to be examined in the current trial.

2.5.1 CARDIOPULMONARY FITNESS

Aerobic capacity, the maximal amount of physiologic work that an individual can do, is measured by oxygen consumption which can be expressed in terms of 'metabolic equivalent' (MET). One MET is equal to the resting metabolic rate obtained during quiet sitting which is equal to an approximate oxygen uptake of 3.5 ml/kg/min (Ainsworth *et al.*, 2000). Aerobic capacity is important for basal metabolic performance, and impacts the amount of energy we have to perform daily tasks; reduced aerobic capacity can make regular daily activities feel as intense as working at anaerobic threshold (Davis and Walsh, 2010). If aerobic capacity is low, the relative workload of activities of daily living (ADL) increases, which may contribute to fatigue and a decrease in overall QoL (Winningham 2001; Velthuis *et al.*2010; Dimeo *et al.* 1997).

When compared to their pre-morbid measures and to healthy adults, cancer survivors have significantly lower aerobic capacity and physical functioning (Burnham and Wilcox, 2002; Kolden *et al.*, 2002; Courneya and Freidenreich, 1999; Wiggins and Simonavice, 2010) and often experience musculoskeletal challenges (Stein, Syrjala, and Adroykowski, 2008), none of which are surprising when taking into consideration the severity of some cancer treatments.

Thirteen to 30% of HL and NHL survivors exhibit reduced aerobic capacity as shown in a decrease of maximal oxygen uptake (VO2max<20ml/kg min) (Adams *et al.*, 2004; Elbl *et al.*, 2006).Chemotherapy used to treat lymphoma can bring about late effects such as cardiopulmonary toxicities and increased risk for cardiovascular disease (Czuczman *et al.*, 2010; Roper *et al.*, 2009) which is the second leading cause of death amongst long term survivors of HL (Ng *et al.*, 2011). For example, anthracyclines and/ or mediastinal radiotherapy increases risk of mortality due to cardiac disease (Ng *et al.*, 2011); 47 of 48 disease-free HL survivors treated with chest radiotherapy revealed subclinical cardiac abnormalities (Hodgson *et al*, 2007).

Radiation therapy for lymphoma, depending on the site, may bring about late effects of lung damage (if radiation is to the chest). Similar to chemotherapy, radiation increases the risk of cardiovascular disease and secondary malignancies (usually 5 to 10 years after treatment finishes) (Ng *et al.*, 2011). Pulmonary toxicity demonstrated by reduced forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) is a common side effect of treatment for HL (Martin *et al.*, 2005; Hirsh *et al.*, 1996; Villani *et al.*, 1997). Lymphoma treatments significantly contribute of pulmonary toxicity, for example, HL survivors who had been treated with bleomycin showed a significant decline in FVC (Hirsh *et al.*, 1996) whereas HL survivors' who were treated with ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) chemotherapy followed by mediastinal radiotherapy showed a significant reduction in FEV_1 (Villani *et al.*, 1997). Pulmonary toxicity has been found to significantly reduce 5-year overall survival rate of HL survivors, especially amongst those over the age of 40 years (Martin *et al.*, 2005).

2.5.2 EXERCISE AND CARDIOPULMONARY FITNESS IN CANCER SURVIVORS

Improvements in cardiopulmonary function have been reported in post-treatment aerobic based exercise and cancer studies (Sprod *et al.*, 2010; Schneider *et al.*, 2007b; Courneya *et al.*, 2003a; Courneya *et al.*, 2003b), specifically in colorectal and breast cancer. A recent systematic review reported improvements in cardiopulmonary fitness (significant increases in peak oxygen uptake ranging from 6-39%) amongst cancer survivors performing resistance, or combined resistance and aerobic exercise (De Backer *et al.*, 2009). The review examined 24 studies of which 10 were RCT, 4 controlled, and 10 uncontrolled; a majority of the studies were breast cancer specific, and the interventions were primarily resistance-based with 8-12 repetitions per set. These findings are promising as most research in the current field intending to increase aerobic capacity used aerobic exercise to do so; theses findings suggest non-aerobic exercise or multi-component exercise may improve not only muscle function, but cardiovascular function.

Exercise training not only counteracts the negative side effects that cancer treatment and the cancer itself have on physical capacity (Dimeo, 2002), but can also improve aerobic capacity (Kolden, *et al.*, 2002; Courneya and Friedenreich, 2001; Mock *et al.*, 2001; Schwartz, 2000; Dimeo

et al., 1999), even after high dose chemotherapy (a common treatment for lymphoma) (Dimeo *et al.*, 2000).

Specific to lymphoma survivors, increases in volume of peak oxygen uptake (VO2) were reported after a 12-week aerobic exercise programme (Courneya *et al.*, 2009). Aerobic capacity also improved amongst HL survivors with CRF who performed 20 weeks of home-based exercise (Oldervoll *et al.*, 2003), but these findings are taken with caution as this was a small pilot study and the participants may present with reduced aerobic capacity compared to other lymphoma survivors, as a result of suffering with CRF. Amongst HL survivors, a significant association has been found between pulmonary dysfunction and exercise tolerance (Bonadonna *et al*, 2004), as well as chronic fatigue (Knobel *et al.*, 2001). Reduced pulmonary function is making it harder for some HL survivors to perform exercise; this may be related in part to heightened relative workload of activities. This highlights the importance of working at an intensity that is tailored to the participant.

In summary, cardiovascular toxicity is a common side effect of lymphoma treatment that can reduce physical capacity and make activities of daily living more challenging. Cardiac disease is one of the leading causes of death amongst HL survivors, so improving cardiovascular health is integral in terms of improving long term survival in this population. It is commonly accepted that exercise brings about improved cardiopulmonary function amongst the general population. Current literature suggests that aerobic capacity may improve amongst cancer patients and survivors with regular participation in physical activity, including resistance or combined exercise (DeBacker *et al.*, 2009), although to date, no RCTs have examined the impact of a combined aerobic and resistance exercise intervention on aerobic capacity of lymphoma survivors. The current RCT examines the impact of a CARP on aerobic capacity and pulmonary function (forced vital capacity (FVC), and forced expiratory volume in one second (FEV_1) of lymphoma survivors.

2.5.3 MUSCLE FUNCTION

A common side effect of cancer treatment is muscle wasting (Al-Majid and Waters, 2008), therefore muscle weakness and reduced functional ability is prominent amongst people with cancer (Argiles *et al.*, 2005; Muscaritoli *et al.*, 2006). Reduced musculoskeletal function negatively impacts responsiveness to treatment, leading to increased morbidity and mortality amongst people with cancer (Andreyev *et al.*, 1998). It is suggested cancer-related muscle atrophy may play a significant role in the development of metabolic syndrome (Mourtzacis and Bedbrook, 2009), which presents serious health concerns, particularly as cause of death for cancer survivors is most often from co-morbidities, for example cardiovascular disease (Ng *et al.*, 2011), not the cancer itself (metabolic syndrome is a known risk factor for cardiovascular disease).

Muscle strength is associated with lower cancer mortality risk in men, independent of other risk factors (Ruiz, et al., 2009). Katzmarzyk and Craig (2002) found abdominal muscular endurance (measured with the Canadian Physical Activity Fitness and Lifestyle Association (CPAFLA) sit-up test) is predictive of mortality in the general population (Katzmarzyk and Craig, 2002). Hand grip strength, which is representative of overall body strength, has recently been associated with cancer survivorship in people with advanced non small cell lung and gastrointestinal cancers and is associated with QoL scores (Kilgour *et al.*, 2013).

One known study has examined musculoskeletal function after lymphoma specifically. Lymphoma survivors, when compared to healthy controls were found to have reduced endurance, speed during tasks and stability on general movement and walking assessments (Lee *et al.*, 2003), all of which can be impacted by musculoskeletal fitness. These findings are consistent with the results seen amongst cancer survivors of varied types (Ness *et al.*, 2006).

A meta-analysis by Speck and colleagues (2010) reported that physical activity interventions for cancer survivors improved muscle strength (upper and lower body) (Speck *et al.*, 2010), but results were not presented by type of exercise so it is not clear what kind of activity produced these findings. The systematic review by DeBacker and colleagues (2009) discussed previously, reported improvements in muscle function (increases in one-repetition maximum ranging from 11-110%) amongst cancer survivors performing resistance, or combined (resistance and aerobic) exercise (De Backer *et al.*, 2009); a variety of tumour types were included in this review, leaving it unclear whether these findings were seen more so in one tumour type over another. Resistance training alone has resulted in increased muscle mass and reduced treatment-related side effects (Galvao *et al.*, 2006), and increased muscle strength amongst men with prostate cancer (Segal *et al.*, 2009; Galvao *et al.*, 2006), but this has not been explored in blood-borne cancers, such as lymphoma. The prostate specific results may be in part due to the type of treatment given to prostate cancer survivors, particularly those that reduce androgen hormones.

In summary, reduced musculoskeletal function is a known side effect of cancer, but few studies have examined muscle strength and endurance after lymphoma treatment. Using a RCT, the current study will look at changes in musculoskeletal function amongst the exercising arm of lymphoma survivors, compared to the control group. It is expected some strength gains will be seen in response to the performance of resistance training exercises, similar to previous studies (De Backer *et al.*, 2009; Galvao *et al.*, 2006)which will, in turn, make it easier to partake in activities of daily living, leading to improved QoL.

2.5.4 BODY COMPOSITION

Two of three studies examining the impact of exercise on body composition of lymphoma survivors were conducted after the current trial began. Haematological patients and survivors in

general (Wolin *et al.*, 2010), as well as lymphoma patients and survivors specifically, showed improvements in body composition with exercise (Courneya *et al.*, 2009). Prior to this, improved body composition was associated with exercise amongst lymphoma survivors with CRF (Oldervoll *et al.*, 2003). More studies are needed to substantiate these findings, specifically amongst lymphoma survivors, as improvements in body composition may reduce risk of mortality.

The current trial attempts to explore the impact of combined exercise on the body composition of lymphoma survivors, which has not previously been examined. Additional anthropometric measurements including waist to hip ratio and body mass index are also reported to describe body weight distribution as they contribute to the overall measurement of overweight and obesity (Heyward, 2010).

2.5.5 INFLAMMATORY IMMUNE FUNCTION

Cancer treatments can have dramatic effects on the immune systems of cancer survivors as medical treatments tend to be immunosuppressive (Fairley *et al.*, 2002). Immunosuppression can negatively impact QoL (Keown, 2001). Lymphoma is distinctive in that immune suppression can last for years post treatment (personal communication, Dr. Ruth Pettengell, July 2013; Hirokawa *et al.*, 2009; King *et al.*, 1976; http://www.cancer.org, accessed May, 2012) which brings a unique challenge of not only providing care that improves psychological and functional health but also improves immune function. Improving health and limiting disease by increasing immune function should enhance QoL.

A significant relationship exists between NHL survival and serum levels of both interleukin-6 (IL-6) and C-reactive protein (CRP) (Legouffe *et al.*, 1998); those with both detectable IL-6 and higher CRP levels reached a median survival of only 8.5 months (Legouffe *et al.*, 1998). IL-6, a cytokine involved in the pathogenesis of lymphoma, is higher amongst lymphoma patients compared to controls (Chopra *et al.*, 2004). After chemotherapy, IL-6 increases in most NHL survivors, particularly those classified as treatment non-responders (the highest levels were obtained for survivors who then died) (Chopra *et al.*, 2004). CRP is an acute phase inflammatory protein (Pedersen and Hoffman-Goetz, 2000), and is a biomarker of cardiovascular disease and indicator of disease risk (Kaptoge *et al.* 2010; Wilund, 2007), such as lymphoma and leukemia and cancers of the liver, lung, skin, kidney, and bladder (Tricholoulos *et al.*, 2006). CRP is an easily tested marker of inflammation and infection, and is a valuable prognostic marker in lymphoma (Legouffe *et al.*, 1998).

2.5.6 EXERCISE AND IMMUNE FUNCTION

Studies examining immune response to exercise in the general population have only starting appearing in the past two decades. Since the start of the current trial, the '2011 Position

Statement, Immune Function and Exercise (part one)'was released. Research shows that participants who are sedentary are more susceptible to infection and disease than are their healthy counterparts, suggesting physical activity enhances immune function (Walsh *et al.*, 2011; Nieman, 2003; Woods *et al.*, 2009), although the mechanism behind the positive impact of exercise is not fully understood (Woods *et al.*, 2009). One hypothesis is that physical activity causes an increase in the systemic levels of some cytokines with anti-inflammatory properties which create an anti-inflammatory environment (Mathur and Pedersen, 2009; Pedersen, 2007; Woods *et al.*, 2009).

Interleukins are cytokines that transmit signals between various cells of the immune system (Gleeson, 2000). Interleukin-6 is a pro-inflammatory cytokine that when released in response to exercise, produces an anti-inflammatory effect by preventing production of TNF-α and elevating levels anti-inflammatory cytokines (Starkie *et al.*, 2003, Petersen and Pedersen, 2006). Thus increased IL-6 during exercise does not cause chronic low grade inflammation; rather, it offers protection against TNF-α induced insulin resistance (Petersen & Pedersen, 2006).

The impact of moderate aerobic exercise on resting CRP levels is somewhat inconsistent within the literature (Kohut *et al.*, 2006; Jae *et al.*, 2006; Albert *et al.*, 2003; Fallon *et al.*, 2001; Mattusch *et al.*, 2000;Kasapis and Thompson , 2005); many of the studies conducted before this trial began had shown reductions in CRP with exercise, whereas some of the newer studies report a lack of change in high-sensitivity CRP (Campbell *et al.* 2008; Church *et al.* 2010; Nassis *et al.*, 2005; Marcell *et al.*, 2005; Stewart *et al.* 2010).

Despite early findings suggesting weight lifting had no impact on levels of CRP (King *et al.*, 2003), recent studies showed that resistance training *has* resulted in lowered CRP levels after exercise (Donges *et al.*2010; Olson *et al.* 2007). Interestingly, Donges and colleagues (2010) compared aerobic to resistance training and found resistance training significantly lowered CRP (by 32.8% ($P < 0.05$) (Donges *et al.*, 2010). Recent trials have reported lowered CRP levels after a combined aerobic and resistance training exercise intervention (Daray *et al.*, 2011; Stewart *et al.* 2007), therefore resistance and combined exercise both appear to be successful in lowering CRP. Reductions in CRP are associated with exercise programmes longer than 8 weeks (most of the studies involving exercise for 12-weeks produced decreases in inflammatory markers) (Woods *et al.*, 2009).

2.5.7 EXERCISE AND IMMUNE FUNCTION IN CANCER SURVIVORS

Although inflammation is linked with the process of tumorigenesis (Coussens and Werb, 2002) and exercise has been linked with decreased inflammation, medical literature pertaining to the immunological response to exercise amongst cancer survivors is scarce. Surprisingly few studies have examined the immunological impact of exercise within the cancer population, specifically in terms of inflammation reduction and anti-tumour immunity (Walsh *et al.*, 2011). In

2002, Fairey and colleagues published a comprehensive review of exercise and immune function in cancer survivors (reviewing studies from 1994- March 2001). During that period only six studies were published in the area and none of these had assessed acute phase proteins (i.e., CRP) or cytokines; it was then suggested that future studies should consider these immune markers (Fairey *et al.*, 2002), but at the start of this trial very few studies had done so.

A recent systematic review shows preliminary evidence that exercise may result in beneficial changes in inflammation and possibly immunity amongst cancer survivors (Ballard-Barbash *et al.*, 2012), but only 11 RCTs were included in the review (Ballard-Barbash *et al.*, 2012). This area is under-studied; further research is needed to examine the relationship between cancer and inflammatory biomarkers, particularly amongst different tumour types, as most studies in the review were specific to breast cancer.

Although limited, literature in this field provides preliminary evidence that exercise affects CRP and IL-6 amongst people with cancer. Exercise reduced resting CRP amongst postmenopausal cancer survivors; concurrently the control group showed an increase in CRP levels suggesting exercise not only improved levels of CRP in circulation, but also potentially prevented an increase in the levels of CRP (Fairey *et al.*, 2005). As well, muscle derived IL-6 decreased the production of TNF-α and IL-1 β (both of which contribute to feelings of fatigue) and therefore may be responsible for the beneficial effects of exercise on cancer related fatigue (Woods *et al.*, 2009). Although this is transitory, immune function improvements may accumulate with chronic exercise training (Timmons, 2007). If improvements are sustained, exercise could be a useful means to reduce the tumour induced immunosuppressive environment (Fairey *et al.*, 2002), which is especially promising for immune-based diseases like lymphoma where immunity can remain compromised well into survivorship. Examination of exercise effects in lymphoma would be beneficial (Walsh *et al.*, 2011) as it would add preliminary evidence in terms of the immune response to exercise amongst cancer survivors, and would show if anti tumour protection is associated with exercise in an immune mediated disease (Walsh *et al.*, 2011).

Thus, in summary, a uniqueness of this trial is the examination of immune response to exercise, and particularly the impact seen amongst cancer survivors. Biomarkers that have recently been examined in exercise and immune function literature include Interleukin -6 (IL-6) and C-reactive protein (CRP). The significance of these markers relates to their unique relationship with exercise; during exercise IL-6 decreases inflammation by blocking the production of TNF-α (Starkie *et al.*, 2003, Petersen and Pedersen, 2006). IL-6 is also a biomarker of interest because of the role of elevated IL-6 in lymphoma (Fayad *et al.*, 1998). C-reactive protein (CRP) has also been examined in recent exercise and cancer related research (Fairey *et al.*, 2005; Galvao *et al.*, 2009). The sparse research in this area provides preliminary evidence that CRP and IL-6 improve with exercise in cancer survivors, but because so little is known about the impact of exercise on

inflammation, specifically in cancer, it is difficult to provide any substantial conclusions in the area, but this does suggest further research is needed.

2.6 SUMMARY

It has been established that exercise ameliorates many of the physical and psychological symptoms and side effects resulting from cancer and its treatment, particularly amongst those with breast tumours (Winters-Stone *et al.,* 2013), but the literature continues to grow and survivors of other types of cancers are showing a positive response to exercise, particularly those with solid tumours. Most research has looked specifically at aerobic exercise, but other modalities, including combinations of exercise types, are becoming more readily examined in the literature (Milne *et al.,* 2008; Herrero *et al.,* 2006).

Lymphoma, often considered a highly curable cancer, is unique in that it is a disease of the immune system, and its treatment is often very hard on the body and comes with debilitating short term and late effects which reduce overall QoL (Bellizzi *et al.,* 2009; Jerkeman *et al.* 2001; Bellizzi *et al.* 2007; Demierre *et al.,* 2006). Thus, treatment associated side effects and immune suppression specific to survivors of this tumour type may cause different responses to exercise than those of solid tumours and even other haematological malignancies, warranting further investigation. Being off versus on treatment will bring about different symptoms and side effects, and the capacity for exercise will differ between patients on treatment compared to survivors who have completed treatment (Burnham and Wilcox, 2002; Kolden *et al.,* 2002; Courneya and Freidenreich, 1999). For example, the goal of exercise during treatment is to maintain (prevent reductions) in psychological health measures, whereas post-treatment, the aim of exercise interventions is to improve health and wellbeing, and in turn improve QoL (personal communication, Dr. Culos-Reed, November 2013).

2.7 THEORY OF PLANNED BEHAVIOUR: DETERMINANTS OF BEHAVIOUR

The effectiveness of an exercise intervention is weighted heavily on the adherence and motivation of the participants. Unfortunately, exercise becomes even more challenging after cancer diagnosis; the negative side effects of cancer and its treatment negatively impact exercise adherence (Courneya and Freidenreich, 1999). With only one quarter of lymphoma survivors meeting the minimum ACSM physical activity requirements for health (Vallance *et al.,* 2005), an understanding of the determinants of exercise behaviour and adherence are imperative.

A theoretical framework provides the basis for an investigation of factors that may influence the desired outcome (Rodgers and Brawley, 1993). Hundreds of studies have successfully used the *Theory of Planned Behaviour* (TPB) (Ajzen *et al.,* 1991) to predicting exercise behaviour in the general population (Biddle & Nigg, 2000); the TPB has been reported as the most validated model for understanding 'why' people exercise (Courneya, 1995). A meta-analysis examining 83

studies using the TPB reported that significant effect sizes were found for the relationships between all constructs as well as intention and behaviour, thus concluding that the TPB can provide a successful framework for predicting exercise (Symons Downs & Hausenblas, 2005).

Rogers and colleagues (2011) suggest a theoretical framework should be used to examine predictors of exercise and to measure the success of an exercise intervention. Using the TPB to measure SN, attitude, PBC and intention, the variables impacting adherence may be identified. A framework that has repeatedly been investigated to examine exercise behaviour in cancer survivors and other populations is the TPB (Ajzen *et al.*, 1991; Courneya *et al.*, 2002). Based on the premise that underlying behavioural, normative and control beliefs inform intention to behave and behaviour itself (Ajzen, 2006), the TPB framework postulates that subjective norm (SN), attitude (Att), and perceived behavioural control (PBC) are key correlates of intention (Courneya *et al.*, 2007); in turn, intention and PBC are each independent correlates of exercise behaviour (Figure 2.1) (Blanchard *et al.*, 2002; Courneya *et al.*, 2001; Courneya and Fredereich, 1997; Courneya and McAuley, 1995; Courneya *et al.*, 1999; Courneya *et al.*, 2007; Courneya and Friedenrich, 1997). The premise of the TPB is that one's intention to behave is a strong predictor of actual behaviour. Research has shown that intention is often the strongest independent predictor of exercise behaviour in cancer survivors (Courneya, *et al.*, 2001; Courneya, *et al.*, 2000). Courneya and colleagues have published a number of TPB-based studies that support the viability of the TPB in the prediction and understanding of exercise for cancer survivors (Karvinen *et al.*, 2009; Karvinen *et al.*, 2007; Courneya *et al.*, 2007; Jones *et al.*, 2006; Courneya *et al.*, 2001; Courneya and Fredereich, 1997; Courneya and McAuley, 1995; Rhodes and Courneya, 2003; Courneya *et al.*, 1999; Courneya and Friedenreich, 1999), but it is apparent from these results that the determinants of exercise vary depending on the cancer group, thus generalising between tumour groups may not be justified.

The determinants are defined as; Att measures one's positive or negative evaluation of performing the behaviour, PBC examines confidence and control over behaviour, and SN measures perceived social support for and against behaviour (Lox *et al.*, 2010).

With the addition of PBC, the TPB is an extension of the Theory of Reasoned Action (TRA) (Fishbein & Ajzen, 1975). The TPB integrates the underlying beliefs that are common in well-known and reliable social cognitive approaches to understanding exercise psychology, for example, subjective and control beliefs from the social cognitive theory (SCT) and self-efficacy theory (SET) (Bandura, 1986) are measured in the TPB. The SET is a reliable model; self-efficacy is a strong predictor of exercise behaviour (McAuley & Blissmer, 2000), but it is limited as it is predictive of behaviour when it is novel or challenging, unlike the TPB that is predictive with all exercisers of all levels (Culos-Reed *et al.*, 2001). The TPB is predictive for An integrative model that would be a distant second in terms of usage in the exercise and cancer field is the

transtheoretical model (TTM) which assesses an individual's readiness to change, and provides strategies to guide the individual through the stages of change to 'action' (Prochaska & DiClemente, 1983). Both the TPB and TTM place importance on behavioural beliefs and control beliefs, but the TPB provides more of a global assessment of attitude and control, and also offers social impact to be considered. The TTM is limited in that the causes of change are not clearly identified. There is some evidence that the TPB outperforms the TTM (Courneya, 1995). A limitation of the TPB is that it may not account for other dispositional variables that influence behaviour (e.g., personality) but it is expected to mediate their effects (Hagger & Chatzisarantis, 2005).

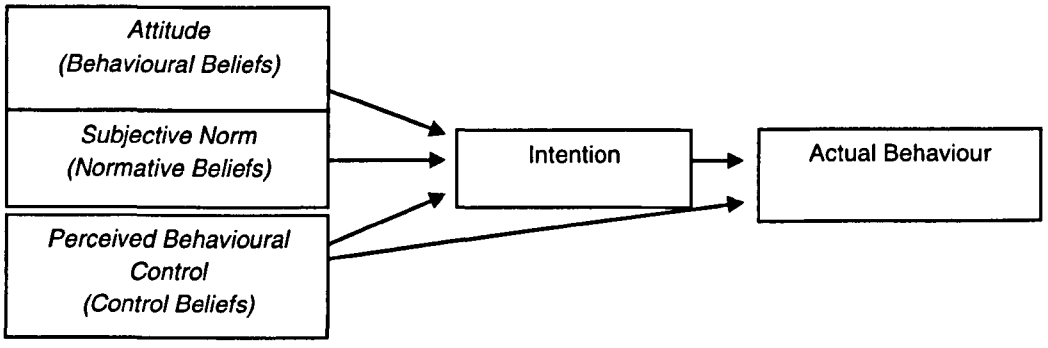


Figure 2.1. A schematic representation of the Theory of Planned Behaviour (TPB) (Ajzen, 1991)

The TPB has generally explained 14% to 35% of the variance in exercise behaviour, and 23% to 68% of the variance in exercise intention in cancer survivors (Courneya *et al.*, 2007). Although there is strong evidence that the TPB has been successful in the prediction and understanding of exercise behaviours of cancer survivors (Karvinen *et al.*, 2009; Karvinen *et al.*, 2007; Courneya *et al.*, 2007; Jones *et al.*, 2006; Courneya *et al.*, 2001; Courneya and Fredereich, 1997; Courneya and McAuley, 1995; Rhodes and Courneya, 2003; Courneya *et al.*, 1999; Courneya and Friedenreich, 1999), these studies also indicate that the relative importance of the TPB determinants vary based on the cancer site studied. The various TPB constructs may vary depending on the cancer survivor groups and therefore cannot be generalized to all cancer patients and survivors (Trinh *et al.*, 2012; Courneya and Blanchard, 2001, Courneya and Freidenreich, 1999; Courneya and Friedenreich, 1997; Karvinen *et al.*, 2007; Rhodes and Courneya, 2003; Rivis and Sheeran, 2003). Cancer related side-effects may impact each of the constructs of the TPB (Karvinen *et al.*, 2007; Jones *et al.*, 2006; Courneya and Friedenreich, 1999). To effectively use the TPB to create supportive care interventions for lymphoma survivors, it is essential to examine the predictability of these constructs specific to this morbidity.

This thesis examines whether the Theory of Planned Behaviour (TPB) is an effectual model for predicting exercise behaviour amongst lymphoma survivors. The determinants, if found to significantly predict intention and behaviour, can be used to increase physical activity in this cohort. Ajzen (2006) suggests that application of theory to practice is to be determined by each researcher and practitioner who should find their own way to incorporate the known determinants into programme design (Ajzen, 2006). Recently Michie and colleagues (2008) suggest that the determinants are associated with certain .behaviour change techniques that can be applied to improve exercise behaviour and adherence (Michie *et al.*, 2008; Ajzen, 2006). Once determinants are identified, associated behaviour change techniques can be used to potentially increase intention and behaviour

2.8 EXERCISE PRESCRIPTION FOR CANCER SURVIVORS: A SUMMARY OF RELEVANT RESEARCH

Although the literature is growing in the area of exercise for cancer survivors, there is a lack detailed consensus towards a putative model for exercise prescription. Ideal exercise prescription relates to the optimal; frequency, intensity, type of exercise amount of time engaged in exercise (FITT principle). Due to the lack of consistency in describing exercise prescription and even testing guidelines, no particular form of exercise has emerged as being superior in the adjunct treatment of any tumour type. In fact, the suggestion of 150 minutes of aerobic activity and 2-3 resistance training sessions per week including exercises for major muscle groups, with stretching most days (Schmitz *et al.*, 2010) is the same as that for healthy adults. Ideally, exercise would be individually described to each particular cancer type (Brown *et al.*, 2011), as each cancer and associated treatment is different (Vallance *et al.*, 2013). Until a large pool of evidence based data relating exercise in cancer survivors is in existence, such guidelines are unlikely to emerge. Thus, the current intervention is designed based on what has been found to be successful in this field, to date.

2.8.1 FITT PRINCIPLE

Frequency. Training programmes for cancer survivors average 3-4 sessions per week (DeBacker *et al.*, 2009; Galvao & Newton, 2005) as this is the minimal amount necessary for optimal progression for beginner exercisers (Kraemer, & Ratamess, 2004). This follows the American College of Sports Medicine (ACSM) recommended exercise guidelines for cancer survivors (which are the same as the ACSMs exercise guidelines for the general population which informed the current trial as no cancer specific guidelines were available at the time (Schmitz *et al.*, 2010).

Intensity. Compared to an apparently healthy population, intensity should be set at a lower threshold or range to accommodate the typical treatment-related fatigue and de-conditioning that afflicts cancer survivors (Wiggins & Simonavice, 2010). The majority (62%) of NHL survivors in

Vallance's study (2006) reported they wanted to take part in moderate intensity exercise, which is also the appropriate intensity for improving QoL (5-6 METS), the primary outcome in the current trial (Ferrer *et al.*, 2011). Moderate intensity exercise is most commonly prescribed for cancer survivors (approximately 11–13 on the Borg rating of perceived exertion (RPE) scale) (Spence *et al.*, 2010) and has been found to produce a number of psychological and functional benefits for people with cancer (Fairey *et al.*, 2005; Courneya *et al.*, 2007; Mock *et al.*, 2005; Oldervoll *et al.*, 2003; Carlson *et al.*, 2006; De Backer *et al.*, 2009; Segal *et al.*, 2009). As previously mentioned, anxiety (Focht *et al.*, 1999; Bartholomew & Linder, 1998) and fatigue (Brown *et al.*, 2011) are most often reduced with moderate resistance exercise but anxiety increases with vigorous exercise (Raglin, *et al.*, 1993; Cassilhas *et al.*, 2007).

It is important to consider exercise limitations specific to people with decreased immune function. For example, exercise intensity has been explored and described using the 'Inverted J Hypothesis' (Figure 2.2), a commonly used working theory in the field of exercise immunity. The Inverted J Hypothesis suggests that enhanced immune system function and reduced susceptibility to cancer occurs with regular moderate exercise, but repeated bouts of exhaustive exercise may lead to suppressed immune system function and elevated susceptibility to cancer (Woods *et al.*, 1999).

The intervention in the current trial is prescribed at a low to moderate intensity with modifications available to reduce intensity if needed. Intensity is monitored using the self-rated Borg RPE Scale, the goal being a rating of 11(fairly light)-13 (somewhat hard) as many participants had just completed treatment. The Borg RPE scale was used to measure intensity during exercise because it can be used in both the supervised and home-based setting.

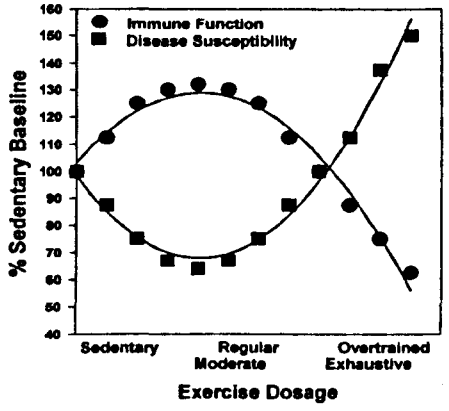


Figure 2.2. The Inverted J Hypothesis. Reprinted from "Exercise and cellular innate immune function" by Woods et al., 1999, Medical Science Sports Exercise, 31, p. 57-66. Copyright 2009 PubMed Central.

Time. A recent meta-analysis showed that the majority of exercise interventions for cancer survivors that included a resistance training component were 12-weeks in duration (DeBacker *et al.*, 2009), which is consistent with previous literature (Matthews *et al.*, 2007; Pinto *et al.*, 2003). It has been recommended that exercise sessions last longer than 8 weeks to show reduced CRP (most of the studies involving exercise for 12-weeks produced decreases in inflammatory markers) (Woods *et al.*, 2009), and those that were 15 to 30 or more minutes in duration for a minimum of 10-12-weeks resulted in the largest improvements in anxiety scores (Guszkowoska, 2004; Herring *et al.*, 2010).

Type of Exercise. A plethora of evidence indicates that there are many health benefits from exercise following cancer treatment, however different modes of exercise bring certain results and an optimal exercise modality has not yet been established (Irwin , 2011; Winters-Stone *et al.*, 2013). Aerobic exercise has been found to positively impact QoL, physical (particularly cardiovascular fitness) and psychosocial health (Courneya *et al.*, 2009; McNeely *et al.*, 2006), whereas resistance training has been shown to provide improvements in muscle function (De Backer *et al.*, 2009; Segal *et al.*, 2009) and psychological outcomes, as well as QoL (Segal *et al.*, 2009). It has recently been recommended that an exercise programme for cancer survivors should involve the "whole body", to include moderate intensity aerobic, resistance, and flexibility training (Sprod, 2009). At the time the current trial began there was a lack of literature pertaining to the effects of combined aerobic and resistance exercise in cancer survivors; since then the handful of studies using multi-component training with cancer survivors have shown improvements in cardiovascular fitness (peak oxygen uptake improvements ranging from 6-39%), and in muscle strength (one-repetition maximum increases from 11-110%) with no adverse effects (DeBacker *et al.*, 2009). It is expected that a combined exercise programme involving both aerobic and resistance training may provide the benefits exhibited from both types of training. Consequently, this thesis examines the efficacy of a combined aerobic and resistance exercise training programme (CARP).

Interest in 'supervised' versus 'non-supervised' activity was similarly ranked in terms of preference amongst NHL survivors; unsupervised exercise was slightly more popular (Vallance *et al.*, 2006). Supervised activity has been deemed advantageous in that survivors can be directly monitored thus reducing risk of injury (Irwin, 2009) as this was a concern for some, as survivors who reported that safety of exercise was a primary concern that influenced their decision to take part in exercise (Sander *et al.*, 2012). Home-based activity on the other hand has been found to improve adherence to exercise because of scheduling flexibility and cost-effectiveness (Irwin, 2009). It is suggested that a combination of both home and supervised activity would bring together the benefits of both forms of practice (Irwin, 2009; Rogers *et al.*, 2011; van Weert *et al.*, 2008; Irwin, 2009).

2.8.2 TIMING OF INTERVENTION IN RELATION TO CANCER TREATMENT: TRANSITION FROM 'PATIENT TO SURVIVOR'

It is commonly accepted that there may be disrupted adjustment at different times during the survivorship experience (Costanzo *et al.,* 2007). For survivors who receive curative intent therapy, the end of treatment transition from patient to survivor is associated with psychological stress (eg, uncertainty, fear of recurrence) and is often accompanied by distressing physical symptoms (Knobf *et al.,* 2007). Recent literature has shown that great focus needs to be placed on the quality of survivorship care during this transition period (Hausman *et al.,* 2011; Rowland *et al.,* 2006; Costanzo *et al.,* 2007) as it may be particularly important to ones cancer recovery (Wolff, 2006). It was reported that 30% of haematological malignancy survivors expressed that 'access to complementary and/or alternative therapy services' would have helped them transition during the first year after treatment had ended (Lobb *et al.,* 2009)., Vallance and colleagues (2006) reported that 38.1% of lymphoma survivors asked stated they would like to st40art exercising within 3-6 months of treatment completion (Vallance *et al.,* 2006). The current trial explores the impact of an exercise intervention for lymphoma survivors during this transition period (within six months from the end of treatment).

2.9 CHAPTER SUMMARY

It is evident from the literature that only a quarter of lymphoma survivors are meeting the ACSM physical activity guidelines and 20% of survivors reported no activity at all (as these are self-reported values, the number of survivors exercising may be even lower than this) (Vallance *et al.,* 2005). With their increased risk of cardiopulmonary toxicity, reduced musculoskeletal function and potential psychological concerns, this lack of physical activity is alarming. To date, limited research has reported improvements in psychological measures of mental health scores and QoL, as well as measures of physical function for lymphoma survivors who perform aerobic activity (Courneya *et al.,* 2009). Much of this was not known at the start of the current trial. The current research study will add to what has been found thus far.

What remains unique about the current trial is the examination of a combined exercise programme (both aerobic and resistance training), which has not been reported before amongst this population. The combined intervention may bring about changes not seen in aerobic-based programmes (i.e. Courneya's recent study in lymphoma (2009), as well as may offer lymphoma survivors another type of exercise to perform: this may improve exercise adoption and adherence (not everyone enjoys aerobic based activity, so the mix with resistance may appeal to a larger number of survivors, or at least it may provide options). The current trial also examines the inflammatory response to exercise, as experienced by lymphoma survivors, which is novel. Exercise has been found to offer a protective, anti-inflammatory effect amongst the general

population, but amongst immune compromised patients, the results are inconclusive. It is relevant, then, to examine the impact of exercise on inflammation in this group as immune response to exercise, a fairly new field of research, does not conclusively state that exercise does not increase inflammation amongst those who are immune suppressed. It is advantageous to examine the chronic effects of exercise on inflammatory response amongst lymphoma survivors as compared to usual care controls to examine the potential protective effect, and to watch for any increased inflammation amongst the survivors, as chronic inflammation is associated with a host of co-morbidities (Petersen & Pedersen, 2006).

Much of the research done in the area of exercise for cancer has been done in breast cancer; even the exercise guidelines published by the ACSM are 'general' in nature and are based largely on trials conducted in breast cancer survivors (Winters-Stone *et al.*,2013). The examination of the impact of exercise by tumour type is essential, as each tumour and its treatment present unique side effects and factors related to exercise (Vallance,*et al.*, 2013). Vallance and colleagues (2013) point out that, for example, NHL survivors report de-conditioning and weakness as major barriers for participating in exercise as this is a major clinical concern amongst this population (Vallance *et al.*, 2006), but this is not common to all other tumour types (Vallance *et al.*, 2013). As mentioned, immune function may be suppressed in lymphoma survivors which is an additional unique effect that may impact the effects of exercise.

In summary, there is an increasing abundance of literature pertaining to the influence of exercise *per se* as an adjunct to standard medical therapy in cancer survivors. Although, many of associated benefits of exercise in cancer survivors would be expected across the range of cancer diagnoses, there is minimal available information on haemostatic cancer survivors. Survivors of haemostatic cancers such as HL and NHL may differ from non-haematological cancer survivors in that they have suppressed immune function and often experience heightened side effects due to the severity of treatment. Further to this, much of the available exercise in cancer literature has focused on aerobic or resistance type activities. There is a paucity of available literature that examines the combination of both exercise modes. A combination of aerobic and resistance type training may be an effective mode of exercise in haematological cancer survivors and warrants investigation. With this in mind, the present thesis seeks to investigate the effects of CARP on QoL in lymphoma survivors, with examination of secondary outcomes of cardiovascular fitness, muscle function, and inflammatory response. The thesis further seeks to investigate the strength of predictability of the TPB and determinants on exercise participation in a cohort of HL and NHL survivors.

Purpose. The current exploratory randomised controlled trial (RCT) aims to examine the use of a CARP to combat the adverse effects associated with surviving lymphoma so as to primarily enhance QoL, but also to explore impact on additional psychological and physical functioning, and immune markers. The current trial includes both HL and NHL survivors, examining the impact of

exercise to the group as a whole (although randomization was stratified by HL and NHL survivors). A usual care control group was used to examine whether the outcome changes seen were due to the exercise intervention or whether these changes are commonly seen amongst lymphoma survivors who are recovering from treatment.

Chapter 3.

THEORETICAL AND METHODOLOGICAL BACKGROUND

3.0 INTRODUCTION

This chapter outlines the scientific theory and analytical techniques involved during the measurement of quality of life (QoL), psychological, and functional outcomes as well as predictability of behaviour using the Theory of Planned Behaviour (TPB) in a cohort of Hodgkin's and non-Hodgkin's lymphoma survivors.

3.1 FEASIBILITY STUDY

As there were no specific guidelines for administering an exercise intervention and testing protocol for cancer survivors at the time that the trial began, a logistics study was performed to test the proposed main study. As with most feasibility studies, this pilot study was conducted to scrutinise testing arrangements, including time required to conduct testing, logistics of testing procedures, and any identification of additional equipment or consumables. The intervention was tested to see if the choice of exercises and intensity was appropriate for beginner exercisers and logistics of the circuit particularly the time it takes to get between the stations. Data collection and analysis were also tried and adjusted as necessary. The proposed randomised controlled trial (RCT) (particularly the intervention, measures and testing protocol) was adjusted based on the findings from this feasibility study.

3.1.1 DESIGN OF THE FEASIBILITY STUDY

After gaining ethical approval from Kingston University institutional review board, the design of the trial, both the testing protocol and exercise intervention were piloted with a small group (n=17) of apparently healthy beginner exercisers from the general population who fulfilled enrolment criteria of; 1) having begun participation in exercise within two months prior to enrolment to the pilot, and 2) having not participated in formal exercise for a minimum of one year prior to recommencing. All 17 beginner exercisers (mean age 40.1 ± 13.5 years) were given an information sheet (Appendix A), to take part in the pilot study. All participants were recruited from a beginner exercise class at Colets Health and Fitness Club in Thames Ditton, Surrey, UK.

Participants were required to attend weekly exercise sessions over 12 consecutive weeks. Pre-testing was performed on all participants; 17 attended the intervention (90% attendance) and 7 completed post-testing at 12-weeks. Participants completed a battery of questionnaires including the European Organisation for Research and Treatment of Cancer – Quality of Life (EORTC-QLQ-30), Functional Assessment of Chronic Illness Therapy Measurement System - Lymphoma Scale (FACT-Lym), The Profile of Mood States (POMS), Hospital Anxiety and Depression Scale (HADS), The International Physical Activity Questionnaire (IPAQ), and the Theory of Planned Behaviour (TPB).

The participants were required to answer the 'cancer specific' questions to describe how they were feeling now, ignoring the cancer specific reference. After completing the Physical Activity Readiness Questionnaire (PAR-Q), the participants took part in a physiological assessment, obtaining heart rate (bpm), blood pressure (mmHg), pulmonary function ($L.min^{-1}$), height (cm), weight (kg), waist and hip circumference (cm), and bioelectrical impedance determined body fat (%). Participants then performed an incremental step test to volitional exhaustion; in addition to maximal number of push-ups in 1 minute, maximal number of sit-ups in 1 minute, grip strength ($kg.cm^2$) using a hand grip dynamometer, and the sit and reach tests. All tests followed guidelines from the Canadian Society for Exercise Physiology (CSEP).

3.1.2 FEASIBILITY STUDY; NOTABLE MATTERS ARISING FROM ASSESSMENT DAYS

The previously validated questionnaires took between 18 and 30 minutes to complete, which is consistent with previous investigation (Culos-Reed *et al.*, 2006). The majority of respondents (14/17) indicated that they 'would prefer not to answer' the question relating to the self-reported satisfaction with their sex life in the Functional Assessment of Chronic Illness Therapy (FACT-Lym). For reliability and validity purposes, it was decided to maintain the complete questionnaire in the subsequent main study. Physiological measurements took between 35 and 75 minutes to complete for each participant. The CSEP step-test was deemed overly challenging as some participants were unable to complete the initial stage. Consequently, the CSEP step test was replaced with the incremental Balke-Ware Treadmill test (Balke and Ware, 1959). The Balke-ware protocol is recommended for use with de-conditioned populations or those with chronic illness (ACSM, 2006), as it allows participants to walk throughout each stage. Increments are achieved by increasing the slope of the treadmill gradient. Due to the amount of time required for the 7-stage sit-up test (approximately 7 minutes to complete), it was replaced with the CSEP sit-up test which requires no more than 25 full sit-ups, thus taking a maximum of 1 minute to complete. The most prominent issue from the feasibility study related to the quantity of participants (n=10) who failed to show up for post-testing appointments. Reasons included; 4 reporting illness, 2 reporting being out of town during testing; 4 did not reply. Consequently, in an attempt to maximise adherence to the main study, participants were permitted to arrange their follow up measurement to suit their schedule.

3.1.3 FEASIBILITY STUDY EXERCISE TRAINING

Rationalizing the exercise training intervention protocol (CARP);

The CARP protocol for the feasibility study was developed using guidance from the available literature in addition to information garnered from the principal investigators previous

involvement in cancer research studies [MSc Study at the University of Calgary, Canada, (2004)] (Culos-Reed *et al.*, 2006). The principal investigator, who held certification in exercise training, administered the exercise intervention. Participants attended a supervised exercise session once per week and were required to participate in two home-based exercise sessions per week with the intention of providing benefits associated with both supervised and home-based activity.

3.1.4 FEASIBILITY STUDY; NOTABLE MATTERS ARISING FROM THE CARP

In general, there was a wide heterogeneity of individual capabilities to perform the exercises. The intensity of the aerobic components was found to be appropriate for 'apparently healthy' beginner exercisers. However, in order to accommodate the typical treatment-related fatigue and de-conditioning that afflicts cancer survivors (Wiggins & Simonavice, 2010), intensity would be regulated to accept a (2 points) lower intensity in the subsequent main study (Matthews *et al.*, 2007).

Lack of compliance was reported during home-based exercise sessions. Reasons included; forgetting the exercises and the fear of incorrectly executing exercises leading to injury. Supervised activity has been deemed advantageous in that participants can be directly monitored thus reducing risk of injury (Irwin, 2009). Two sessions of home-based activity, were chosen as this has been found to improve adherence to exercise because of scheduling flexibility and cost-effectiveness (Irwin, 2009). A combination of both home and supervised activity bring together the benefits of both forms of practice (Irwin, 2009; Rogers *et al.*, 2011; van Weert *et al.*, 2008). Participants were administered with detailed documentation listing exercises with graphical instructions and photos for all at home exercises (Appendix Q).

The findings from the feasibility study dictated some minor changes to the subsequent main study;

Aerobic exercise bouts administered to achieve a rating of perceived exertion (RPE) of 13-15 on the Borg scale (Appendix L) were reduced to stay within a Borg RPE of 11-13 (Borg, 1982); although because it is easier to rate exertion from 1-10, the modified RPE scale was provided to the participants (Appendix L).

Participants were each administered with Thera-Band rubberized tubing (with of 6 colors indicating a different level of resistance) and a Physio Ball for home use; participants were required to follow a set protocol of exercises which they logged and reported in their training diary.

3.1.5 DATA COLLECTION AND TESTING

Feasibility study data were analysed using SPSS (PASW) version 17.0. T-tests were employed to compare pre and post intervention data. Adequate statistical power was not achieved. However, clinically significant mean improvements were seen in BMI, muscular endurance ($p<0.05$), pulmonary function (forced vital capacity) ($p<0.05$), and POMS derived levels of anxiety ($p<0.05$).

3.1.6 SUMMARY

The main findings of the feasibility study dictated the following amendments to the subsequent main study. Exercise intensity would be moderated to achieve a Borg (1982) rating of 11-13 (equivalent to 110-130 beats per minute). There was some slight adjustment to exercise testing battery in order to reduce the amount of time required to achieve baseline and follow-up data. The Balke-ware incremental treadmill test was chosen to replace the CSEP step test which was demonstrated to be largely unfeasible. Further to this assessment, assessments were conducted privately and individually booked to accommodate participants' schedules and reduce the time wasted whilst they waited for other participants to be tested.

3.2 STUDY DESIGN

The main study employed a randomised controlled trial (RCT) parallel-group design. Randomization was stratified by tumour type; Hodgkins Lymphoma (HL) and Non-Hodkgins Lymphoma (NHL). The intervention arm took part in a 12 week combined aerobic and resistance exercise training programme performed 3 times weekly; assessments at baseline (T0) and 12 weeks (T1) were compared to the usual care control group. The primary outcome measure was Quality of Life (QoL); secondary outcome measures comprised of additional variables of health-related quality of life (HRQoL); Mood Disturbance, Anxiety, Depression, and Fatigue. Secondary physiological outcome measures included the determination of aerobic capacity (METS), pulmonary function (FVC and FEV_1), muscle strength (grip strength) and muscular endurance (push-ups and sit-ups), flexibility (sit and reach) in addition to anthropometry (BMI, body composition, girth) and selected immune biomarkers of IL-6, and CRP. Tertiary outcomes were examined; all subscales of the listed questionnaires were explored.

A second component to the trial examined whether the theory of planned behaviour was an effectual model to predict exercise intention and behaviour at baseline. By group, predictive strength of the determinants of behaviour were compared at 12-weeks. This study was conducted at St. George's Hospital, London England. The location and setting of both testing and the intervention remained the same for all participants throughout the trial.

3.2.1 ETHICAL APPROVAL AND CHANGES TO METHODS

The protocol was approved by the Wandsworth London regional ethics committee (REC). Deviation from originally approved protocol involved moderation of the existing protocol, and inclusion of an additional component. Protocol changes were further approved by the same ethics committee.

The intervention was originally a 12-week programme with three optional monthly exercise sessions upon completion. It was decided that the monthly sessions would be removed from the programme due to lack of available space in the exercise facility being used for the study (shared with other programmes). The Theory of Planned Behaviour (TPB) questionnaire was modified appropriately (change approved by ethics).

A clinical management decision was made to remove proposed bi-monthly follow-ups, keeping the 12-month follow-up assessment point to examine long-term intervention associated effects. It was originally set up to bring participants in for testing during their regularly scheduled follow-up appointments with the oncology team, but the duration between these appointments were not consistent, so these were removed before the trial began.

Primarily due to financial constraints, the 12-month follow-up data collection point was limited to include only psychological measures and 'amount of physical activity performed' acquired using only the questionnaire which could be mailed out to participants.

3.3 SELECTION OF PARTICIPANTS

Participants were recruited from a specialist Lymphoma Clinic at St. Georges Hospital, London (SGH) between June 2009- July 2010. Eighty-nine lymphoma survivors were assessed for eligibility. Eligible participants (n=76) were provided with a participant information sheet (PIS) (Appendix B)._Interested participants (n=57) provided written informed consent, which was ethically approved by Wandsworth Research and Ethics Committee (REC) and SGUL Research and Development (R&D) before recruitment commenced (REC 08/H0803/188)) (Appendix E).

Of those recruited (n=57), 10 were removed before pre-testing and before randomization (due to needing further treatment (n=3), death (n=2), and the rest (n=5) were no longer interested in taking part). All pre-tested participants (n=47) were then randomised (stratified by tumour type). Participants who completed the RCT (n=41) were included in the analysis (per protocol analysis). Accession was high at 12-month follow-up, only 36% of the participants from the RCT took part in the assessment (n=15).

A letter was sent to each intervention participants' general practitioner to advise them that their patient was taking part in an exercise study (Appendix F).

Inclusion Criteria: Patients with histologically confirmed lymphoma who were being treated with chemotherapy and/or radiation therapy or high dose therapy were considered for this study. Inclusion criteria consisted of a good performance status (European Cooperative Oncology Group (ECOG) 0-2, Appendix G), being clinically able to carry out an exercise training programme on a regular basis, ability to give informed consent, and to begin the programme, patients must have completed treatment within the past 6 months. Participant eligibility was confirmed by the resident clinical oncologist lymphoma specialist. Dr. R. Pettengell.

Exclusion Criteria: Patients were excluded from the study if they were currently participating in an exercise program, demonstrated poor performance status (ECOG $\geq$3, see Appendix G), if they were suffering with unstable angina, cognitive impairment (sufficient to limit ability to perform quality of life questionnaires or understand instructions) musculoskeletal disease limiting mobility, abnormal resting ECG unexplained by further cardiological work-up, and/or progressive disease, and if they had completed treatment more than 6 months prior to the commencement of the study.

3.4 INTERVENTION LOCATION

Each subject arrived in the Lymphoma clinic laboratory in the Lanesborough Ward, St. Georges Hospital, London England, at their appointed time having followed the preliminary testing instructions (Appendix J) which includes abstaining from food, smoking, and beverages (including caffeinated beverages) for at least 2 hours prior to testing, and abstaining from alcohol and exercise for a minimum of 6 hours prior to examination. Questionnaires were completed in the lymphoma clinic and then blood was collected in either the lymphoma clinic or the St. James Blood testing room (St. Georges Hospital) by a hospital phlebotomist. Functional testing took place in the Atkinson Morley Ward at St. Georges Hospital, London England. The exercise intervention took place at the Atkinson Morley Ward at St. Georges Hospital, London England.

3.4.1 CRITERIA FOR THOSE PROVIDING THE INTERVENTION

The investigator performed all testing and assessment and was the exercise trainer for the study, with assistance from a certified physiotherapist. It was decided that the investigator and physiotherapist would conduct functional testing and teach the intervention despite tester bias, as the trial is a student led project, limited funding was available, and testing protocol followed standard guidelines leaving very little room for personal interpretation. The principal investigator was a certified exercise trainer and CSEP fitness assessor (15 years) and held a Masters degree in Kinesiology (exercise for cancer survivors), and had experience of conducting exercise interventions with cancer patients and survivors.

3.5 INTERVENTION and CONTROL

The participants randomly assigned to the intervention group took part in a 12-week exercise intervention; the controls followed usual care.

3.5.1 THE COMBINED AEROBIC AND RESISTANCE EXERCISE TRAINING INTERVENTION PROGRAMME (CARP)

Following a detailed review of the available literature and accounting for the associated effects specific to lymphoma survivors it was decided that the current trial should examine the impact of an intervention including both aerobic and resistance training that may provide the benefits exhibited from both types of training. This allowed the achievement of ACSM recommended exercise guidelines of 150 minutes of aerobic activity and 2-3 resistance training sessions per week for general population (Thompson *et al.*, 2010) (it is the same for cancer patients and survivors, although these guidelines were not produced until after the trial began) (Schmitz *et al.*, 2010).

Combined Exercise Training

In the current trial, combined exercise training is defined as a combination of aerobic and resistance training, followed by gentle stretching. The exercises were performed in a circuit format, alternating resistance with aerobic exercise as this is recommended for new exercise participants because the stations provide distraction and prevent boredom, and the duration of cardiovascular exercise is manageable in small bouts (Waller *et al.*, 2011).

Exercise training was taught on a one to one basis by the lead trainer (with assistance from the physiotherapist). The circuit-based programme was modified based on the individual needs of the participant. If at any time during the intervention a participant was feeling unwell or no longer wished to participate, they were asked to slow down (cool down if possible) and were monitored until it was safe for them to leave (as per ACSM Exercise Testing and Prescription Guidelines) (ACSM, 2006).

Aerobic Exercise Training

Aerobic exercise was performed in the form of walking, jogging (on a stationary treadmill), or cycling (on a stationary recumbent bike). Participants performed a 10 minute warm-up staying at a subjective rating of perceived exertion (RPE) of 4 out of 10, approximately 40-45% of maximal heart rate (MHR); the bike resistance or treadmill speed was determined by the participant (using the RPE scale, Appendix L) and adjusted the level appropriately until the participant reaches the pre-determined t rating of perceived exertion. After completing the warm-up, the participant alternated between the stations and the aerobic equipment in 3and 5 minute intervals; 3 minutes of resistance training (one exercise repeated for the duration) followed by 5

minutes of aerobic exercise. The participants completed 6 resistance stations alternating with 6 bouts of aerobic exercise.

Resistance Exercise Stations

Each resistance station offered a variety of levels and alternatives (so as to be suitable for the fitness level of the participant). Based on the participant's ability to perform the activity correctly for the time allotted for the station, the trainer advised the participant of which level of the exercise they were to perform. Before advancing a participant to the next level, the instructor waited for the participant to complete the current level with ease. If participants reported the exercises were challenging (approximately 5-7 on the RPE scale (Appendix L) which is approximately 11-13 on the traditional Borg RPE Scale), they would stay at the same exercise level; above or below resulted in either a reduction in the level of exercise, or an increase. Equipment for the stations included dumbbells (a variety of weight was available), physio balls (diameters of 55cm and 65 cm were available), and elastic stretch bands of various resistances. A physio ball and a band were supplied to each participant at the start of the CARP to allow convenient home-based resistance training, along with a copy of the RPE scale (to help the participant keep at the appropriate intensity), and a booklet of the exercises with descriptions and photographs to remind participants how to execute the exercise. When at home, participants were given a programme to follow (provided in a detailed exercise booklet) (Appendix Q) similar to the one they performed during their supervised session, and were asked to maintain an RPE of 5-7 (refer to Appendix L).

The six stations consisted:

1. Isometric Balance and core stabilization (seated or kneeling on physio-ball)
2. Wall squat (partial or full)
3. Lunges (partial or full; stationary or walking; walk holding railing for assistance or independently)
4. Bicep curls, tricep overhead press, deltoid raises (anterior and medial) (options with bands instead of dumbbells)
5. Push-ups (modified box; from knees; from toes)
6. Isometric balance and core stabilization (body weight resistance, no equipment)

Between resistance stations, the participant walked back to the bike or treadmill and performed 5 minutes of aerobic exercise at approximately 55-65% MHR (RPE 5-7). The aerobic exercise bouts increased in intensity as the participant progressed throughout the 12 weeks (individually assessed as a result of the participant's comfort and fitness level). The upper limit for exercise intensity was 80% MHR; if this limit was reached, participants were asked to reduce

resistance and speed until HR was reduced below the limit. Maximum heart rate (MHR) was calculated using a formula by Jackson et al. (2007):

MHR = 206.9 - (0.67 x age).

Although heart rate values were observed by the trainers, the subjective values (RPE) were used when interacting with the participant so that they were comfortable using the RPE scale at home. Level and options of the exercises in each exercise programme was prescribed on an individual basis to ensure suitability and to promote adherence to the programme. Attendance was recorded for each participant.

Participants were given an Exercise Log (Appendix K) and asked to record the frequency, duration, intensity and RPE (Rating of Perceived Exertion) of any activities they did for the duration of the study.

3.5.2 THE CONTROL GROUP

Participants allocated to the control group were given the 'Exercise for Cancer Participants' information sheet adapted (with permission) from the American Cancer Society website for their perusal (Appendix M). They were also given an exercise log book and were asked to record any exercise they performed (if any at all) for the duration of the study. The control group was not given any exercise programme or guidelines. Participants in this group were not expected to perform any exercise or activity outside of their normal activity habits, nor were they asked to avoid activity. Control participants attended their regular lymphoma clinical appointments (same as the intervention group), and were tested at the same time intervals as the intervention group (T0, T1, and T2).

3.6 STANDARDIZATION

Testing and intervention locations were standardized in the current trial. Functional testing followed the appropriate gold standard procedures for each test (Canadian Sport and Exercise Physiology Exercise Testing and Prescription Guidelines and American College of Sports Medicine Guidelines for Exercise Testing and Prescription).

The CARP followed the same outline in terms of duration of each activity, and type of activity, although level of activity was modified based on the ability of the participant as well as how they were feeling on a particular day. To assist with 'at home' exercise sessions, all intervention participants were given a manual (made by the student investigator) with pictures and descriptions of different exercises to perform at home (Appendix Q). All participants received the same booklet but were allocated different levels of the same activity to perform at home.

3.7 OUTCOMES and MEASUREMENT TOOLS

The primary outcome with respect to the impact of a CARP for lymphoma survivors was change in QoL scores (between groups) from baseline (week 0, T0) to post-intervention (12-weeks, T1). Follow-up was also measured at (T2) 12-month follow-up (12+/-2 months). Secondary outcomes included HRQoL, mood disturbance, anxiety, depression, and fatigue, cardiopulmonary and muscle function, and inflammatory markers of CRP and IL-6. Tertiary outcomes were examined; all subscales of the listed questionnaires were explored. It was also examined whether the theory of planned behaviour was an effectual model to predict exercise intention and behaviour (development of the TPB questionnaire is outlined in Appendix I).

Primary Aim 1 Identify whether a 12-week combined aerobic and resistance exercise training programme (CARP) is effective at improving quality of life (QoL) in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Secondary Aims

Aim 2 Determine whether a 12-week combined aerobic and resistance exercise training programme (CARP) is effective at improving standard measures of muscle function and cardio-respiratory fitness in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Aim 3 Examine whether a 12-week combined aerobic and resistance exercise training programme (CARP) affects inflammatory environment and/or immune function in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Aim 4 Examine whether theory of planned behaviour (TPB) may be an effectual model to predict exercise behaviour in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Further to the four main aims of the thesis, an additional component was added. The objective of this auxiliary qualitative exploratory study was to further explore, with the intention of gaining a greater understanding of how a convenient sample of participants perceived the CARP may have impacted their lives.

3.7.1 HYPOTHESES

In addressing these thesis aims, the following hypotheses were tested;

Hypothesis 1 12-weeks of combined aerobic and resistance exercise training (CARP) will positively affect quality of life (QoL) and QoL subscales in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Hypothesis 2 12-weeks combined aerobic and resistance exercise training (CARP) will produce measurable improvements in musculo-skeletal and cardiovascular fitness in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Hypothesis 3 12-weeks of combined aerobic and resistance exercise training (CARP) will demonstrate beneficial effects on the inflammatory environment and immune function in Hodgkin's and Non-Hodgkin's lymphoma survivors.

Hypothesis 4 theory of planned behaviour (TPB) will be an effectual model in the predication of exercise behaviour in Hodgkin's and Non-Hodgkin's lymphoma survivors.

3.7.2 TESTING PROTOCOL LOGISTICS

First, the Physical Activity Readiness Questionnaire (PAR-Q) was completed, followed by the questionnaire package (Appendix H). The questionnaire package included the following:

European Organisation for Research and Treatment of Cancer -Quality of Life (EORTC-QLQ-30), Functional Assessment of Chronic Illness Therapy Measurement System-Lymphoma Scale (FACT-Lym), The Profile of Mood States (POMS) Questionnaire, Hospital Anxiety and Depression Scale (HADS), and The International Physical Activity Questionnaire (IPAQ).

3.7.2.1 QUESTIONNAIRES

QoL and the domains of QoL were measured using the European Organisation for Research and Treatment of Cancer – Quality of Life (EORTC-QLQ-30). The QLQ-C30 (Aaronson *et al.,* 1993) is a reliable, valid questionnaire which measures different aspects of quality of life relevant to people with cancer and has specifically been used with Hodgkin Lymphoma (Miltényi *et al.,* 2010; Heutte *et al.,* 2009). The questionnaire contains 30 items and assesses QoL in people with cancer. It consists of six functional scales (physical, role, cognitive, emotional, and social functioning, and global QoL), three symptom scales (fatigue, nausea/ vomiting, and pain) and six individual items assessing sleep disturbance, constipation, diarrhoea, appetite loss, dyspnoea, and the financial impact of the disease and treatment. A linear transformation was performed to standardise raw

data, therefore all scales range in score from 0 to 100. A high score for a functional scale represents a high level of functioning; a high score for a symptom scale indicates a high level of symptoms (Fayers *et al.*, 2001). Internal reliability coefficients range from 0.52 to 0.89 (Aaronson *et al.*, 1993).

HRQoL and the subscales of HRQoL were measured using the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System- Lymphoma Scale. HRQoL is often measured using the Functional Assessment of Chronic Illness Therapy (FACIT) (Fong *et al.*, 2012). The full FACIT is comprised of the core measure FACT-G (the general version of the cancer-specific measure) and a 15-item lymphoma-specific additional concerns module (FACT-Lym) (Eremenco *et al.*, 2004; Webster *et al.*, 2005; Cella *et al.*, 2005). The FACT-G consists of four subscales, physical well-being (scored 0–28), social well-being (scored 0–28), functional well-being (scored 0–28), and emotional well-being (scored 0–21). The Function Assessment of Chronic Illness Therapy–Lymphoma (FACT-Lym) total score is calculated by adding the score obtained on the FACT-G to the score obtained on the Lym module (total possible score is 168, which indicates the highest possible HRQoL score).The FACT-Lym has good internal consistency ($\alpha = 0.70$) (Ermenco *et al.*, 2004) and validity (Webster *et al.*, 2005). Scoring of the FACT-Lym followed the FACIT scoring guidelines for each functional subscale and a FACT-Lym total mean score as well as the FACT-Lym trial outcome index (TOI) score (which includes only physical well-being, functional well-being and Lym scores added together). Mutrie and colleagues (2007) found no significant difference in the general QoL (FACT-G), but when adding the cancer-specific measure, they found significant improvements in results, suggesting the addition cancer-specific measure (i.e. the FACT-Lym in the current study) is valuable.

Both EORTC and the FACIT were chosen in the current trial because previous literature suggested that the two questionnaires measure markedly different aspects of QoL (Kemmler *et al.*, 1999). The FACIT is commonly used to measure HRQoL (Fong *et al.*, 2012). Chang and Cella (1997) reported that the FACIT showed better precision in measuring HRQoL amongst cancer participants (lower SEM). Differences have been highlighted between the two scales (Luckett *et al.*, 2011). The EORTC is relatively objective in its measure of function, whereas the FACT is more reflective and focuses on thoughts and feelings (Luckett *et al.*, 2011). For example, social functioning assesses impact on social activities and family life, while social well-being assesses social support and relationships: low correlations between the EORTC social functioning and FACT-G's social well-being highlights differences in what is being assessed by each questionnaire (Conroy *et al.*, 2000). In future trials it may be useful to use one of the two questionnaires

as there is some overlap between the two, but which to use will depend on the aim of the study.

Mood Disturbance and subscales were measured using The Profile of Mood States (POMS) Questionnaire. The POMS (McNair *et al.,* 1971) questionnaire is a useful descriptive measure for assessing behavioural, as well as subjective measurement of feeling, affect, and mood. This 65-point adjective scale considers six clearly defined mood states. These include tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia and confusion-bewilderment. This scale has often been used to determine mood disturbance in cancer patients and survivors (Cella *et al.,* 1987; Carlson *et al.,* 2002; Culos-Reed *et al.,* 2006).

Anxiety and Depression were measured separately (as well as part of the POMS questionnaire above) using the Hospital Anxiety and Depression Scale (HADS). Anxiety and Depression were measured using the HADS as well as the POMS because of the importance of the outcomes. It was thought that using a scale on its own may provide a more rigorous analysis of the outcomes. The HADS (Zigmond and Snaith, 1983) is useful in assessing the symptom severity of anxiety disorders and depression in somatic psychiatric and primary care patients as well as in the general population (Bjelland, *et al.,* 2002). It consists of 14 questions, seven for anxiety and seven for depression. Questions were answered by using a four-point (i.e. zero to three) response category, which had separate anxiety and depression scores that ranged from 0 to 21. Higher scores represent higher levels of depression and anxiety. In previous studies, the Cronbach's alpha for HADS-Anxiety varied from .68 to .93 (mean .83) and from .67 to .90 (mean .82) for HADS-Depression (Bjelland, *et al.,* 2002).

Fatigue was measured using the European Organisation for Research and Treatment of Cancer- Quality of Life Scale (EORTC-QoL-30) (fatigue subscale), the Functional Assessment of Cancer Therapy- Fatigue (FACIT) and the Profile of Mood States (POMS) subscale. The two uni-dimensional scales that have been recommended to measure cancer-related fatigue are the European Organisation for Research and Treatment of Cancer-Quality of Life Scale (EORTC-QoL-30) (fatigue subscale) and the Functional Assessment of Cancer Therapy- Fatigue (FACT F) (Minton & Stone, 2009). Both of these scales were used in the current study, although the lymphoma specific version of the FACIT questionnaire was used instead of the fatigue specific FACT questionnaire, but the lymphoma version still provides a fatigue score. The Profile of Mood States (POMS) questionnaire was used to measure overall mood state; this included a subscale of fatigue, which was also reported. Although three fatigue scores are not necessary, all are included as subscales of other variables being measured. The three fatigue scores will be reported

and discussed. In future studies it may be preferable to choose one measure of fatigue, as three was unnecessary.

To subjectively measure how much activity each participant was taking part in, The International Physical Activity Questionnaire (IPAQ) was used. The International Physical Activity Questionnaire (IPAQ) was developed to measure health-related physical activity. The 'Short Last 7 Days Self-Administered' version of the IPAQ was used. The short version IPAQ has been tested extensively and has been found to have acceptable validity when assessing levels and patterns of physical activity (Hagströmer, Oja, and Sjöström, 2005). The items in the short IPAQ form were structured to provide separate scores on walking, moderate-intensity and vigorous-intensity activity. Using the Ainsworth et al. (2000) compendium, an average MET score was derived for each type of activity. Vigorous-intensity activity was assumed to correspond to 8 METs, moderate-intensity activity to 4 METs and walking to 3.3 METs.

Using these values, four continuous scores are defined (Ainsworth *et al.*, 2000):

> Walking MET-minutes/week = 3.3 X walking minutes X walking days
>
> Moderate MET-minutes/week = 4.0 X moderate-intensity activity minutes X moderate days
>
> Vigorous MET-minutes/week = 8.0 X vigorous-intensity activity minutes X vigorous days
>
> Total physical activity MET-minutes/week = sum of the above three values MET-minutes/week.

Total weekly physical activity was calculated in accordance with the official IPAQ scoring protocol (1 MET= resting energy expenditure) (www.ipaq.ki.se). METS were also categorized into levels of activity, low=1 (<600METS weekly), moderate=2(601-1500 METS weekly) or high=3(>1501 METS weekly) to be used in the Theory of Planned Behaviour regression analysis.

The Theory of Planned Behaviour (TPB) was used to evaluate intention to exercise and actual physical activity behaviour from the variables of attitude, subjective norm, and perceived behavioural control (consisting of confidence and self- efficacy, each taken as separate variables). Previous literature using the theory of planned behaviour has supported the assertion that attitude, social support, and perceived control predict intention, and intention and perceived control predict actual behaviour. The TPB was chosen over other social cognitive models because of its extensive testing in exercise studies with cancer survivors (Courneya, Karvinen and Vallance, 2007), and its emphasis on intentional behaviour.

Two resources were used to construct questions to measure the constructs of the TPB in the current study; 'Constructing questionnaires based on the theory of planned behaviour: A manual for health services researchers (Francis *et al.*, 2004) and 'Constructing a TPB Questionnaire: Conceptual and Methodological Considerations' by Ajzen (2002). The questionnaire design for this

thesis can be found in Appendix I. The constructs measured within the TPB include attitude, social support, PBC, self-efficacy, intention, and actual exercise behaviour (Ajzen, 2002; Armitage and Conner , 2001; Culos-Reed *et al.,* 2004; Rhodes and Courneya, 2003). These theoretical constructs are latent variables; they must be inferred from observable responses (Ajzen, 2002). All constructs are designed around a specific behaviour which is clearly defined. Ajzen suggests including a Target, Action, Context, and Time frame (TACT) for the behaviour; this behaviour should be used throughout the questionnaire and was found to be compatible with the different constructs. In the current study, the behaviour, 'to engage in three exercise sessions per week for the next six months' was repeated throughout the questionnaire.

The predictors are analysed using a number of questions. Because the purpose of the study is to examine the variance in behavioural intentions (predictive), a12-item questionnaire therefore suffices (Francis *et al.,* 2004). Selected questions are similar to those used in a previous study by the current author (Culos-Reed *et al.,* 2006), but were adapted appropriately to follow the current study design. The current questionnaire was successfully piloted during the feasibility study conducted for this trial.

Attitude toward behaviour is defined as a person's overall evaluation of performing the behaviour in question (Ajzen, 2002). **'Attitude'** was measured using ten 7-point semantic differential adjective scales; both instrumental (e.g. worthless-useful, harmful-beneficial) and experiential or affective (e.g. not enjoyable-enjoyable, stimulating-dull) aspects of attitude. Cronbach's alpha (α) for this scale was 0.929.

'Social support' was measured by four items rated on 7-point scales that ranged from 1 (strongly disagree) to 7 (strongly agree). The items include socially perceived value towards attending class, social support to exercise, social pressure and expectations to exercise, and approval to attend the program. Cronbach's alpha (α) for this scale was 0.75.

Perceived behavioural control measures ones confidence that they are capable of performing the specified behaviour. The 2 components of 'perceived behavioural control' are 'control' and 'self-efficacy'. Control was measured with 2 items measured on a 7-point scale, and assessed feelings of control around exercise. Self-efficacy was measured with 2 items which considered confidence to perform specific exercise and ease of performing exercise for a specified time. Cronbach's alpha (α) for this scale was 0.788.

Although the relationship between behavioural intention and actual behaviour is not perfect, the premise of the TPB is that intention can be used as a proximal measure of behaviour (Francis *et al.,* 2004). **'Intention'** was assessed by two items questioning expectation to engage and desire to engage in activity using a 7-point scale. Measuring intention with only one or two items is common within TPB research (Ajzen, 1991). Cronbach's alpha (α) for this scale was 0.967.

3.7.2.2 PHYSICAL OUTCOMES

Outcomes were measured using objective, standardized tests. The present thesis conformed to the guidelines of regulatory governing bodies, CSEP and ACSM. Participants were pre-screened and followed the preliminary testing guidelines from the Canadian Physical Activity, Fitness and Lifestyle Appraisal (CPAFLA) testing protocol (CPAFLA manual, 3rd Edition, 2003) (Appendix J). Testing protocol followed the CPAFLA manual (CPAFLA manual, 3rd Edition, 2003) and ACSM manual (ACSM's Guidelines for Exercise Testing and Prescription, 7th Edition, 2006). Outcomes were measured at baseline (T0) and post-intervention (T1).

Treadmill Calibration. Functional exercise testing was performed on a motorised treadmill. The treadmill was calibrated prior to testing at a range of velocities ($5km.hr^{-1}$) and gradients (0.5% - 15%) that would be encountered during the study. Treadmill velocity was checked manually by measuring the length of the treadmill belt and recording the time taken to complete 50 revolutions. These calculations were verified automatically using a tachiometer (Compact, CT2, UK). Treadmill gradient (%) was validated using a spirit level and a setsquare. The % gradient was calculated as the sine of the angle (sin θ), in which sin θ equalled the vertical rise over the hypotenuse.

Determination of Body Index (BMI). Following the CPAFLA guidelines, each participant was instructed to remove excessive clothing (e.g. jackets, sweaters) and footwear prior to the measurement of body fat using a balanced weighing scales (Seca, Cardiokinetics, Salford, UK) and height was measured with a stadiometer (Seca, Cardiokinetics, Salford, UK). The weighing scales was calibrated prior to each 'weigh in' with a 5kg free mass. The accuracy of the stadiometer was verified with a steel tape measure. Body Mass Index (BMI) was calculated by dividing participants' weight in Kilograms by the square of the subject's height in metres.

Determination of Waist and Hip Circumference. Waist and hip circumference was measured using a K-E Anthropometric tape measure. While the participant stood relaxed with arms loosely by their sides, waist circumference was taken with the measuring tape positioned horizontally midway between the bottom of the ribcage and iliac crest (measurement taken at end of normal expiration) (recorded to nearest 0.5cm). Hip circumference was also taken from the right hand side of the body and is the widest part of the hips at or below the iliac crest (recorded to nearest 0.5cm).

Determination of Body Fat Percentage. 'Bodystat®1500 bioelectrical impedance analyser' was used for testing. Participants were asked to expose their right hand and foot, and lie supine to perform this test. Electrodes were placed on exposed skin on the right hand and the right foot of the participant. The two main cable leads were attached to the tabs on the electrodes. The subject's gender, age, height, weight and waist/hip measurements were entered into the bioelectrical impedance analyser. A safe battery-generated signal was sent through the body measuring the impedance at a fixed frequency of 50 kHz, from which percentage of body fat was calculated and reported.

Determination of Arterial Blood Pressure. Systemic arterial blood pressure (BP-mmHg) was measured in the brachial artery non-invasively using the ausculatory method outlined in the American College of Cardiology Position Paper (AHA, 2005). Using a mercury sphygmomanometer (Accoson *Freestyle*, Cardiokinetics, UK) and stethoscope (littmann, 3M, USA), systolic pressure was recorded at the first appearance of clear repetitive tapping sounds (Korotkoff Phase 1) and diastolic pressure was recorded at the disappearance of repetitive sounds (Korotkoff Phase 5). In some subjects in whom sounds continued until the zero point, diastolic pressure was determined at the distinct muffling of repetitive sounds (Korotkoff Phase 4). Heart rate was measured by palpating the radial artery for 15 seconds; the value was then multiplied by 4. Electronic measurements of blood pressure and heart rate were taken to confirm manual measurements.

Perceptual Scales. Each subject subjectively rated how hard they were working during exercise using the modified Borg scale ratings of perceived exertion (RPE) (Borg, 1982) which is based on the original Borg exertion scale (Borg, 1982). This scale ranges from 1 to 10 (Appendix L) Subjects were instructed to indicate their perception of exercise intensity by communicating verbally or pointing at the scale.

3.7.2.3 RESPIRATORY MEASUREMENTS

Spirometery. The forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured using a hand-held micro spirometer (Micro Medical micro spirometer). Three expiratory manoeuvres were completed to meet reproducibility criteria (all must be within 200mL of each other for each measurement); the first value was reported if the following two tests were within 200mL of the first. The percentages of predicted values were calculated. The measured results were compared to the predicted normal values based on the participant's age, gender, and height. To obtain the percentage of predicted values, the equations of Crapo, Morris, Clayton, and Nixon CR (1982) were used.

Crapo et al. (1982) predicted values calculation equations (taken from 'The Johns Hopkins Pulmonary Function Laboratory' http://www.hopkinsmedicine.org/pftlab/predeqns.html):

FVC pred = 0.1524*Height(inches) - 0.0214*Age(years) - 4.6500 [Men]
FVC pred = 0.1247*Height(inches) - 0.0216*Age(years) - 3.5900 [Women]

FEV1 pred = 0.1052*Height(inches) - 0.0244*Age(years) - 2.1900 [Men]
FEV1 pred = 0.0869*Height(inches) - 0.0255*Age(years) - 1.5780 [Women]

FEV1% = Predicted FEV1 / Predicted FVC

3.7.2.4 ENERGY EXPENDITURE MEASUREMENTS

Determination of Maximal Aerobic Capacity .The Balke-Ware Treadmill test (Balke and Ware, 1959) was used to assess aerobic capacity, quantified as the duration of symptom limited maximal exercise (Blair *et al.,* 1989; Balke and Ware, 1959). The Balke-ware protocol is made up of small incremental increases in incline (less than 1 MET per stage), whilst speed stays constant at 3.3mph. The Balke-ware protocol is recommended for use with deconditioned populations or those with chronic illness (ACSM, 2006). Grade was increased at each stage (minute) starting at 2% at 2 minutes and was increased to 26% if necessary. For the first two minutes of the test the incline was 0, speed was 3.3mph. At two minutes the incline was increased to 2%. Thereafter, the incline was increased by 1% at each minute. The test ended when either the participant chose to stop due to fatigue, or when the tester terminated the assessment (indications for terminating exercise as per the ACSM guidelines include the following: nervous system symptoms, confusion, dizziness, decreased alertness, fatigue, shortness of breath, wheezing, muscle cramps). At no point was the participant encouraged to continue beyond the level within which they wished to stop. During the test both heart rate and rate of perceived exertion were monitored. The 'ACSM Guidelines for Exercise Testing and Prescription, 7th Edition' (Whaley, Brubaker, Otto, 2006) provides the associated metabolic cost for each stage of the Balke-Ware exercise protocol (Figure 5.3, pps. 100-101). The MET value achieved was then used to determine oxygen consumption per unit body mass (1 MET =3.5ml/kg/min).

The Balke-Ware Treadmill test (Balke and Ware, 1959) was used to assess cardiorespiratory fitness, quantified as the duration of symptom limited maximal exercise (Blair *et al.,* 1989; Balke and Ware, 1959). The Balke-ware protocol comprises incremental increases in incline (less than 1 MET per stage), whilst speed stays constant at 3.3mph, allowing participants to walk throughout the test. The Balke-ware protocol is recommended for use with deconditioned populations or those with chronic illness (ACSM, 2006). Grade was increased at each stage (minute) starting at 2% at 2 minutes and was increased to 26% if necessary. For the first two minutes of the test the incline was 0, speed was 3.3mph. At two minutes the incline was increased to 2%. Thereafter, the incline was increased by 1% at each minute. The test ended when either the participant chose to stop due to fatigue, or when the tester terminated the assessment (indications for terminating exercise as per the ACSM guidelines include the following: nervous system symptoms, confusion, dizziness, decreased alertness, fatigue, shortness of breath, wheezing, muscle cramps). At no point was the participant encouraged to continue beyond the level within which they wished to stop. During the test both heart rate and rate of perceived exertion were monitored. The 'ACSM Guidelines for Exercise Testing and Prescription, 7th Edition'(Whaley, Brubaker, Otto, 2006) provides the associated metabolic cost for each stage of the Balke-Ware exercise protocol (Figure 5.3, pps. 100-101). The MET value achieved was then used to determine oxygen consumption per unit body mass (1 MET =3.5ml/kg/min).

3.7.2.5 MUSCLE FUNCTION MEASUREMENTS

Determination of Peripheral Skeletal Muscle Function. Hand grip strength was chosen to assess muscle strength, push-ups and partial curl-ups assessed muscular endurance, and the 'sit and reach' test was used to assess flexibility. All of the musculo-skeletal assessments followed the CPAFLA guidelines provided by CSEP.

CSEP Grip Strength:

Maximal grip strength was measured using an adjustable dynamometer (TKK 5001 Grip-A, Takei Scientific Instruments Co., Ltd, Japan). Participants held the dynamometer in line with the forearm at the level of the thigh and were instructed to squeeze vigorously and attempt to exert maximal force. Three attempts were made with each hand, with the highest score being recorded (to the closest 1kg). A total grip strength was calculated by adding the right and left hand grip strength together.

CSEP Push-Up:

Push-up testing was performed to assess muscular endurance of the upper body. The participant is asked to correctly perform as many consecutive push-ups as possible, with no time limit. As per the CPAFLA criteria, set-up begins with the participant lying on a mat on their stomach, hands pointing forward placed under their shoulders and feet together. To begin the push-up movement, the participant is asked to lengthen their arms to an extended position, keeping their back straight. Females performed modified push-ups (from knees); men performed full push-ups (from toes). As the participant bends their elbows, they should bring their chin to the mat: stomach and thighs should not touch the mat during any part of the push-up movement. If the movement did not meet the above criteria, it was not counted. After two improper repetitions, or when the participant no longer wished to continue, the test was stopped.

CSEP Partial Curl-up:

After the initial set-up, the participant was asked to lie supine on the mat, with their arms down by their sides. The participant places their middle finger on a starting line. Using a set square, the participants knees are bent to 90° with their feet and legs hip-width apart. The curl up began by lifting the head and shoulders off the mat whilst moving the fingers (palms staying on the mat) from the finger tip start line to the finger tip finish line (10 cm ahead). On the return, the participants brought their head and shoulders back to the mat, as their finger tips returned to the start line (palm staying on the mat). Feet maintained contact with the mat the entire time. Participants performed as many curl- ups as possible, keeping in time to a set cadence (50 beats per minute). The test continued until the participant could no longer keep in time with the set cadence or when the curl-ups were not performed correctly on two consecutive repetitions.

CSEP 'Sit and Reach' Test:

The sit-and-reach test was used to measure hamstring and low back flexibility. Participants sat with legs extended with shoeless feet placed 6 inches apart on the sit-and-reach (flexometer) box. With legs extended and without jerking, the participant reached as far forward as possible (holding reach for a minimum of 2 seconds). The measurement was taken twice and the farthest reach was recorded (to the nearest 0.5cm).

3.7.2.6 DETERMINATION OF BIOMARKERS OF IMMUNE FUNCTION

Blood Sampling. Each subject assumed a seated, resting position for a 10-minute period prior to blood collection to allow for a stabilisation of plasma volume. A tourniquet was secured to the right arm with the minimum of constriction required to obtain a blood sample (Bachorik, 1982). When collection procedures were finished, the puncture site was cleaned with swabs saturated with 70% v/v Isopropyl alcohol (Medi Swab, Smith and Nephew, UK) and covered with a cotton dressing. Venous blood samples were obtained from an antecubital forearm vein and collected into vacuutainer tubes (Becton Dickinson, Rutherford, NJ, USA). Samples were allowed to clot and were then centrifuged at 2,000 rpm for 20 minutes. Serum and plasma were then extracted and placed into eppendorfs and stored at $-80^{o}C$ for subsequent biochemical analysis at the university hospital pathology laboratory.

Interleukin 6 (IL-6) and C-Reactive Protein (CRP)

Serum samples were incubated in duplicate wells of the micro titer plates, which had been pre-coated with antigen specific (IL-6, CRP) monoclonal antibodies. During this incubation IL-6 or CRP present in the standards or serum samples was immobilized by their specific pre-coated antibodies (form antigen antibody complexes). Repeated washing and aspiration was conducted to remove all other unbound materials from the assay plate prior to incubation with specific antibody-enzyme reagents. The assay plates were washed again and incubated with a substrate solution and colour developed in proportion to the amount of antigen bound in the initial step of the individual assays. The colour development was stopped with the addition of an acid solution and the intensity of color was read using a programmable micro titer plate based spectrophotometer. The concentrations of IL-6 and CRP serum samples were determined by interpolation from individual standard curves composed of human IL-6 or CRP.

Coefficient Of Variation (CV%);

The calculated inter-assay coefficients of variation (CV) for IL-6 and CRP immunoassays in our laboratory were 5.78% and 6.28%. Calculated intra-assay CVs for IL-6 and CRP were 3.24% and 2.63% respectively. The calculated detection limits (sensitivity) for IL-6 and CRP and were 0.14 pg/ml, 1 ng/ml respectively.

3.8 CHANGES TO TRIAL OUTCOMES

The only changes to this study related to the removal of follow-up measurement of functional and immunological measures at 1 year on commencing the intervention The primary reason for this unplanned removal related funding constraints that were beyond the influence of the principal investigator. A further amendment was the addition of a 6 person focus group towards the completion of the study.

3.9 SAMPLE SIZE

The sample size was originally calculated on cardiorespiratory fitness (see original determination of sample size, below), but upon realising that sample size should be based on the primary outcome, sample size was recalculated.

A recalculation was performed based on the weighted mean effect size (WMES) of 0.842 for QoL (physical function and physical well-being subscales of QoL for exercise) (McNeely *et al.*, 2006).

To detect improvement in QoL post-intervention, with an anticipated mean difference of 0.75, a power of 0.80 and an alpha value of 0.05, a sample size of 21 participants per group was necessary. To account for drop-outs/ withdrawals (10%), a minimum of 47 participants were recruited (57 participants were recruited in the current trial).It was expected that recruitment of 47 participants would take 12 months.

Calculation: Based Hinkle, *et al.*, 1998, two-tailed tests (page 323):

$n= 2(.842 - (-1.96))^2 /(\text{effect size})^2$ (where effect size = .865)

$n= 2(.842 -(-1.96))^2 / .865 * .865$

$n= 15.702/.748$

$n= 15.702 /.748 = 20.99$ cases

Therefore 21 cases per group provide an effect size of .748 (a medium to large effect size) (Hinkle *et al.*, 1998, page 325).

The focus group was selected as a convenience sample. All intervention participants were invited to attend (n=20). Six participants attended the focus group.

3.10 RANDOMISATION

Stratified randomisation was employed in the current trial to balance the numbers of NHL and HL survivors in each group. For allocation of participants, computer generated randomisation algorithms were used (Microsoft Excel). Algorithms were made by Dr. A. Petroczi from Kingston University who was completely impartial and not involved in the current trial. Two separate algorithms were used- one for HL and another for NHL survivors (participants were randomised by tumour type in order to keep the balanced). Both randomisation algorithms were made with a total number; the NHL randomisation

calculation allowed for 50 total participants whereas the HL randomization calculation was set in blocks of 8. This was done to keep the numbers in the groups balanced.

Allocation concealment mechanism and implementation. Computer generated randomisation algorithms were used to allocate participants to groups were created before the recruitment for the trial began (by Dr. A Petroczi who had no involvement in the current trial). Only after assessing eligibility (done by Dr. R Pettengell, Consultant at the Lymphoma Clinic at SG Hospital), presenting and discussing the PIS (The student investigator, L. Daroux-Cole presented the PIS to all eligible participants), obtaining informed consent (done by the student investigator), participants were stratified by tumour type and then randomised into the intervention or control arm. Allocation to groups was done by the student investigator who referred to the computer generated randomisation algorithm and gave the participant the next number in the study which was allocated either an intervention or group placement. The allocation sequence was available to the student investigator, but the order in which participants joined the study was unknown so group allocation could not be modified or manipulated by the researcher or the participant. In future trials it would be useful to have third party assignment to remove any risk of selection bias and to increase internal validity.

3.11 BLINDING

All blood biochemistry was performed with biochemist blinded to the study. The questionnaires (psychological outcomes) were subjective and therefore could introduce bias into the trial. Although not notified of group allocation, healthcare providers were not formally blinded in the current trial. General practitioners were notified of which group their patient was allocated to, but they were not at all involved with the trial. The participants and the student investigator (who both taught the intervention and assessed outcomes) were not blinded in the current trial. The student investigator played a number of roles in the current trial because it was a student-led trial and there was limited funding. The overlap in roles was discussed by the committee, and it was decided that it was worthwhile running the trial as designed, noting the biases that comes from lack of blinding. In future trials it would be worthwhile to have healthcare providers, data collectors and outcome adjudicators unaware of group allocation to reduce differential bias and increase the integrity and internal validity of the trial.

3.12 STATISTICAL PROCEDURES USED TO COMPARE GROUPS

All collected data were entered into PASW 18.0 (PASW- SPSS for Windows, Chicago, IL, USA: SPSS Inc.). Participants who contributed at least two assessments (pre- and post- testing) were used in the analysis, thus a *per protocol analysis* was conducted. If data were missing within a subscale, it was imputed from the completed data points within that subscale as long as more than 50% of the items were answered within each subscale. Total scales were considered appropriate to score as long as the overall item response rate was greater than 80% (Webster *et al.,* 2003).If the participant withdrew before post-testing (i.e. death, morbidity, relapse), they were not included in the analysis (thus the analysis was per protocol). If withdrawal occurred after T1 (post-testing), but before follow-up (n=26), their data from T0 and T1 were used, but T2 (no data) was not.

3.12.1 QoL AND PSYCHOLOGICAL DATA: LINEAR MIXED MODELS ANALYSIS FOR BETWEEN GROUP REPEATED MEASURES

The primary outcome in the trial was the impact of the CARP on QoL scores, aiming to assess whether data provided evidence of superiority amongst the intervention group compared to the controls. Secondary outcomes of HRQoL, as well as mood disturbance, anxiety, depression, and fatigue were also hypothesised to show mean change (over time) between groups. All repeated measures (parametric) data were analysed using a linear mixed models analysis procedure (subscales for these outcomes were also analysed using the same analysis). Mixed models analysis is beneficial in that it makes use of all data (no list-wise deletions) therefore power is increased due to increased n, and spacing of time intervals between testing is not an issue. This was chosen instead of Repeated Measures ANOVA due to the low number of respondents taking part in the 12-month follow-up. Data were collected at baseline (pre-intervention/ pre-control), post (post-intervention/ post-control), and follow-up (12-month follow-up). A priori contrasts were examined at $p<0.05$ within groups for all psychological data.

Minimal Clinically Important Difference (MCID). Subjective interpretation of trends is often heavily influenced by reporting of the p-value, but the *P*-value is largely contingent on sample size, thus larger studies more likely to report statistical significance. As well, the *P*-value is often set at .05, and indicates only whether or not observed changes are large enough to conclude that such differences were not caused by chance (Brawley *et al.,* 2002).Clinical significance, or minimal clinically important difference (MCID) may not involve statistical significance (Fethney, 2010) but is considered a marker of the effectiveness of the practical importance of treatment effects (Sloan *et al.,* 2006). Magnitude of clinical relevance in the EORTC-QLQ-30 was calculated for QoL and associated domains (Osoba *et al.,* 1998), a small magnitude of clinical relevanance is a mean change in score of 5 to 10; moderate change is 10 to 20; and a large change is greater than 20. Minimal important difference (MID) using the Fact-Lym questionnaire is acceptable in a range of 3–5 points per scale or 5–8% of the scale range (Hlubocky *et al.,* 2013). For the measures that did not have specific guidelines for calculating MCID, clinical significance was determined using 0.5

SD of the baseline measure (Sloan, 2005). Pre-post mean differences larger than 0.5 SD on that scale is an indicator of "meaningful difference" thus is considered clinically significant (Sloan *et al.*, 2006).

Three variables were significantly different between groups at baseline; HADS depression, POMS depression, and POMS tension/anxiety. It is acceptable to analyse outcomes that are significantly different at baseline in an RCT because differences are caused by chance. HADS depression, POMS tension/anxiety, and nausea/ vomiting variables were deleted because normality, a requirement for linear mixed models linear analysis, could not be met (transforming and removing outliers did not work as the n became too low); the option of examining these data using non-parametric analysis was decided against as the statistician suggested there were already a large number of variables, and this was only a subscale measure. In hindsight, all variables should have been analysed and reported to meet ITT guidelines and following CONSORT, variables with statistically significant differences at baseline do not need to be removed from analysis because in an RCT, differences are caused by chance (Schultz *et al.*, 2010).

All psychological data met the requirements of a balanced design and were normally distributed with the exception of total mood disturbance, fatigue (FACIT), and anger/hostility scores, which due to a skewed distribution, were transformed (square root) to achieve normality (the total mood disturbance scores were also adjusted to make all positive scores). Homogeneity of variance was met.

3.12.2 PHYSICAL DATA: MULTIVARIATE ANALYSIS OF VARIANCE

Secondary outcomes, aerobic capacity, pulmonary function, muscle function, body composition and flexibility data were collected at baseline (T0) and post-intervention (T1). A series of Multivariate analysis of variance (MANOVA's) were conducted to test the hypothesis that there would be one or more mean differences (over time) between groups on the dependent variables in each MANOVA. The variables that fit into a logical group (with high internal consistency) were grouped together, Internal consistency was found for the dependent variables participating in each multiple ANOVA sets (Chronbach's alpha >0.70).

Some cases were removed (maximum of four cases per variable) to ensure normal distribution (skewness and kurtosis within the range of -1 to +1). Any skewness or kurtosis outside the absolute value of 1 is outlined in the results section. Although non-parametric testing may have offered an alternative to removing cases, too many tests would be needed. Box's M values were ignored for all MANOVAs due to balanced design.

Univariate comparisons were conducted on each dependent variable between groups and time: post-hoc contrasts examined the group by time interactions for all variables.

Four variables- resting heart rate, body composition, metabolic equivalent, and sit and reach- did not attain normality when put with other variables, or did not reach an acceptable

internal consistency with other variables and were independently analysed using repeated measures ANOVA. Correction wasn't used because tests were all for different categories/ types of data (e.g. strength versus cardiovascular).

3.12.3 IMMUNE MARKERS: REPEATED MEASURES ANOVA

Repeated Measures Univariate ANOVA was used to analyse immune markers of CRP and IL-6. Blood was collected at baseline (T0) and post-intervention (T1). Groups were compared at baseline using T-tests; there were no differences between groups on immune markers.

3.12.4 THEORY OF PLANNED BEHAVIOUR: CORRELATIONS AND REGRESSIONS

Level of correlation between TPB variables (low (<0.33), moderate (0.34-0.66), or high (>0.67)) was reported from the correlation matrix.

Regression analysis was used to examine the predictive value of the TPB variables upon intention to exercise, and TPB variables and intention upon actual behaviour. Simultaneous Multiple Regressions were used first to determine the equation for each model. Linearity was examined by inspecting the scatter of the points to see if a line makes sense. Stepwise Multiple Regressions were used to examine the impact of each variable on the dependent variable to find the best model of prediction (highest R^2 with smallest amount of variables). Collinearity was checked and reported. There were no significant differences in variables between groups at baseline (as examined using T-tests), therefore all subjects were collapsed into one group for the baseline analysis. Groups were analysed separately post-intervention.

All regressions were run both at baseline (collapsed group) and at post (by group: intervention and control) to explore the strength of attitude, subjective norm and perceived control (both control and self-efficacy) in predicting intention to exercise and in predicting actual behaviour.

Chapter 4.

RESULTS

4.0 INTRODUCTION

The current randomized controlled trial (RCT) compared lymphoma patients who took part in a 12-week exercise intervention programme (performed three times weekly) to a control group. Psychological, physical and biological indices were examined at baseline (after completion of chemotherapy/ radiation treatment), and at 12-weeks (at the end of the structured programme). Additional assessments were performed on variables of exercise behaviour and psychological indices at 12(+/- 2) months following the end of the structured programme. A total of 41 participants completed the study, 21 controls and 20 intervention participants.

4.1 PARTICIPANT RECRUITMENT AND ADHERENCE TO STUDY

Recruitment. Of the 89 lymphoma patients assessed, 76 were eligible for the current study. Participants were recruited (n=57) from a specialist Lymphoma Clinic at St. Georges Hospital, London (SGH) between June 2009- July 2010; n= 47 were randomised. Of the 47 pre-tested, n=41 participants took part in, and were analysed in the RCT. Follow-up data collection occurred 12 +/- 2 months after programme initiation, between June 2010- August 2011; n=15 participants took part in the follow-up analysis.

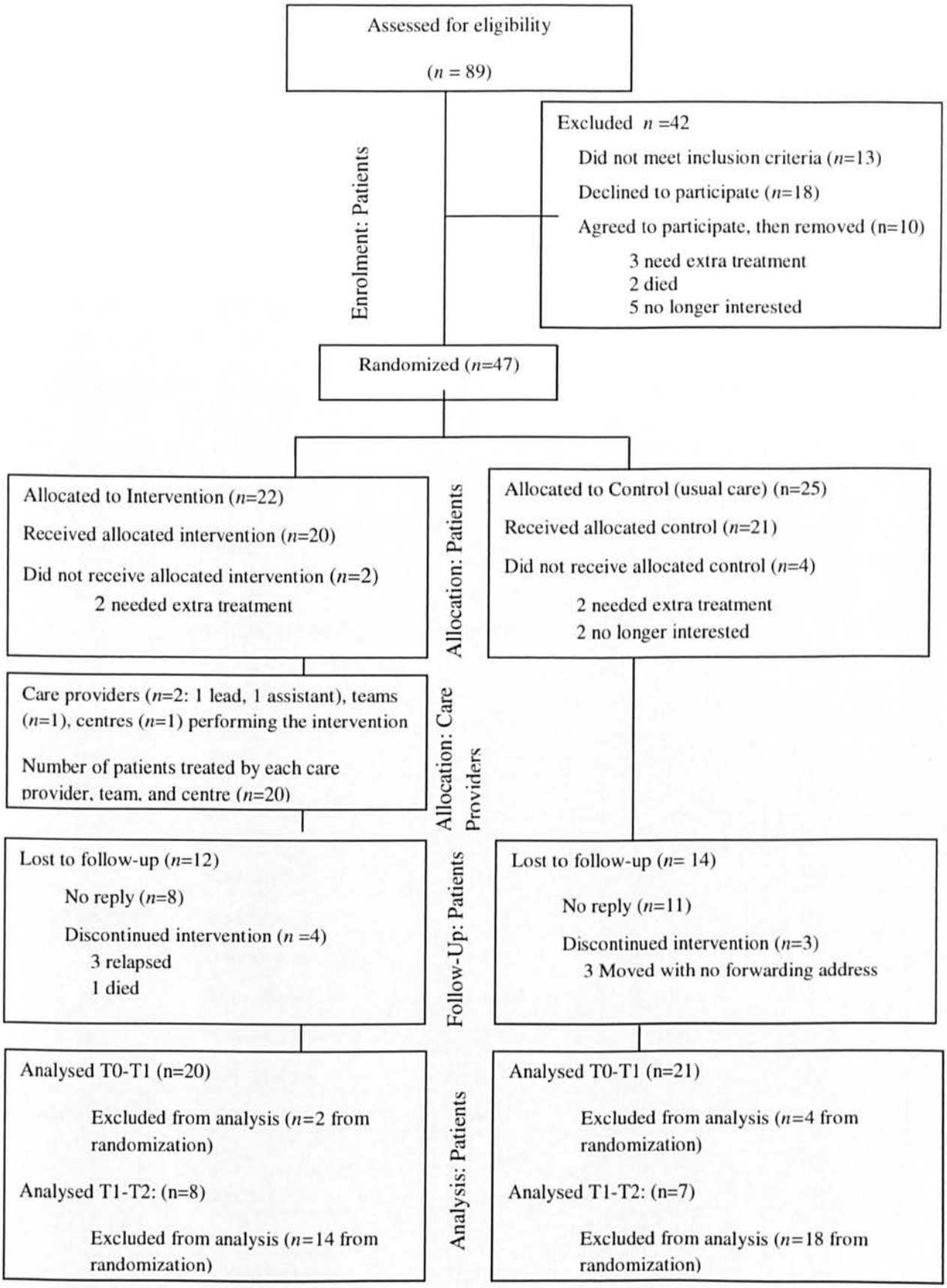
Trial Ended. Recruitment ended when the sample size quota (40 plus 10 to account for drop-outs) was achieved (n=50) (an additional 7 participants were added on the last day of recruitment).

Losses and Exclusions. Of the 89 lymphoma patients considered for the trial, 13 were ineligible.Of the 76 were eligible, 57 completed the consent form, but before before pre-testing and randomization, 5 became ineligible(n=3 needed extra treatment, n=2 died) and 5 no longer wished to take part. Participants attended pre-testing (T0) and were then randomised (n=47). Of the 47 pre-tested and randomised, n=6 were lost before the intervention began (4 controls, 2 intervention). Protocol violators include 4 participants who needed extra treatment and were no longer eligible (2 per group), and 2 participants from the control group stated they were no longer interested. The current trial followed a 'per protocol' analysis as only participants who had completed the RCT were used for analysis (accepting the bias associated with this protocol). All participants in that were randomized (n=47) were not included in the analysis, thus an intention to treat (ITT) analysis was not conducted and therefore the trial is more of an efficacy trial than an effectiveness trial, despite the original intent).

Numbers Analysed. Consequently, 41 participants were analysed in the RCT, 20 intervention and 21 control participants. A follow-up assessment at 12 (=/-2) months was performed to measure whether QoL scores, psychological outcomes, and current activity levels changed one year after the intervention had ended; 15 participants completed follow-up testing (8 intervention and 7 controls). Of the 26 participants lost to follow-up, 19 did not reply when contact was attempted (8 from the intervention group and 11 from the control group), 7 discontinued the study; from the intervention

group, 3 relapsed, 1 died; from the control group, 3 moved from the local area and did not provide forwarding address.

Figure 4.1. Flow diagram of progress through the phases o f a randomized trial of two groups



4.2 BASELINE DATA (T0)

Forty one participants, 20 male and 21 females, with a mean age of 54.07 (*SD* = 18.30) completed the trial: twenty participants were in the intervention group and 21 in the control group. Eleven participants had Hodgkin lymphoma, 30 had non-Hodgkin lymphoma (20 aggressive, 7 indolent, 3 marginal). Baseline testing took place 35.8 days from the last treatment (on average). The majority of participants were married, completed University education, were retired, and did not smoke. Refer to Table 4.1 for demographic and clinical details of the groups.

Table 4.1. Baseline Data including age, sex, type of lymphoma, days since last treatment, marital status, education, employment, smoking status: Reporting all participants and by group. Standard deviation is provided for mean data; proportions (by group) for categorical data.

DEMOGRAPHICS		**ALL SUBJECTS**	**INTERVENTION**	**CONTROL**
N		41	20	21
AGE mean (SD)		54.07 (18.3)	51.95 (18.1)	56.38 (18.8)
SEX	Male	20 (48.8%)	8 (40.0%)	12 (57.1%)
	Female	21 (51.2%)	12 (60.0%)	9 (42.9%)
TYPE	Hodgkin Lymphoma	11 (26.8%)	5 (25.0%)	6 (28.6%)
	Non Hodgkin Lymphoma (aggressive/indolent/marginal)	30 (20/7/3) (73.2%)	15 (12/2/1) (75.0%)	15 (8/5/2) (71.4%)
DAYS SINCE TREATMENT mean (SD)		35.8 (38.5)	36.1 (37.2)	35.6 (40.7)
MARITAL STATUS	Married	24 (58.5%)	13 (65.0%)	11 (52.4%)
	Divorced/ separated	5 (12.2%)	1 (5.0%)	4 (19.0%)
	Widowed	2 (4.9%)	2 (10.0%)	0 (0.0%)
	Never married	10 (24.4%)	4 (20.0%)	6 (28.6%)
EDUCATION	Some high school	7 (17.1%)	6 (30.0%)	1 (4.8%)
	Completed high school	11 (26.8%)	3 (15.0%)	8 (38.1%)
	Some college/ University	6 (14.6%)	5 (25.0%)	1 (4.8%)
	Completed University	13 (31.7%)	5 (25.0%)	8 (38.1%)
	Graduate school	4 (9.8%)	1 (5.0%)	3 (14.3%)
EMPLOYMENT	Full-time	12 (29.3%)	4 (20.0%)	8 (38.1%)
	Retired	16 (39.0%)	7 (35.0%)	9 (42.9%)
	Part-time	2 (4.9%)	2 (10.0%)	0 (0.0%)
	Unemployed	5 (12.2%)	4 (20.0%)	1 (4.8%)
	Sick/ disability leave	6 (14.6%)	3 (15.0%)	3(14.3%)
SMOKING	Smoker	6 (14.6%)	5 (25.0%)	1 (4.8%)
	Non-smoker	35 (85.4%)	15 (75.0%)	20 (95.2%)

4.2.1 RETENTION

Retention for our primary end point was 87.2% (41 of 47). By group, retention was 90.1% for the intervention group and 84.0% for controls.

At follow-up, only 8 of 22 (36%) participants in the intervention group and 7 of 25 (28%) participants in the control group completed follow-up testing. Retention at follow-up from initial group allocation was 31.9% (15 of 47).

4.2.2 ADHERENCE

Adherence to the CARP was 90.8%.

4.3 OUTCOMES

The current chapter lists mean scores for all outcomes. Although CONSORT guidelines (Schultz *et al.*, 2010) suggest results should be reported for all planned primary and secondary end points, this chapter includes only the statistically significant relationships, whereas those that were not significant can be found in Appendices N, O, and P.

4.3.1 PRIMARY OUTCOME

QoL. Quality of life (QoL), social (SF), physical (PF), cognitive (CF), and role (RF) increased in both groups from baseline (T0) to post-testing (T2); only emotional function (EF) scores decreased, in both groups at this time. At follow-up (T2), scores of QoL and EF increased in both groups; SF, PF, CF, and RF scores continued to increase for the control group, whereas amongst the intervention group, these scores decreased. Linear mixed model analyses were used to examine statistical relationships.

Table 4.2. QoL and domains of QoL measured by EORTC-QLQ-30 for Intervention group (INT) compared with control (CON). Values are in arbitrary units (mean ± SD)

	QoL		**SF**		**PF**		**EF**		**CF**		**RF**	
	INT	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*
T0	62.50 ± 22.4	58.03 ± 25.1	66.67 ± 35.5	80.34 ± 14.7	83.46 ± 11.6	79.53 ± 22.4	78.07 ± 21.0	86.75 ± 15.6	85.00 ± 19.4	87.87 ± 13.0	91.03 ± 8.7	86.74 ± 15.6
T1	68.54 ± 18.3	69.68 ± 16.7	84.45 ± 21.9	91.21 ± 14.1	90.57 ± 10.2	89.14 ± 12.6	73.80 ± 24.7	84.46 ± 18.9	89.20 ± 9.8	91.43 ± 11.5	94.44 ± 11.4	98.26 ± 4.4
T2	69.80 ± 19.4	76.19 ± 20.7	81.25 ± 31.4	100.00 ± 0.0	82.50 ± 20.1	93.33 ± 12.8	77.08 ± 27.0	97.62 ± 6.3	85.42 ± 16.5	92.86 ± 13.1	85.42 ± 24.3	100.00 ± 0.0

No statistically significant differences were seen between groups or within groups for QoL scores. Domains of SF and PF showed significant change from baseline to T1; the intervention group showed significant improvements in SF (p=0.020) whereas significant improvements in PF (p=0.049) were seen in the control group at the same time.

None of the follow-up scores were statistically significant, although trends lean towards improvement amongst the control group in PF, RF, SF and a slight increase in CF, whilst in the intervention group these scores decreased. EF and QoL scores increased in both groups at follow-up.

Table 4.3. QoL and QoL Domains: Summary of Significant Relationships (Mixed Model Analysis & A priori Contrasts), Significance ($p<0.05$)

Variable	**Interaction (time)**	**F**	**Std Error**	**Df**	**Probability**
PF	Control (0-1)		4.777	63.89	0.049
EF	Group	8.180		1(36.71)	0.007
SF	Time	4.285		2(29.24)	0.023
	Group	6.016		1(37.09)	0.019
	Time 0 to Time 1		5.309	64.88	0.026
	Intervention (0-1)		7.443	65.34	0.020

Clinically significant change was reported in both groups on QoL (small clinically important difference for the intervention group, moderate for controls), and clinically important difference for intervention on SF. A small clinically important difference was seen in the reduction of RF amongst the intervention group from between T1 and T2. All other clinically significant changes were seen in the control group only; PF from T0 to T1 showed a small clinically important difference, RF a moderate effect at the same time; a moderate clinically important difference was seen in EF from T1 to T2. From T0-T2, increased QoL was clinically relevant, reductions in SFand RF in the intervention group were clinically relevant, as were increased QoL, SF, PF, EF, and RF in the control group.

Table 4.4. Magnitude of Clinical Relevance of change scores: QoL and domains of QoL measured by EORTC-QLQ-30

	T1-T0		T2-T1		T2-T0	
	INT	*CON*	*INT*	*CON*	*INT*	*CON*
QoL	small	moderate	-	small	small	moderate
SF	moderate		-	small	moderate	moderate
PF	-	small	-	-		moderate
EF	-	-	-	moderate		small
CF	-	-	-	-		
RF	-	moderate	small (-)	-	small (-)	moderate

4.3.2 SECONDARY OUTCOMES

HRQoL. HRQoL scores improved in the intervention group from T0-T1,but slightly decreased amongst the control group. Both groups saw increases in HRQoL at T2. Trial outcome index scores (TOI) (physical and functional well-being plus the lymphoma specific subscale) improved in both groups over time.

Increases were seen by both groups in physical well-being (PWB), functional well-being (FWB), and lymphoma scale (LymS) T0 to T1. Social well-being (SWB) scores decreased in both groups, whilst emotional well-being (EWB) scores increased in the intervention group but decreased in the control group from T0- T1. At follow-up, PWB, FWB, EWB scores decreased amongst the intervention group but increased in the control group; SWB measures showed a slight increase in the intervention group but a decrease in the control group. Both groups showed large increases in LymS

Table 4.5: HRQoL and Subscales of HRQoL measured by FACT-Lym for Intervention group (INT) compared with control (CON). Values are in arbitrary units (mean ± SD)

	HRQoL		SWB		PWB		EWB		FWB		LymS		TOI	
	INT	CON	INT	CON	INT	CON	INT	CON	INT	CON	INT	CON	INT	CON
T0	93.29 ± 5.8	93.44 ± 5.4	22.611 ± 1.3	21.51 ± 1.3	22.61 ± 3.5	22.39 ± 3.0	18.41 ± 5.3	21.10 ± 2.4	18.72 ± 3.8	17.30 ± 5.5	44.26 ± 10.4	47.73 ±11.5	53.60 ± 5.5	50.50 ± 6.0
T1	98.87 ± 7.0	93.00 ± 10.2	21.24 ± 2.3	20.13 ± 4.3	24.93 ± 1.7	25.03 ± 3.0	20.96 ± 1.9	19.86 ± 3.4	21.83 ± 2.8	19.62 ± 4.3	50.89 ±5.1	50.69 ±9.4	55.06 ± 5.3	51.60 ± 6.7
T2	137.00 ± 17.0	147.43 ± 13.5	21.86 ± 3.2	19.29 ± 4.4	22.14 ± 5.8	26.67 ±	17.00 ± 7.0	22.57 ± 2.5	20.00 ± 7.3	23.57 ± 4.0	51.00 ±4.9	55.86 ±4.1	96.17 ± 14.0	105.57 ± 8.1

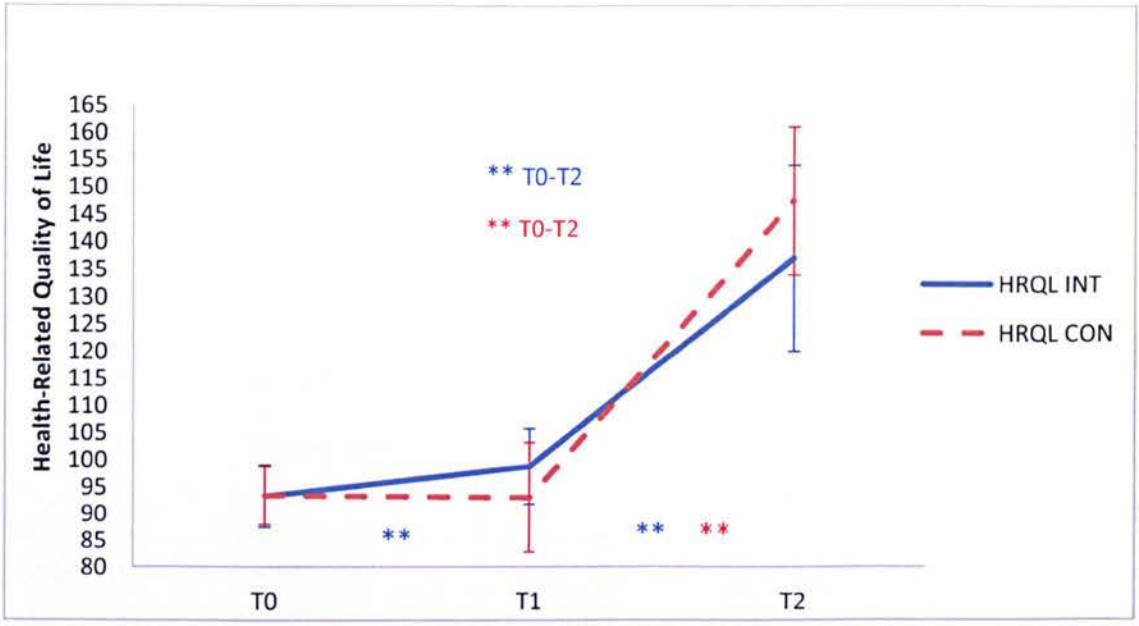


Figure 4.2. HRQoL scores for intervention (INT) and control (CON) participants' pre (T0), post (T1) and 12 months following (T2) 12-weeks CARP intervention. Data are presented as Mean ± SD; * indicates $p<0.05$, ** indicates $p<0.01$

HRQoL scores (Figure 4.2) significantly increased over time in the intervention group (T0-T1) (p=0.044), pre to follow-up (p=0.000) and post to follow-up (p=0.000) and marginally decreased at post in the control group, but then significantly increased at follow-up (pre- to follow-up (p=0.000) and post- to follow-up testing (p=0.000).

Lymphoma Trial outcome index (TOI) scores significantly increased pre- to follow-up and post- to follow-up in both groups, all significant at (p=0.000).

Emotional well-being scores revealed a significant interaction (F=4.542, p=0.022) and treatment effect (F=4.874, p=0.039). The intervention group saw a significant increase in emotional well-being scores from pre to post (p=0.029) with an insignificant decline at follow-up; the controls showed an insignificant decrease on the measure of emotional well-being at post-testing, but this increased at follow-up.

Physical (p=0.022) and functional (p=0.025) well-being scores improved in the intervention group (significantly) and the control group (significantly only for physical function, p=0.010), whereas social well-being scores decreased in both groups from baseline to post testing.

Lymphoma specific symptoms and concerns (LymS) significantly increased T0-T1 (p=0.034) and T0-T2 (p=0.036) amongst the intervention group, and T1-T2 (p=0.0 11) and T0-T2 (p=0.048) amongst controls.

At follow-up, the control group saw improvements in physical, emotional, and functional well-being scores, whereas the intervention group scores on these variables decreased. The measure of

social well-being showed improvement amongst the intervention group at follow-up, but the control group showed a decrease in social well-being scores.

From baseline to follow-up the control group saw a significant increase in functional (p=0.021) and physical (p=0.043) well-being scores.

Table 4.6. HRQoL and HRQoL Subscales: Summary of Significant Relationships (Mixed Model Analysis & A priori Contrasts), Significance (p<0.05)

Variable	**Interaction (time)**	**F**	**Std Error**	**Df**	**Probability**
Lymphoma HRQoL	Time	62.107		2(18.786)	0.000
	Time 0 to Time 2		4.389	12.819	0.000
	Time 1 to Time 2		4.156	14.30	0.000
	Intervention (0-1)		2.695	45.13	0.044
	Intervention (0-2)		6.374	12.317	0.000
	Intervention (1-2)		6.584	13.95	0.000
	Control (0-2)		6.034	13.41	0.000
	Control (1-2)		6.183	14.71	0.000
Lymphoma TOI	Time	112.65		2(19.2)	0.000
	Time 0 to Time 2		3.323	14.17	0.000
	Time 0 to Time 1		3.294	13.74	0.000
	Intervention (0-2)		4.799	13.34	0.000
	Intervention (1-2)		4.808	13.45	0.000
	Control (0-2)		4.598	15.14	0.000
	Control (1-2)		4.504	14.07	0.000
Physical WB	Time	6.269		2(22.74)	0.007
	Time 0 to Time 1		0.703	65.08	0.002

	Intervention (0-1)		0.989	64.76	0.022
	Control (0-1)		1.000	65.36	0.010
	Control (0-2)		1.934	15.301	0.043
Emotional WB	Group	4.874		1(20.46)	0.039
	Time X Group	4.542		2(22.34)	0.022
	Intervention (0-1)		1.142	65.64	0.029
Functional WB	Time	4.969		2(22.968)	0.016
	Time 0 to Time 1		0.967	75.34	0.038
	Intervention (0-1)		1.367	73.98	0.025
	Control (0-2)		2.461	17.40	0.021
Lymphoma Subscale	Time	5.861		2(47.27)	0.005
	Intervention (0-1)		3.049	57.40	0.034
	Intervention (0-2)		3.103	40.94	0.036
	Control (0-2)		3.287	42.96	0.011
	Control (1-2)		2.525	35.40	0.048

A minimal clinically important difference (MCID) was seen in HRQoL amongst the intervention group over both time periods, as well as the control group from T1-T2. The intervention group showed a MCID aon EWB both T0-T1 and T1-T2, and for FWB from T0 to T1. Both groups showed a MCID from T1-T2 in Lymphoma TOI.

Table 4.7. Clinicall Relevant Changes in HQOoL and Domains as Measured by FACT-Lym

	T1-T0		**T2-T1**		**T2-T0**	
	INT	***CON***	***INT***	***CON***	***INT***	***CON***
HQOoL	yes	no	yes	yes	yes	yes
SWB	no	no	no	no		
PWB	no	no	no(-)	no		yes
EWB	yes	no	yes(-)	no		
FWB	yes	no	no (-)	yes		yes
Lym Subscale	yes	no	no	yes	yes	yes
TOI	no	no	yes	yes	yes	yes

Total Mood Disturbance

Psychological outcomes of anxiety, depression, vigour, anger, confusion, fatigue and total mood disturbances were examined in the current trial.Anxiety decreased at post for the intervention group, but increased amongst the controls, where as the opposite occurred at follow-up. Both the control and intervention groups showed a reduction in anger, confusion, fatigue, depression, and total mood disturbance at T1, but at follow-up anger and total mood disturbance increased, but only amongst the intervention group (decreasing for controls), confusion increased in both groups, and fatigue continued to decrease for both. Vigour- inertia increased over time in both groups. HADS Depression scores were significantly different at baseline between the two groups, thus results are interpreted with this in mind. Depression showed a decrease in scores amongst the intervention group post intervention; the control group showed a small reduction on the HADS depression scale.

At follow-up, mean scores of confusion, vigour, anger, HADS depression, and total mood disturbance increased amongst the intervention group (participants showed lower fatigue scores at follow-up), whereas the control group showed improvements on measures of anger, vigour, fatigue, depression and total mood disturbance, while confusion stayed roughly the same.

Table 4.8. Anxiety, Depression, Vigour, Anger, Confusion, Fatigue and Total Mood Disturbances measured by HADS and POMS for Intervention group (INT) compared with control (CON). Values are in arbitrary units (mean ± SD)

	POMS		POMS		POMS		POMS		POMS		HADS		HADS	
	Total Mood Dist.		Vigour		Anger		Confusion		Fatigue		Anxiety		Depression[1]	
	INT	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*
T0	7.15 ± 2.1	6.11 ± 1.8	13.87 ± 3.7	16.3 ± 6.1	2.29± 1.4	2.15 ± 1.0	6.02 ± 3.4	5.13 ± 2.9	2.98 ± 1.1	2.38 ± 1.3	2.33 ± 0.9	1.76 ± 1.1	5.55 ±0.8	3.15 ±0.8
T1	6.40 ± 2.1	6.0 ± 2.1	17.56 ± 4.7	19.82 ± 1.7	1.96 ± 1.2	1.94 ± 1.2	5.52 ± 2.8	4.84 ± 2.9	2.34 ± 0.6	2.25 ± 1.3	1.93 ± 1.1	2.09 ± 0.9	3.90 ±0.7	2.50 ±0.8
T2	7.53 ± 3.1	5.01 ± 2.8	16.38 ± 8.3	21.0 ± 7.0	2.53 ± 1.5	1.33 ± 1.4	8.38 ± 6.5	5.0 ± 5.2	2.25 ± 1.8	1.73 ± 1.4	4.43 ± 0.5	0.17 ± 0.4	3.38 ±1.1	1.86 ±1.2

[1] =Baseline scores were significantly different between groups

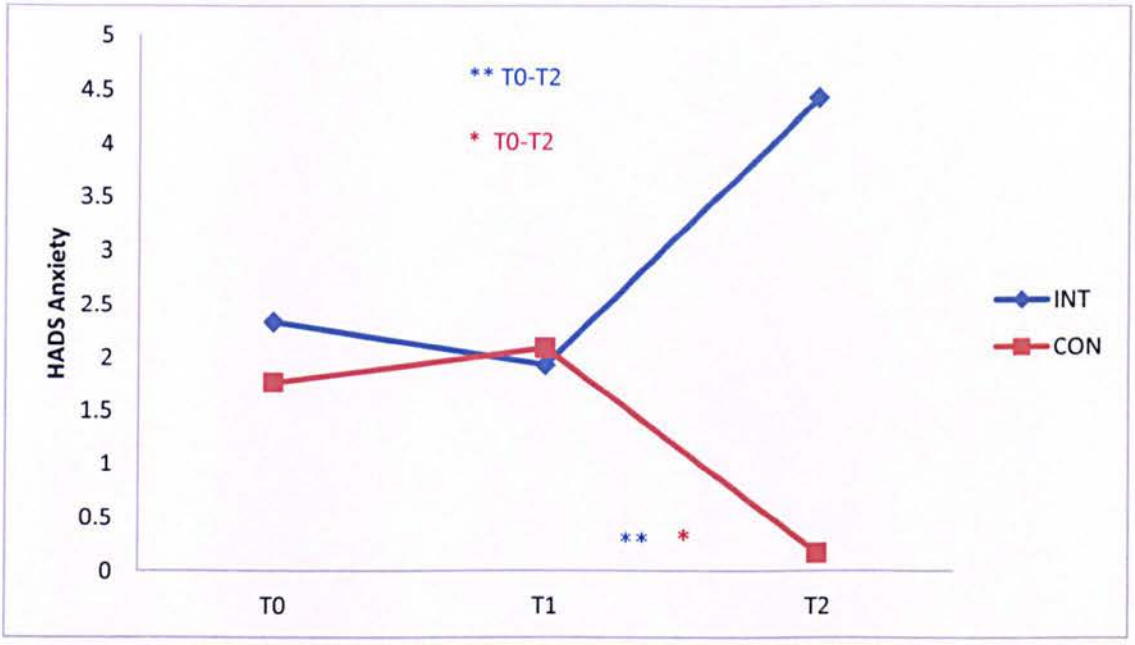


Figure 4.3. Anxiety scores for intervention (INT) and control (CON) participants' pre (T0), post (T1) and 12 months following (T2) 12-weeks CARP intervention. Data are presented as Mean ± SD; * indicates $p<0.05$, ** indicates $p<0.01$

Only one variable of mood showed a significant interaction effect: HADS anxiety. HADS anxiety data show the control and intervention groups saw opposing change over time; the intervention group showed decreased anxiety at T1, and then an increase in anxiety at T2, whereas the control group showed higher anxiety at T1, but a decrease in anxiety at T2. HADS anxiety was statistically significant on both interaction effect (between groups over time) ($F = 19.08$, $p = 0.000$), and treatment effect ($F = 35.53$, $p = 0.000$), but there was no significant time effect ($p > 0.05$). *A priori Contrast* analysis showed significant relationships ($p<0.05$) within the intervention group between time 1 to 3 (mean increase from 2.33 to 4.43) and time 2 to 3 (mean increase from 1.93 to 4.43), and within the control group between time 1 to 3 (mean decrease from 1.76 to 0.17) and time 2 to 3 (mean decrease from 2.09 to 0.17): the significant relationships are due to the changes in anxiety at follow-up (an increase in anxiety for the intervention group and a decrease in anxiety for the control group).

The additional POMS measures (anger, confusion, fatigue, vigour, and total mood disturbance) showed improvement amongst the intervention and control groups from T0 to T1, significantly only on the measure of vigour: exercise group ($p=0.011$) and control group ($p=0.023$), although the intervention group showed greater improvement in mean scores.

Table 4.8. Anxiety, Depression, Vigour, Anger, Confusion, Fatigue and Total Mood Disturbances: Summary of Significant Relationships (Mixed Model Analysis & A priori Contrasts), Significance ($p<0.05$)

Variable	**Interaction (time)**	**F**	**Std Error**	**Df**	**Probability**
POMS Total Mood Disturbance	Group	0.853		1(20.97)	0.042
HADS Anxiety	Group	35.530		1(23.81)	0.000
	Time X Group	19.088		2(22.35)	0.000
	Intervention (0-2)		0.488	17.18	0.000
	Intervention (1-2)		0.490	17.36	0.000
	Control (0-2)		0.520	16.26	0.007
	Control (1-2)		0.524	16.73	0.002
POMS Vigour/Inertia	Time	6.311		2(23.55)	0.006
	Time 0 to Time 1		1.036	69.37	0.003
	Intervention (0-1)		1.411	67.62	0.011
	Control (0-1)		1.516	69.98	0.023

Only one variable of mood showed a significant interaction effect: HADS anxiety. HADS anxiety results show the control and intervention groups saw opposing change over time; the intervention group showed decreased anxiety at T1, and then an increase in anxiety at T2, whereas the control group showed higher anxiety at T1, but a decrease in anxiety at T2. HADS anxiety was statistically significant on both interaction effect (between groups over time) ($F = 19.08$, $p = 0.000$), and treatment effect ($F = 35.53$, $p = 0.000$), but there was no significant time effect ($p > 0.05$). *A priori Contrast* analysis showed significant relationships ($p<0.05$) within the intervention group between

time 1 to 3 (mean increase from 2.33 to 4.43) and time 2 to 3 (mean increase from 1.93 to 4.43), and within the control group between time 1 to 3 (mean decrease from 1.76 to 0.17) and time 2 to 3 (mean decrease from 2.09 to 0.17): the significant relationships are due to the changes in anxiety at follow-up (an increase in anxiety for the intervention group and a decrease in anxiety for the control group).

The additional POMS measures (anger, confusion, fatigue, vigour, and total mood disturbance) showed improvement amongst the intervention and control groups from T0 to T1, significantly only on the measure of vigour: exercise group (p=0.011) and control group (p=0.023), although the intervention group showed greater improvement in mean scores.

Table 4.9. Minimal Clinical Important Difference (by SD) of change scores: POMS and HADS

	T1-T0		**T2-T1**		**T2-T0**	
	INT	***CON***	***INT***	***CON***	***INT***	***CON***
POMS Total Mood Disturbance			yes	yes(-)		yes (-)
POMS Vigour	yes	yes	(-)	yes	yes	yes
POMS Anger				yes (-)		yes (-)
POMS Confusion			yes		yes	
POMS Fatigue	yes(-)				yes (-)	yes (-)
HADS Anxiety			yes	yes(-)	yes	yes(-)
HADS Depression[1]	yes(-)	yes(-)	yes(-)	yes(-)	yes(-)	yes(-)

Clinically relevant change was seen in in depression scores over time in both groups, and vigour was also showed clinically relevant increases over time in both groups, except from T1-T2 in the intervention group. Fatigue showed a clinically relevant decrease in the intervention group from T0-T1 and both groups showed a reduction from T0-T2. Mood disturbance increased in the intervention group from T1-T2, but decreased in the control group, and over time showed a clinically relevant decrasase in the controls. The control group showed clinically relevant decreases in aniiety and anger both at T1-T2 and T0-T2, whereas the intervention group showed clinically signficinat increases in anxiety and confusion over the same times.

Cancer- Related Symptoms

Cancer-related symptoms that were measured in the current trial include fatigue, pain, insomnia, appetite loss, constipation, financial difficulty and dyspnea. In both groups, scores of fatigue, constipation, financial difficulty and dyspnoea decreased over time (T0 to T1). Post-intervention, both groups saw improved scores in pain, insomnia (appetite loss scores increased amongst the

intervention group but decreased in the control group at post, whereas both groups showed an increase in scores on this measure at follow-up). At follow-up the control group continued to see improvements in scores on measures of pain, and insomnia, but the intervention group showed large increases in both pain and insomnia scores.

Table 4.10. Symptoms measured by EORTC-QoL30 for Intervention group (INT) compared with control (CON). Values are in arbitrary units (mean ± SD)

	Fatigue		Pain		Insomnia		Appetite Loss		Constipation		Financial Diff.		Dyspnea	
	INT	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*	*INT*	*CON*
T0	40.4 4 ± 19.5	44.8 6 ± 31.1	10.1 9 ± 13.0	19.6 9 ± 22.4	35.0 0 ± 29.6	36.5 1 ± 34.8	13.33 ± 25.1	24.1 6 ± 31.4	15.0 0 ± 27.5	18.8 7 ± 32.2	30.00 ± 35.7	36.68 ± 39.3	12.2 8 ± 16.5	22.8 4 ± 24.8
T1	25.1 5 ± 18.3	21.4 8 ± 20.3	5.68 ± 8.3	8.50 ± 10.7	24.2 6 ± 21.2	19.0 1 ± 19.5	17.04 ± 29.4	12.5 0 ± 25.2	11.8 5 ± 22.3	7.24 ± 17.0	28.06 ± 37.9	20.50 ± 25.1	10.0 0 ± 21.9	11.1 1 ± 16.2
T2	20.6 3 ± 14.9	12.7 0 ± 12.0	31.2 5 ± 41.2	0.00 ± 6.3	50.0 0 ± 39.8	9.52 ± 16.3	12.50 ± 35.4	0.00 ± 0.0	8.33 ± 15.4	0.00 ± 0.0	20.83 ± 35.4	0.00 ± 0.0	8.33 ± 23.6	9.52 ± 16.3

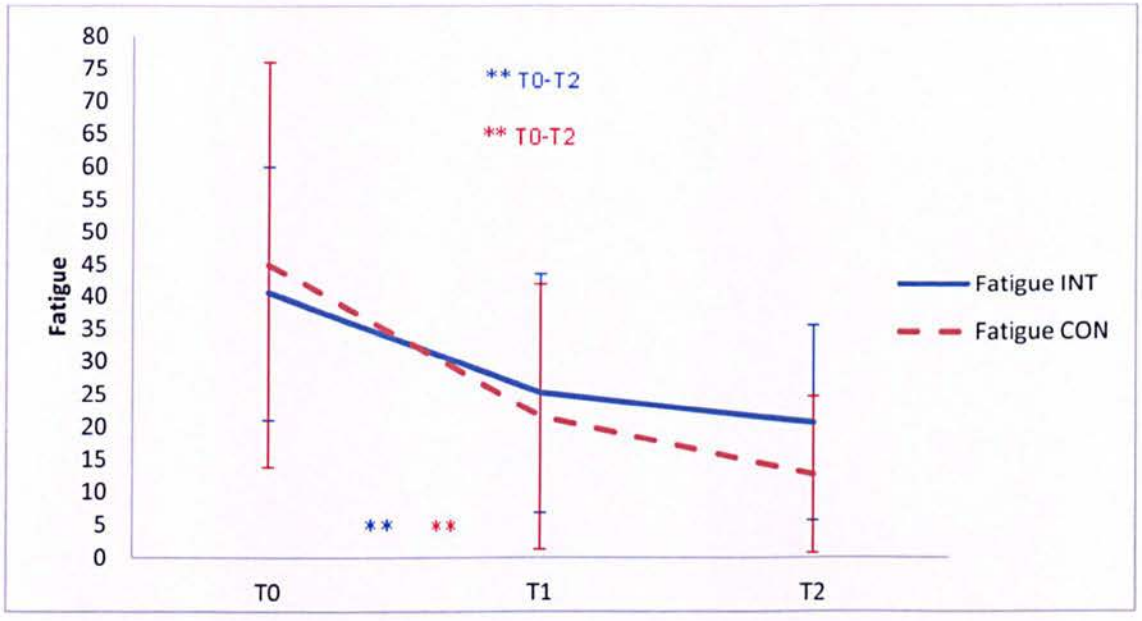


Figure. 4.4. Mean EORTC-QLQ-30 derived fatigue scores for intervention (INT) and control (CON) participants' pre (T0), post (T1) and 12 months following (T2) 12-weeks CARP intervention. Data are presented as Mean ± SD; * indicates $p<0.05$, ** indicates $p<0.01$

The EORTC symptoms of fatigue, pain, insomnia, constipation, financial difficulty, and dyspnoea scores all improved from pre to post testing in both groups. The improvements were significant amongst the intervention group on the measure of fatigue (p=0.039), and fatigue (p=0.002), pain (p=0.025), and insomnia (p=0.041) amongst the controls. Appetite loss scores increased in the intervention group, but decreased in the control group.

Fatigue, appetite loss, constipation, financial difficulty, and dyspnoea scores improved in both groups at follow-up; pain and insomnia scores continued to decrease amongst the control group, but significantly increased in the intervention group: (pain (p=0.043) and insomnia (p=0.045).

Within groups, there was some significant change seen from pre testing to follow-up. On the measure of fatigue, both the intervention (p=0.028) and control (p=0.001) groups showed significant improvement pre to follow-up, whereas constipation (p=0.019), financial difficulty (p=0.007), and dyspnoea (p=0.007) scores significantly improved amongst only the control group.

Note, fatigue was measured both using the POMS and EORTC questionnaires. Fatigue decreased in both groups using both questionnaires, but statistical significance was only found using the EORTC.

Table 4.11. Symptoms: Summary of Significant Relationships (Mixed Model Analysis & A priori Contrasts), Significance ($p<0.05$)

Variable	Interaction (time)	F	Std Error	Df	Probability
Fatigue	Time	10.682		2(32.58)	0.000
	Time 0 to Time 1		5.121	71.76	0.001
	Time 0 to Time 2		6.084	32.87	0.000
	Intervention (0-1)		7.263	70.97	0.039
	Intervention (0-2)		8.651	33.32	0.028
	Control (0-1)		7.219	72.50	0.002
	Control (0-2)		8.556	32.42	0.001
Pain	Intervention (1-2)		11.412	13.21	0.043
	Control (0-1)		4.862	54.46	0.025
Insomnia	Group	4.822		1(29.47)	0.036
	Intervention (1-2)		11.955	17.64	0.045
	Control (0-1)		8.41	66.47	0.041
Constipation	Control (0-2)		7.823	51.34	0.019
Financial Difficulty	Time	3.312		2(34.80)	0.048
	Time 0 to Time 2		8.919	33.89	0.044
	Control (0-2)		12.784	32.29	0.007
Dyspnoea	Control (0-2)		12.784	32.29	0.007

Physical Activity

Physical activity was subjectively measured using the IPAQ, resulting in total number of METS expended in one week. Both groups saw an increase in METS scores at post and a decrease in scores at follow-up (a greater decrease was seen in the control group score).

Table 4.12. Physical Activity measured by IPAQ for Intervention group (INT) compared with control (CON). Values are in METS (mean ± SD)

	IPAQ Physical Activity (METS)	
	INT	***CON***
T0	1122.18 ± 1006.8	1391.35 ± 1205.3
T1	2168.67 ± 1567.7	2513.11 ± 1576.9
T2	1905.71 ± 578.5	1533.25 ± 950.4

Amount of exercise being performed (as subjectively reported) significantly increased in both the intervention (p=0.029) and control (p=0.019) groups during the intervention, and decreased at follow-up (more so amongst the control group).

Table 4.13. Physical Activity (METS): Summary of Significant Relationships (Mixed Model Analysis & A priori Contrasts), Significance (p<0.05)

Variable	**Interaction (time)**	**F**	**Std Error**	**Df**	**Probability**
IPAQ	Time	5.509		2(40.806)	0.008
	Time 0 to Time 1		329.042	58.79	0.005
	Intervention (0-1)		467.291	59.26	0.029
	Control (0-1)		463.373	58.31	0.019

Table 4.14. Minimal Clinical Important Difference (by SD) of change scores: Physical Activity

	T1-T0		**T2-T1**		**T2-T0**	
	INT	***CON***	***INT***	***CON***	***INT***	***CON***
IPAQ	yes	yes		yes	yes (-)	yes

Physiological Outcomes

All participants were assessed on a number of physical measures. Testing occurred at baseline and 12-weeks post intervention in both groups. Variables were separated into groups and analysed using MANOVA and ANOVA. MANOVAs were organised by

practical relationship of variables (i.e. all strength based measures were put together) and by standardised reliability coefficients.

Cardiorespiratory fitness was assessed using blood pressure, resting heart rate, symptom limited maximal exercise (using the Balke-Ware treadmill test), and pulmonary function. Anthropometric analysis included weight, height (body mass index), waist to hip circumference, and body composition. Musculoskeletal performance was examined using partial curl-ups and push-ups for muscular endurance, and grip strength for muscular strength. Flexibility was measured using a sit and reach test.

Cardiorespiratory Fitness

Limited maximal exercise and resting heart rate were examined using independent ANOVAs, as they did not produce reasonable internal consistency with other variables within cardiorespiratory fitness.A MANOVA was used to examine the change in blood pressure (systolic and diastolic). Another MANOVA was used to examine pulmonary function, measured with FEV_1predicted (%) and FVC predicted (%).

Energy Expenditure: Metabolic Equivalent

METs (energy expenditure achieved during a treadmill test) achieved increased from T0 to T1 amongst the intervention group (by 1.000), but decreased in the control group by 0.571.

Table 4.15. Objective Metabolic Equivalent for Intervention group (INT) compared with control (CON). Values are in METS (mean ± SD)

	INT Group (n=9)		**CON Group (n= 7)**	
-	**T0**	**T1**	**T0**	**T1**
Energy Expenditure (METS)	5.78 ±1.99	6.78 ±1.92	7.43 ±2.15	6.86 ±1.68

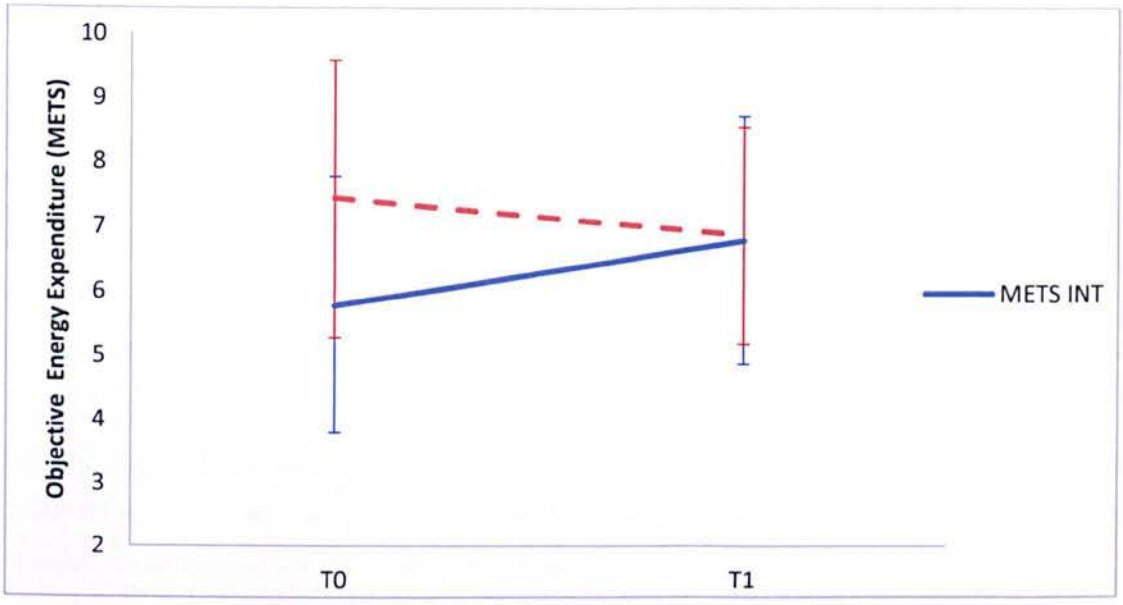


Figure 4.5. Objective Metabolic Equivalent (MET) scores for intervention (INT) and control (CON) participants' pre (T0) and post (T1) CARP intervention. Data are presented as Mean ± SD; ** indicates $p<0.05$

The ANOVA Results for Metabolic Equivalent (METS) were statistically insignificant (results are in Appendix O). Data met the requirements of a balanced design and were normally distributed, skewness and kurtosis within /1/. The repeated measures ANOVA showed that the difference in METS achieved between groups over time (pre to post) was statistically insignificant, ($F(1,14)=2.010, p=0.178$). There was no time effect ($F(1,14)=0.150$, $p=0.705$) or group effect ($F(1,14)=1.149$, $p=0.302$). Pairwise comparisons were insignificant.

Pulmonary Function Tests

FVC% predicted and FEV1% predicted decreased in both groups over time, more so in the intervention group than the control group). FVC% predicted decreased by 9.6% in the intervention group and 3.7% in the control group, whereas FEV1% predicted decreased by 7.5% amongst the intervention group and 1.5% in the control group.

Table 4.16. Pulmonary Function for Intervention group (INT) compared with control (CON). Values are percentage (mean ± SD)

-	**INT Group (n=18)**		**CON Group (n= 13)**	
	T0	**T1**	**T0**	**T1**
Forced Vital Capacity FVC% predicted (%)	73.44±13.784	63.84±18.01	71.05±2.67	67.37±10.32
Forced Expiratory Volume % predicted (%)	79.58±17.22	72.06±24,01	79.84±8.27	78.72±17,10

The standardized reliability coefficient is 0.929. Box's M (p=0.095) was insignificant. Data met the requirements of a balanced design and were normally distributed, skewness and kurtosis within /1/ with the exception of the intervention group pre FVC% predicted (kurtosis= 1.104), and control group pre FEV1% predicted (kurtosis= 1.024).

The MANOVA suggested a significant time effect (F (2,28)=4.241, p=0.025), but insignificant interaction (F(2,28)=0.679,p=0.515) and group effect (F(2,28)=0.840, p=0.442). The multivariate comparison showed a significant multivariate relationship within the intervention group, F(2,28)=4.745, p=0.017.

The FVC% predicted variable showed a significant time effect, F(1,29) =7.031, p=0.013; the intervention group was significant at p=0.006. FEV1% predicted showed a trend towards significance amongst the intervention group (p=0.069).

Table 4.17. Pulmonary Function; Summary of Significant Relationships (MANOVA)

Variable	**Interaction (time)**	**F**	**Std Error**	**Df**	**Probability**
FVC% predicted and Fev1% predicted	Time	4.241		2,28	0.025
FVC% predicted and FEV1% predicted	Intervention (0-1)	4.745		2,28	0.017
FVC % predicted	Time	7.031		1,29	0.013
	Intervention (0-1)	Mean Diff 0.096	0.033		0.006

Resting Heart Rate

Resting heart rate decreased by 7.13 beats per minute (bpm) in the intervention group; the control group resting heart rate decreased by 0.33 bpm.

Table 4.18. Resting Heart Rate for Intervention group (INT) compared with control (CON). Values are in bpm (mean $\pm$ SD)

	INT Group (n=16)		**CON Group (n= 12)**	
	T0	**T1**	**T0**	**T1**
Resting Heart Rate (bpm)	87.75 ±16.39	80.63±310.52	79.58±10.52	79.25±12.45

The data met the requirements of a balanced design and were normally distributed, skewness and kurtosis within /1/, with the exception of control group post resting heart rate (kurtosis=-1.126). There was no significant time effect (F(1,26)=2.172, p=0.153), group effect (F(1,26)=1.435, p=0.242), or time by group interaction (F(1,26)= 0.801, p=0.191) on resting heart rate between groups, over time. There was a trend towards a significant difference between groups at pre-testing (significant difference at baseline would cause concern). The intervention group was significant over time (p=0.041).

Table 4.19. Resting Heart Rate; Summary of Significant Relationships (ANOVA)

Variable	**Interaction (time)**	**F**	**Std Error**	**Df**	**Probability**
Resting Heart Rate	Intervention (0-1)	4.625 Mean Diff 7.125	3.313	1,26	0.041

Blood Pressure

Systolic pressure decreased in both groups over time, but more so in the control group (mean change of 3.918mmHg compared to a negligible decrease of 0.018 millimetres of mercury (mmHg) in the intervention group). Diastolic pressure decreased over time in the intervention group (1.316 mmHg) whereas the control group saw a slight increase in diastolic pressure (0.462).

Table 4.20. Blood Pressure for Intervention group (INT) compared with control (CON). Values are in mmHg (mean ± SD)

-	**INT Group (n=19)**		**CON Group (n= 13)**	
	T0	**T1**	**T0**	**T1**
Systolic (mmHg)	125.18±19.38	125.16±19.62	132.43±14.30	128.51±9.44
Diastolic (mmHg)	75.47±14.15	74.16±11.50	81.15±7.22	81.62±4.54

Blood pressure included both systolic and diastolic blood pressure. The standardized reliability coefficient is 0.901. Box's M (p = 0.035) significant results can be ignored due to a balanced design. The data met the requirements of a balanced design and were normally distributed, skewness and kurtosis within /1.15/.

Table 4.21. Blood Pressure; Summary of Significant Relationships (MANOVA)

Variable	Interaction (time)	F	Std Error	Df	Probability
Diastolic	Time 1* group	4.897	3.370	1(30)	0.035

The MANOVA shows that there is no significant interaction, time or group effects overall or by variable. All post-hoc analyses were insignificant for systolic pressure, but a significant simple effect on diastolic pressure was found between groups at post-testing ($F(1,30)=4.897$, $p=0.035$).

Anthropometric Measures

A MANOVA examined the interaction between groups over time on variables of weight, waist to hip ratio, and body mass index. Body composition was analysed using ANOVA.

Weight, Waist to Hip Ratio, and Body Mass Index

Mean values show that the intervention group saw a very slight increase in weight while the control group increased weight by 1 kg over time. Waist to hip ratio decreased in both groups at post-testing, but more so amongst the intervention group (0.02 versus control, 0.001). BMI decreased amongst the intervention group whereas the control group BMI score increased at post-testing.

Table 4.22. Weight, Waist to Hip Ratio, and Body Mass Index for Intervention group (INT) compared with control (CON) (mean $\pm$ SD)

	INT Group (n=15)		CON Group (n= 14)	
-	T0	T1	T0	T1
Weight (kg)	71.35±12.10	71.4±12.79	73.84±19.91	74.98±19.72
Waist to Hip Ratio (cm)	0.89±0.08	0.87±0.08	0.87±0.09	0.87±0.07
Body Mass Index (kg/m^2)	25.85±3.39	25.71±3.46	24.74±4.43	25.04±4.05

The standardized reliability coefficient was 0.792.The data met the requirements of a balanced design and were normally distributed, skewness and kurtosis within /1/ with the exception of the intervention group pre and post weight (kurtosis= -1.16 and 1.32, respectively) and intervention post waist to hip ratio (kurtosis= 1.446). Box's M (p=0.008) significant results can be ignored due to a balanced design. The MANOVA of weight, waist to hip ratio, and BMI were statistically insignificant on all effects.

Body Composition

Body Composition increased over time in both groups; the control group saw a larger increase (1.529) than did the intervention group (0.533).

Table 4.23. Body Composition for Intervention group (INT) compared with control (CON) (mean ± SD)

	INT Group (n=19)		**CON Group (n= 17)**	
	T0	**T1**	**T0**	**T1**
Body Composition	32.83±10.7	33.38±9.33	28.55±11.90	30.08±11.57

The data met the requirements of a balanced design and were normally distributed, skewness and kurtosis within /1/, with the exception of intervention group pre and post body composition (kurtosis=-1.025 and 1.091, respectively). The ANOVA produced no significant time ($F(1,34)=1.784$, $p=0.191$), group ($F(1,34)=1.146$, $p=0.292$) or interaction effect ($F(1,34)=0.393$, $p=0.535$) for the dependant variable of body composition.

Musculoskeletal Performance

Sit-ups, push-ups and grip strength were examined using a MANOVA. Flexibility was analysed using ANOVA.

The intervention group showed greater improvements in mean scores on all three variables. The intervention group increased curls-ups at post-testing (an increase of 6 curl-ups), compared to the control group who reduced the number of performed curl-ups by approximately 1. Push-ups increased in both groups, but more so by the intervention group (2 compared to 0 amongst controls). The same was seen with grip strength (the intervention group increased by 4.24kg whereas the controls increased by 2.72kg at post-testing).

Table 4.24. Muscular Strength and Endurance for Intervention group (INT) compared with control (CON) (mean ± SD)

	INT Group (n=19)		**CON Group (n= 14)**	
	T0	**T1**	**T0**	**T1**
Curl-Ups	8.42±10.60	14.50±10.42	16.07±15.36	15.29±12.31
Push-Ups	4.26±5.86	6.37±7.35	11.14±15.98	11.86±18.25
Grip Strength (kg)	49.79±19.93	54.03±20.66	62.96±34.85	65.68±29.55

The standardized reliability coefficient is 0.767. Box's M (p=0.039) significant results can be ignored due to balanced design. The data met the requirements of a balanced design and were normally distributed, skewness and kurtosis within /1/ with the exception of the intervention group pre and post weight (kurtosis= -1.16 and 1.32, respectively) and intervention post waist to hip ratio (kurtosis= 1.446).

The MANOVA shows that there is no significant interaction, group or time effect. The multivariate comparison within the intervention group showed trend towards significance, F (3,29)=2.878, p=0.053.

The intervention group sit ups score significantly improved post-intervention (p=0.018).There was a trend towards a significant interaction effect amongst sit-ups, F(1,31)=3.363, p=0.076.

There were no significant relationships within push-ups, although a trend towards a significant difference between groups was seen at pre-testing (significant difference at baseline would cause concern).

Grip strength shows a significant time effect F(1,31)=4.185, p=0.049; there is a trend towards significance (p=0.065) within the intervention group, over time.

Table 4.25. Muscular Strength and Endurance; Summary of Significant Relationships (MANOVA)

Variable	**Interaction (time)**	**F**	**Std Error**	**Df**	**Probability**
Curl Up	Intervention (0-1)	Mean Diff 6.079	2.438		0.018
Grip Strength	Time	4.185		1,31	0.049

Flexibility

Flexibility decreased over time in both groups, more so amongst the control group who reached 1.273cm less at post testing than at pre (the intervention group saw a decrease in reach distance of 0.062cm).

Table 4.26. Flexibility for Intervention group (INT) compared with control (CON) (mean ± SD)

	INT Group (n=16)		CON Group (n= 11)	
-	T0	T1	T0	T1
Flexibility (cm)	-3.219±11.57	-3.281±9.30	-6.182±12.30	-7.455±11.95

The data met the requirements of a balanced design and were normally distributed, skewness and kurtosis within /1/. The ANOVA showed that there was no significant time by group interaction effect ($F(1,25)=0.093$, $p=0.763$), time effect ($F(1,25)=0.113$, $p=0.740$), or group effect ($F(1,25)=0.837$, $p=0.369$) for the Sit and Reach variable. As expected, none of the post-hoc tests were significant.

Immune Markers

C-reactive protein and Interleukin- IL-6

C-reactive protein (CRP) increased in both groups although both changes were statistically insignificant.

Changes in Interleukin- 6 (IL-6) levels over time were not statistically or clinically significant. All subjects, control and intervention, gave absorbance lower than the absorbance produced by the lowest concentration of standard (when the standard concentration was 0ng/ml, the Abs was 0.168 (average). Only one subject gave values higher than abs 0.168, therefore the absorbance from the remaining samples were too low.

Table 4.27. Immune Markers for Intervention group (INT) compared with control (CON) (mean ± SD)

	INT Group (n=11)		CON Group (n=9)	
-	T0	T1	T0	T1
C-reactive protein (CRP)	5.62± 3.04	7.04± 4.50	7.02± 6.77	8.61± 8.04
Interleukin-6 (IL-6)	0.07± 0.03	0.73± 0.04	0.065± 0.16	0.66± 0.17

The data met the requirements of a balanced design and were normally distributed, skewness and kurtosis within /1/. The ANOVA showed that there was no significant time by group interaction effect ($F(1,17)=0.582$, $p=0.456$), or time effect ($F(1,17)=0.296$, $p=0.593$) for CRP. The ANOVA showed that there was no significant time by group interaction effect ($F(1,18)=0.072$, $p=0.949$) or time effect ($F(1,18)=1.319$, $p=0.266$) for IL-6.

Chapter 5.

PREDICTING EXERCISE BEHAVIOUR USING THE THEORY OF PLANNED BEHAVIOUR

5.0 INTRODUCTION

With only 30-47% of survivors are meeting the ACSM physical activity recommendations for cancer survivors, and less than half are returning to pre-diagnosis activity levels after treatment (Blanchard, Courneya, & Stein, 2008; Irwin *et al.,* 2003), it is necessary to understand what determinants of change are most likely to motivate cancer survivors to engage in exercise. Lymphoma survivors are even less active; only 23.7% of lymphoma survivors are meeting the minimum ACSM physical activity requirements for health (Vallance *et al.,* 2005).Optimal programming for adherence and maintenance is still undetermined within the cancer survivor population (Vallance *et al.,* 2006) despite various predictors of exercise adherence having been studied. To improve exercise adherence and decrease drop-out rates in exercise interventions it is important to identify factors that motivate and those that form barriers to exercise (Ajzen *et al.,* 1991).

The *Theory of Planned Behaviour* (TPB) has repeatedly been used to examine determinants of exercise behaviour in cancer patients and survivors (Ajzen *et al.,* 1991; Courneya *et al.,* 2002). The TPB proposes that subjective norm (SN), attitude, and perceived behavioural control (PBC) are key correlates of intention (Courneya *et al.,* 2007) and intention and PBC are each independent correlates of exercise behaviour (Refer to figure 2.2 in Chapter 2, page 34) (Blanchard *et al.,* 2002; Courneya *et al.,* 2001; Courneya and Fredereich, 1997; Courneya and McAuley, 1995; Courneya *et al.,* 1999; Courneya *et al.,* 2007; Courneya and Friedenrich, 1997). Attitude is a measure of one's positive or negative evaluation of performing the behaviour, PBC examines confidence and control over behaviour, and SN measures perceived social support for and against behaviour (Lox *et al.,* 2010). The TPB has generally explained 14% to 35% of the variance in exercise behaviour, and 23% to 68% of the variance in exercise intention in cancer survivors (Courneya *et al.,* 2007). A plethora of literature support the viability of the TPB in the prediction and understanding of exercise for cancer survivors (Karvinen *et al.,* 2009; Karvinen *et al.,* 2007; Courneya *et al.,* 2007; Jones *et al.,* 2006; Courneya *et al.,* 2001; Courneya and Fredereich, 1997; Courneya and McAuley, 1995; Rhodes and Courneya, 2003; Courneya *et al.,* 1999; Courneya and Friedenreich, 1999); though the results have indicated that the determinants of exercise and vary depending on the cancer group. This indicates that generalisations between tumour groups may not be warranted. Few studies have examined whether the TPB is an effectual model to predict exercise behaviour in lymphoma survivors.

After reviewing the most prominent theories in the field of exercise psychology, the TPB was chosen for the current trial because its measures strong predictors of exercise behaviour (as seen in previous theories) and it been found to be an effectual model to predict exercise adherence in both the general population and amongst different cancer groups, Once the predictability of determinants are identified in a certain population, behaviour change techniques associated with

those determinants can be tried as a means to increase intention and behaviour; Michie and colleagues (2008) provide a list of determinants with associated behaviour change techniques that may work to increase intention and behaviour (Ajzen, 2006).

5.1 METHODOLOGY

Trial Design: Please refer to the details highlighted in the methods section (*Chapter 3, Theoretical and Methodolgical Background)* for details on recruitment and randomization criteria and the intervention programme.

5.1.1 EXPERIMENTAL OVERVIEW

The purpose of the current study was to examine determinants of exercise that may influence exercise intention and behaviour in lymphoma patients at the end of their treatment. Resulting information may offer guidance for exercise prescription for lymphoma survivors. A secondary aim was to examine how determinants of exercise influence lymphoma patients who have completed an exercise intervention and those who have not. The findings from the intervention group can be used to assist with long term exercise adherence in lymphoma survivors, while the control group results can assist with programming for lymphoma patients within the first year after they have completed treatment.

TPB was assessed at baseline (groups collapsed) and following 12-weeks of a multi-component exercise training programme (CARP). Initial assessment of the determinants of exercise was performed at baseline to examine how the theory of planned behaviour variables predict intention to exercise and actual exercise behaviour amongst lymphoma patients shortly after completing chemotherapy and/or radiotherapy treatment. Additional follow up measurements were obtained one year following the completion of the CARP.

5.1.2 OUTCOME MEASURES (DETAILS CAN BE FOUND IN CHAPTER 4. METHODOLOGY)

Two questionnaires (Appendix H) were used to measure behaviour, intention to behave, and variables impacting intention and behaviour: the Theory of Planned Behaviour (TPB) and International Physical Activity Questionnaire (IPAQ). Details regarding both the IPAQ and the TPB questionnaire can be found in *Chapter 3, Theoretical and Methodolgical Background.* A table outlining the constructs and associated questionnaire design can be found in Appendix I.

5.2 STATISTICAL ANALYSIS

All analyses were conducted using PAWS/ SPSS version 18.0 (SPSS, Chicago, IL). Internal consistency was examined for all items making up each predictor variable. The reliability coefficient (>0.075) was acceptable for all items selected for each predictor, so all items were used to make composite variables. Correlations and Regressions were used to analyse the data: details of the analysis can be found in *Chapter 3, Theoretical and Methodolgical Background.*

5.3 RESULTS

Table 5.1. Summary of determinants of exercise (TPB) in intervention and control groups, pre and post intervention. Data are mean (± SD), n is reported for each variable

Variable	Group	N	Mean ±SD
Pre Attitude	Intervention	20	5.65 ±1.0
	Control	16	5.49 ±1.4
Post Attitude	Intervention	19	5.84 ±0.8
	Control	16	5.36 ±1.4
Pre Self-Efficacy	Intervention	20	4.80 ±1.4
	Control	19	4.89 ±2.0
Post Self-Efficacy	Intervention	20	4.88 ±1.2
	Control	19	5.32 ±1.5
Pre Social Support	Intervention	20	4.48 ±1.1
	Control	19	4.28 ±1.8
Post Social Support	Intervention	20	4.70 ±1.3
	Control	18	4.26 ±1.5
Pre Control	Intervention	20	6.33 ±1.0
	Control	18	5.78 ±1.4
Post Control	Intervention	20	5.70 ±1.3
	Control	19	6.16 ±1.1
Pre Intention	Intervention	20	5.45 ±1.6
	Control	20	5.23 ±2.1
Post Intention	Intervention	20	5.30 ±1.5
	Control	18	5.54 ±1.8
Pre IPAQ (categorized)	Intervention	20	1.75 ±0.9
	Control	17	1.88 ±0.9
Post IPAQ (categorized)	Intervention	20	2.45 ±0.8
	Control	16	2.56 ±0.7

5.3.1 REGRESSIONS PERFORMED ON BASELINE DATA

Pearson Correlation Matrix

Table 5.2. Pearson Correlation Matrix of all TPB variables, Attitude, Self-Efficacy, Control, Intention and Actual Behaviour at Baseline

Pearson Correlation	Pre Attitude	Pre Self-Efficacy	Pre Social Support	Pre Control	Pre Intention	Prel Behaviour IPAQ (categ.)
Pre Attitude		.636**	.409*	.414*	.632**	.232
Pre Self- Efficacy			.512**	.684**	.727**	.650**
Pre Social Support				.612**	.725**	.247
Pre Control					.651**	.360*
Pre Intention						.316

Significance (2-tailed): $*p \leq 0.05$, $**p \leq 0.01$

The correlation matrix shows baseline actual behaviour correlates at a low level with baseline attitude, social support and intention, and moderately with control and self efficacy. Intention is highly correlated (>0.66) with self-efficacy and social support and moderately correlated (0.33-0.66) with attitude and control. The variables themselves are moderately correlated (control and self-efficacy are highly correlated which is expected as they together make up a score of 'perceived control').

Multiple Regressions

TPB determinants predicting intention

The simultaneous regression model shows significance beyond the 0.01 level (R^2=0.723, F(4,30)=19.595, p=0.00). The model predicts 68.6% of the variation in intention at baseline. The simultaneous multiple regression equation of intention upon attitude, self-efficacy, social support and control at time 1:

Predicted intention = -1.600+0.410 X pre attitude +0.347 X pre self efficacy +0.502 X pre social support +0.127 X pre control.

Table 5.3. Regression Analysis Summary for Baseline TPB Variables Predicting Baseline Intention to Exercise

Variable	**B**	**Standardised Regression scores** **Beta (z-scores)**	***P***	***Collinearity Condition Index***
Attitude Time 1	0.410	0.258	0.053	9.069
Self efficacy Time 1	0.347	0.314	0.046*	9.407
Social support Time 1	0.502	0.389	0.004*	14.609
Control Time 1	0.127	0.084	0.560	22.282

Note: R^2=.723 (n=34, *$p<0.05$)

Condition indices between baseline 'control' and intention show strong collinearity, therefore results specific to control may be erratic. This does not impact the model as a whole.

Stepwise Multiple Regression examines how each variable predicts intention, and if necessary, adjusts the model. Using stepwise regression, two models were produced. The stepwise procedure entered two predictors that explained 66.5% (adjusted $R^{2)}$ of the variance in intention, significant beyond 0.01 (R^2=.684, F(2,32)=34.696,p=0.00). It was found that self efficacy significantly predicted intention (β= 0.495,t=4.400, p=0.000), as did social support (β=0.469, t=4.168,p=0.000). The condition indices show low correlation (<15), indicating there should be no issues using the stepwise regression.

The stepwise procedure was useful in specifying the best model for predicting intention in this case. When behavioural intention was regressed (stepwise) the procedure showed self efficacy and social support to be the best predictors and removed those variables that lacked predictive value. The multiple correlation coefficient was only slightly smaller from the stepwise regression (using only self-efficacy and social support to predict intention) compared to the multiple correlation coefficient from the simultaneous regression (which used all variables to predict intention). This demonstrates a lack of predictive value of the two excluded variables, attitude and control.

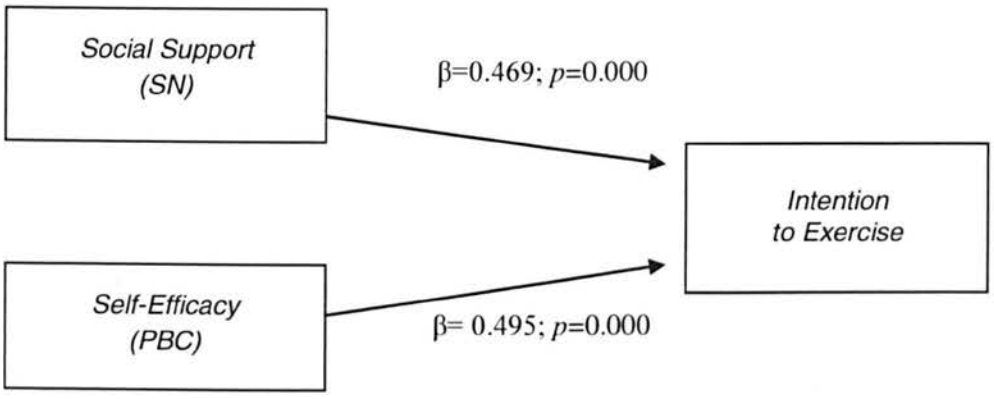


Figure 5.1. Best model (R^2=0.684; p=0.00) for predicting intention at baseline (T0)

Intention and TPB determinants predicting actual behaviour

The simultaneous regression model shows significance beyond the 0.01 level (R^2=.458, F(5,33)=4.738, p=0.003). The model predicts 36.2% of the variation in actual behaviour at baseline. The simultaneous multiple regression equation of actual behaviour upon intention, attitude, self-efficacy, social support and control at time 1:

> Predicted actual behaviour = 1.028+-0.115 X pre attitude +0.501 X pre self efficacy +0.038 X pre social support +-0.051 X pre control +-0.163 X pre-intention.

Table 5.4. Regression Analysis Summary for Baseline Intention and TPB Variables Predicting Baseline Actual Behaviour

Variable	**B**	**Standardised Regression scores Beta (z-scores)**	***P***
Attitude Time 1	-0.115	-0.156	0.436
Self efficacy Time 1	0.501	0.980	0.000*
Social support Time 1	0.038	0.064	0.761
Control Time 1	-0.051	-0.070	0.754
Intention Time 1	-0.163	-0.348	0.228

Note: R^2=.458 (n=33, *$p<0.05$)

Stepwise regression was performed and the model found one predictor explained 35.1% of variation in actual behaviour (R^2 =0.371, F(1,33)=18.837, p=0.000). It was found that self efficacy significantly predicted actual behaviour (β= 0.609, t=4.340, p=0.000). In this case, the other TPB variables could be excluded from the model as they did not greatly impact overall predictability of actual behaviour.

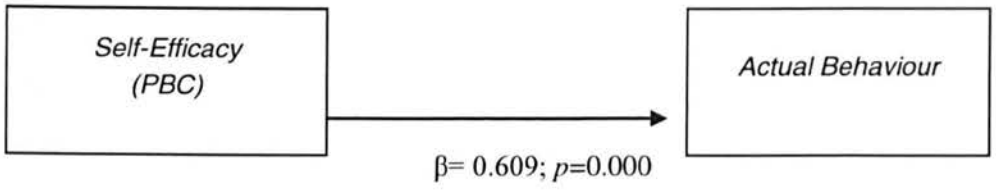


Figure 5.2. Best model (R^2=0.371; p=0.00) for predicting actual behaviour at baseline (T0)

5.3.2 REGRESSIONS PERFORMED ON POST-TESTING (12-WEEKS) DATA

Table 5.5. Pearson Correlation Matrix of all TPB variables, Attitude, Self-Efficacy, Control, Intention and Actual Behaviour at Post-Intervention/ Control (12-weeks)

Pearson Correlation	Post Attitude	Post Self-Efficacy	Post Social Support	Post Control	Post Intention	Post Actual Behaviour IPAQ (categ.)
Post Attitude		.184	.436**	.478**	.629**	-.026
Post Self-Efficacy			.268	.227	.576**	.000
Post Social Support				.268	.654**	-.095
Post Control					.471**	-.080
Post Intention						-.023

Significance (2-tailed): *≤ 0.05, **≤ 0.01

The correlation matrix shows actual behaviour (IPAQ) at 12-weeks correlates at a low (0.01-0.33) level with intention and the TPB variables (inversely with all variables except self-efficacy). Intention and all TPB variables are moderately correlated (0.33-0.66), and the determinants themselves correlate at a low to moderate level.

Regressions were used explore the strength of the TPB variables at predicting intention and behaviour at post-testing. Groups were examined separately.

Multiple Regressions

Control Group

TPB determinants predicting intention (Control Group)

The simultaneous regression model shows significance beyond the 0.01 level (R^2=0.831, F(4,15)=13.557, p=0.00). The model predicts 77.0% of the variation in intention at post-testing amongst the control group. The simultaneous multiple regression equation of intention upon attitude, self-efficacy, social support and control at post-testing (for controls):

> Predicted intention = -2.143+0.843 X post attitude +0.379 X post self efficacy +0.268 X post social support +-0.006 X post control.

Table 5.6. Regression Analysis Summary for Post-Testing TPB Variables Predicting Post-Testing Intention to Exercise (Control Group)

Variable	**B**	**Standardised Regression scores Beta (z-scores)**	***P***	**Collinearity Condition Index**
Attitude Time 2	0.843	0.692	0.003	7.468
Self efficacy Time 2	0.379	0.237	0.202	12.242
Social support Time 2	0.268	0.248	0.121	17.375
Control Time 2	-0.006	-0.004	0.987	29.126

Note: R^2=.831 (n=15, *$p<0.05$)

Stepwise regression was then performed and the model found one predictor explained 72.8% of variation in intention in the control group (R^2 =0.746, F(1,15)=41.049, p=0.000). It was found that attitude significantly predicted intention to exercise (β= 0.864, t=6.407, p=0.000).

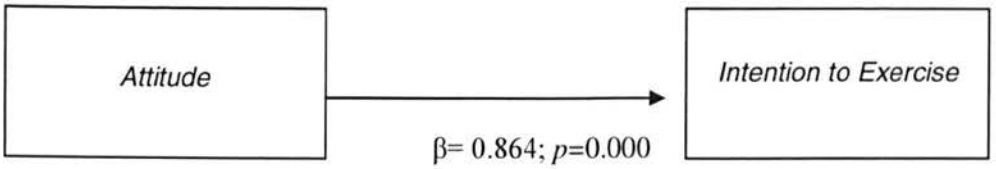


Figure 5.3. Best model (R^2=0.746; p=0.00) for predicting intention to exercise at post-testing (T1) in the Control Group

Intention and TPB determinants predicting actual behaviour (Control Group)

The simultaneous regression model was insignificant (R^2=0.294, F(5,13)=0.668, p=0.659). The model predicts only 14.7% of the variation in actual behaviour at post-testing amongst the control group. The simultaneous multiple regression equation of actual behaviour upon intention, attitude, self-efficacy, social support and control at post-testing (for controls):

> Predicted actual behaviour = 5.156+-0.458 X post attitude +-0.318 X post self efficacy +-0.171 X post social support +-0.166 X post control +0.237 X post intention.

Table 5.7. Regression Analysis Summary for Post-Testing Intention and TPB Variables Predicting Post-Testing Actual Behaviour (Control Group)

Coefficients	**B**	**Standardised Regression scores Beta (z-scores)**	***P***	**Collinearity Condition Index**
Intention Time 2	0.237	0.385	0.474	10.292
Attitude Time 2	-0.458	-0.634	0.213	13.855
Self efficacy Time 2	-0.318	-0.446	0.336	18.384
Social support Time 2	-0.171	-0.291	0.421	26.978
Control Time 2	0.166	0.206	0.664	33.532

Note: R^2=.294 (n=13, *$p<0.05$)

Condition indices show that collinearity was a concern for variables of self-efficacy, social support and control (>15).

Stepwise regression was performed and the model was insignificant (R^2 =0.292, F(2,13)=2.265, p=0.150). Intention (β=-0.578, p=0.058) and self- efficacy (β=0.287, p=0.318) were included in the model.

Intervention Group

TPB determinants predicting intention (Intervention Group)

The simultaneous regression model shows significance beyond the 0.01 level (R^2=0.701, F(4,18)=8.189, p=0.001). The model predicts 61.5% of the variation in intention at post-testing amongst the intervention group. The simultaneous multiple regression equation of intention upon attitude, self-efficacy, social support and control at post-testing (for the intervention group):

> Predicted intention (intervention) = -0.725+0.108 X post attitude +0.298 X post self efficacy +0.669 X post social support +-0.133 X post control.

Table 5.8. Regression Analysis Summary for Post-Testing TPB Variables Predicting Post-Testing Intention to Exercise (Intervention Group)

Coefficients	**B**	**Standardised Regression scores Beta (z-scores)**	**P**	**Collinearity Condition Index**
Attitude Time 2	0.108	0.056	0.758	8.735
Self efficacy Time 2	0.298	0.248	0.206	11.471
Social support Time 2	0.669	0.610	0.006	16.149
Control Time 2	0.133	0.112	0.517	17.404

Note: R^2=.701 (n=18, *$p<0.05$)

Stepwise regression was performed and the model found one predictor explained 62.0% of variation in intention in the intervention group (R^2 =0.641, F(1,18)=30.313, p=0.000). It was found that social support significantly predicted intention to exercise (β= 0.800, p=0.000) amongst the intervention group.

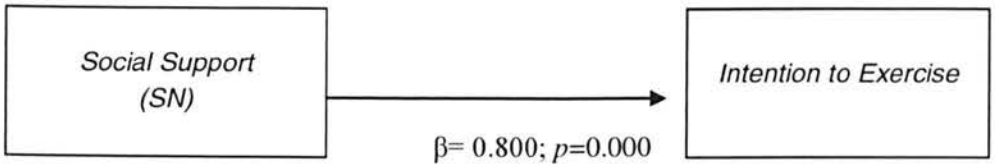


Figure 5.4. Best model (R^2=0.641; p=0.00) for predicting intention to exercise at post-testing (T1) in the Intervention Group

Intention and TPB determinants predicting actual behaviour (Intervention Group)

The simultaneous regression model was insignificant (R^2=0.139, F(5,18)=0.419, p=0.827). The model predicted only 19.2% of the variation in actual behaviour at post-testing amongst the intervention group. The simultaneous multiple regression equation of actual behaviour upon intention, attitude, self-efficacy, social support and control at post-testing (for the intervention group) is:

> Predicted actual behaviour (intervention) = -0.517+0.387 X post attitude +0.029 X post self efficacy +-0.102 X post social support +-0.039 X post control + 0.039 X post intention.

Table 5.9. Regression Analysis Summary for Post-Testing Intention and TPB Variables Predicting Post-Testing Actual Behaviour (Intervention Group)

Coefficients	**B**	**Standardised Regression scores Beta (z-scores)**	***P***	**Collinearity Condition Index**
Attitude Time 2	0.387	0.394	0.234	8.945
Self efficacy Time 2	0.029	0.048	0.894	12.811
Social support Time 2	-0.102	-0.181	0.684	17.935
Control Time 2	-0.039	-0.064	0.835	20.947
Intention Time 2	0.039	0.076	0.874	27.676

Note: R^2=.139 (n=18, *$p<0.05$)

Condition indices show that collinearity was a concern for variables of social support, control, and intention (>15).

Stepwise regression was performed and the model was insignificant (R^2 =0.11.3, F(3,18)=0.635, p=0.604). Intention (β=0.316, p=0.346), self-efficacy (β=0.009, p=0.979), and control (β=-0.203, p=0.440) were included in the model. There was high collinearity amongst variables.

5.4 DISCUSSION

Summary of main findings

The main findings of the present study indicate that the TPB is an effectual model to predict intention to exercise. Both groups collapsed at baseline, the model predicts 68.6% of the variation in intention, and 36.2% of the variation in actual behaviour. The model predicts 77.0% of the variation in intention, but only 14.7% of the variation in actual behaviour at post-testing amongst the control group, and 61.5% of the variation in intention, but only 19.2% of actual behaviour at post-testing amongst the intervention group.

Self efficacy (β=0.495) and social support (β=0.469) predict intention to exercise among lymphoma survivors and self-efficacy (β=0.609) alone predicts actual behaviour (shortly after treatment cessation) whereas for lymphoma survivors who are already exercising, social support (β=0.800) predicts intention to exercise. At three months post-treatment, attitude (β=0.864) predicted intention to behave. Nothing significantly predicted actual behaviour in either group..

The examination of the determinants of exercise may be useful for developing future interventions. Using the TPB, the current study examined the determinants of exercise specific to lymphoma survivors, both at baseline (shortly after finishing chemotherapy or radiotherapy), and after the exercise intervention (separately by group). Extending the work of Courneya and colleagues at University of Alberta, Canada, the TPB was found to be an effectual model to predict exercise adherence in cancer survivors.

Baseline (Pre-CARP) Measurement

Amongst lymphoma survivors who recently finished treatment (all participants collapsed into one group), the TPB explained 36.2% of the variance in exercise behaviour: this is consistent with previous studies utilising the TPB in cancer survivor groups (Courneya & Friedenreich 1997; Karvinen *et al.* 2007, 2009; Peddle *et al.* 2008; Stevinson *et al.*, 2009; Speed-Andrews *et al.*, 2012). Further analysis showed self- efficacy was a significant predictor of exercise behaviour: self-efficacy explained 35.1% ($P < 0.001$) of the variance in behaviour. Incongruent with previous studies, intention was not a significant predictor of actual behaviour. Intention is often seen as a reliable predictor of behaviour (Francis *et al.*, 2009); previous studies have explained 23–68% of the variance in intention to exercise in cancer survivors using the TPB (Speed-Andrews *et al.*,

2012, Courneya *et al.*, 2000, Courneya and Friedenreich 1997; Courneya *et al.* 1999, 2004; Karvinen *et al.* 2007, 2009; Peddle *et al.* 2008; Stevinson *et al.* 2009). Recent studies examining the TPB model have included an additional variable- planning- to the theory of planned behaviour, suggesting it mediates the relationship between intention and actual behaviour (Araújo-Soares *et al.*, 2009; Speed- Andrews *et al.*, 2011; Trinh *et al.*, 2012). It may have been useful to examine planning when predicting actual behaviour within the current study, as this may have impacted the predictive value of intention. Equally, intention may not have predicted behaviour in the current study because a long timeline was used in the TPB questionnaire; shorter goals (targets) may have been more practical. These two factors would be useful to consider in future research designs.

The TPB model suggests that intention can be used as a proximal measure of behaviour; it is purported that the model can be used to determine the effectiveness of implementation interventions even without a readily available measure of actual behaviour (Francis *et al.*, 2009). Specific to NHL survivors, Courneya and colleagues (2005) reported the TPB explained 55% of the variance in exercise intention. The current study showed that self-efficacy and social support significantly predicted intention to exercise: intention had 66.5% ($P < 0.001$) of its variance explained by perceived self-efficacy (($\beta = 0.495$, $p<0.001$), and social support ($\beta=0.469$, $p<0.001$) which were moderately correlated. The two variables appear to work together to impact intention. Previous literature showed social support play an important role, not only by impacting exercise intention but also by virtue of its relationship with PBC (Courneya and McAuley, 1995). PBC, consisting of both self-efficacy and control, is associated with greater use of cognitive and social coping strategies during exercise (i.e., asking for assistance, seeking social support and positive coping self-statements) (LaChapelle *et al.*, 2001). The findings from the present study are not surprising. It would be expected that upon finishing treatment, lymphoma patients may be influenced by subjective norm as cancer itself may have caused them to feel isolated and 'different'. Many patients strive for 'normality' during the transition period from patient to survivor. The participants may look to others for what is deemed 'normal'. Something like exercise, although often reported to be safe and effective for cancer survivors, may also bring about fear. The participants may question whether they are doing the 'right' kind of exercise and may fear the unknown in terms of how their bodies (and potentially, cancer) may respond to the exercise. By examining what others are doing post-treatment may give participants some comfort in what is 'safe' ('strength in numbers' so to say). Self-efficacy is the belief one holds about their ability to perform a task/ operation. The participants feelings of whether or not they are capable of performing exercise is a reasonable determinant of whether or not they plan to take part in exercise. Having come from a fairly 'unknown' or unstable position as a cancer patient, it is acceptable that the participant chooses to take part in activities he or she feels they are capable of doing. Taking on a challenge that they are not sure they can succeed in may bring about some anxiety shortly after finishing cancer treatment.

The current findings provide some useful information for exercise prescription for lymphoma survivors. If recruiting patients immediately following treatment, it would be useful to consider ways to improve self-efficacy to enhance exercise participation. It may be useful to consider including educational sessions on what 'exercise post-treatment' would involve and give patents tools that outline what exercises are recommended. Any support provided by the medical team may also influence self-efficacy, and in turn, potentially behaviour. To impact upon intention, providing social support along with self-efficacy may impact intention to behave (which has previously been shown to impact actual behaviour, although that was not the case in the current study). Again, this support may come from the patients' trusted medical team, from other survivors, supporters (family and friends), and possibly exercise specialists who are specifically trained to work with cancer survivors. Removing the 'unknowns' about exercise should help to remove barriers: this should improve self-efficacy.

Following Intervention (POST CARP) measurement

Following 12-weeks CARP, the TPB constructs were obtained in order to predict intention to exercise and actual exercise behaviour amongst the intervention group and control group, separately. Attitude predicted 72.8% of intention amongst the control group, which has previously been found to be a significant predictor of intention within the cancer population (Speed-Andrews *et al.,* 2012; Karvinen *et al.,* 2007; Karvinen *et al.,* 2009). Social support explained 62% of the variance in intention in the intervention group. Interestingly, this same group expressed, during a qualitative exploratory focus group, the importance of social support during exercise and the impact it played in their motivation to continue. The exercise experience may provide a greater value for social support which may possibly explain its predictive strength amongst the exercising group. This can be practically applied to future interventions; it may be useful to plan exercise sessions with a social focus to increase intention to exercise and adherence. It would also be useful to create a partner system, or a set of follow-up sessions for the group to enhance long term activity once the structured programme has finished. Karvinen and colleagues (2009) found descriptive norm (others being active) was more important to bladder cancer survivors than injunctive norm. It would be worthwhile, in future research, to measuring social support by descriptive norm and injunctive norm as that would help determine what form of social support would be most beneficial within the specified population (Karvinen *et al.,* 2009).

Unexpectedly, the TPB did not significantly predict actual behaviour amongst the intervention group or control group at post-testing. This may be due to the wording of the intervention questions used in the questionnaire (the time frame may have been too long), or possibly due to inaccurate reporting of actual behaviour on a subjective questionnaire (IPAQ). The condition indices also showed high collinearity on 3 of the variables used to predict actual behaviour both in the intervention and control group which impacts the stability and variance of the regression estimates.

5.5 SUMMARY

Predicting exercise behaviour using the TPB is novel in this population. The current trial provides researchers with a description of the determinants of exercise intention and behaviour that can be used to design future interventions. Based on the current findings, it would be beneficial to focus on enhancing both self efficacy and social support in lymphoma survivors (shortly after treatment cessation) when planning exercise interventions in order to increase exercise intention. This could be done both during treatment, recruitment, and within the intervention itself. For lymphoma survivors who are already exercising, social support is integral to the intention to exercise: this differs from the general population where social support is found to be a weak predictor of intention.

Knowledge translation from theory to practice is of particular importance and has become a focus of many researchers in the exercise and cancer field (personal communication, Culos-Reed, 2013). Until recently, the application of the TPB involved some creativity on the part of the researcher and practitioner, as Ajzen (2006) had proposed that the practitioner could apply the information to their intervention design, but gave little suggestion of how to do so. Recently Michie and colleagues mapped appropriate behaviour change techniques to determinants of behaviour, including the TPB determinants (Michie *et al.,* 2008).By applying the suggested behaviour techniques for the strong predictors, the behaviour is expected to change (Michie *et al.,* 2008). In the current trial, for example, an intervention for lymphoma survivors that is to take place shortly after treatment ends should focus on enhancement of self-efficacy and social support. Therefore, techniques to enhance social support such as modelling behaviour and demonstration by others, as well as social encouragement, social pressure and supportive behaviour from the practitioners should be at the forefront when planning an intervention (Michie *et al.,* 2008). Tools used to promote self-efficacy should be applied such as self-monitoring, feedback, self-talk, and motivational interviewing (Michie *et al.,* 2008).

5.6 FUTURE RECOMMENDATIONS

Further analysis is needed to determine what kind of social support would be most useful amongst lymphoma survivors, for example, examining who is providing the social support (other group members, the instructor or team leader, or an external partner, friend, family, etc), and how this support is given (descriptive, injunctive).

Future research should consider expanding upon the current TPB by exploring the antecedents in further detail. Recent literature has examined the impact of the TPB constructs using two lower order factors per variable which gives a more specific explanation of the predictors impacting exercise. Although the current study design examined the PBC using two components (self-efficacy- the confidence in ability to exercise, and perceived control- ones perceived control

over exercise) both attitude and social support can also be examined in more detail. Attitude can also be measured by two sub-variables: attitude consists of affective (enjoyment of exercise) and instrumental (perceived benefits of exercise) components. Subjective norm is comprised of descriptive (perception that others perform the activity) and injunctive (perception that others approve of exercise) components (Karvinen *et al.*, 2007). It may be useful to explore the different lower order factors within each of the TPB variables in order to gain a greater understanding of how and why each variable contributes (or doesn't contribute) to the model.

In addition to expanding the current TPB variables, considering additional predictors may be useful. Another component that has been added to the TPB model is *planning* (Norman and Conner, 2005; Araújo-Soares *et al.*, 2009; Speed- Andrews *et al.*, 2011; Trinh *et al.*, 2012). Planning is simply measuring the extent to which the participant has made plans for exercise. Speed-Andrews and colleagues (2012) found that the TPB explained 71% of the variance in planning and 62% of the variance in intention, in a recent study of cancer survivors. The transtheoretical model of change (TTM) by Prochaska and DiClemente (1983) takes into account (indirectly) ones plan to change, with the goal being adoption of the behaviour (exercise). The addition of this construct may offer a greater understanding of how best to influence behaviour, and may offer additional tools to assist with promoting exercise and adherence, e.g. goal setting and planning tools. Courneya and colleagues (2010) recently examined predictors of exercise within a group of lymphoma survivors' 6-months after completing an exercise intervention. It was found that accepting a post-intervention exercise prescription (a *plan*) was a strong predictor of exercise behaviour at 6-month follow-up.

Interestingly, when Courneya and colleagues (2010) examined 16 variables that may influence exercise behaviour of lymphoma survivors at 6 months post-intervention, of the five variables entered in the stepwise regression model, change in PBC and post-intervention intention were the only TPB constructs that were selected (other significant predictors included higher peak power output, accepting the exercise plan, and having HL). In future studies, it may be important to consider other variables, outside the TPB, as predictors of intention and exercise behaviour.

A limitation of the current study was sample size, specifically when the groups were separated. The inclusion of the lower factors for each construct would have given a greater understanding of what specifically predicted intention and behaviour in the current study. The length of time used in the questionnaire could have been reduced so that participants did not have to plan so far in advance. The wording of the questionnaire could be improved by providing specific behaviour within a reasonable amount of time. It is commonly known that up to 50% of participants often drop-out from an exercise programme within the first 6 months of initiating it (most in the first 12-weeks) (Dishman and Sallis 1994: by asking the participants their intention to exercise for 6 months may have been intimidating and was likely too long of a commitment.

Chapter 6.
FOCUS GROUP STUDY

6.0 INTRODUCTION

There are numerous quantitative studies that endorse the usefulness of exercise to combat physical and psychological stressors specific to cancer; however, qualitative examination has been less common.

Previous exercise related qualitative study of cancer survivors, report improvements in mental outlook mood, confidence, physical functioning (increased energy), motivation and social support (Korstjens *et al.,* 2008; Mitgaard *et al.,* 2011; Spence *et al.,* 2011; Stevinson and Fox, 2006). Unique to the qualitative literature has been discovery that high levels of distress are commonly associated with the transition from being a cancer patient to becoming a survivor. Physical activity has been useful in helping survivors regain a sense of 'normality' (Hennessy, Stevinson, & Fox, 2005). The purpose of this qualitative component was to further explore the perspectives of the participants who took part in the exercise intervention (CARP). Ethical approval for the addition of the focus group study was granted by Wandsworth Research and Ethics Committee entitled Amendment version 10.

6.1 METHODOLOGY

Focus groups are used to explore views on health issues, programs, interventions, and research (Tong *et al.,* 2007). This focus group method allowed interaction between participants with the intention of surfacing additional information that may not show in an individual interview (Krueger & Casey, 2000). The group setting enabled participants to ask questions of each other, as well as to reconsider and re-evaluate their own views and interpretations of their specific experiences (Kitzinger, 1995). This thesis chapter conforms to the consolidated criteria for reporting qualitative studies (COREQ; Tong *et al.,* 2007).

Domain 1. Research team and reflexivity

The focus group took place in a meeting room at the St. Georges Hospital, Lanesborough Ward, London, UK, and was moderated by two experienced female researchers, who were independent to the study. Interviewers had no association with exercise related studies for cancer survivors.

Domain 2. Study Design

Methodological orientation and theory: The interview transcripts were subjected to thematic analysis. Thematic analysis remains the most commonly used method of analysis in qualitative research and has recently been recognized as its own branch of systematic qualitative inquiry (Braun & Clarke, 2006; Joffe, 2012). Through organizing, labelling, and interpreting qualitative

data, thematic analysis seeks to be authentic in representing participant's words and perceptions (Joffe, 2012).

Braun and Clarke (2006) recommend that is good practice to make transparent the theoretical framework in which the analysis was conducted; the current thematic analysis was conducted from an essentialist/realist approach, therefore, themes were identified at a semantic level (Braun & Clarke, 2006). The essentialist paradigm assumes the relationship between language, experience, and meaning are uni-dimensional; language is a tool that allows us to articulate meaning and experience, thus interpretation is direct and straight-forward. Unlike discourse analysis and conversation analysis, thematic analysis does not attempt to analyze the structure of talk or language (Braun & Clarke, 2006).

Participant Selection:

An invitation letter (Appendix C) was sent to the 20 lymphoma survivors who completed the exercise intervention arm of the study. Thirty percent (6/20) of participants attended the focus group and were used as a representative sample of the exercising cohort, and provided with a participant information sheet (Appendix D) Reasons for not attending the focus group meeting were; 'lack of time' (n=11) while others (n=3) were 'uninterested'. Details on recruitment to the study are found in *Chapter 3 Theoretical and Methodolgical Background.*

Setting: The sample consisted of three male and three female participants. Ages ranged from 40-70 years (mean= 55.2 $\pm$ XXyears). All six participants were married, and two were smokers. The focus group interview took place on a weekday morning; of the six participants only one was currently working full-time, one part-time, one on sick leave, the remaining three were retired. The time between their last treatment to the start of the exercise programme ranged from 11-94 days (mean= 37.3 days). A table outlining participant demographics is located in Appendix P.

Data Collection: Moderators loosely followed a topic guide (Appendix R), which highlighted four areas of importance; a) participant perception of the overall impact of the study, b) participant perception of how the programme affected daily life, c) commitment to exercise, and d) programme evaluation. Only one focus group was conducted; this lasted for 1 hour, 12 minutes.. The interview was audio recorded and transcribed verbatim by 'Page Six Transcription Services Ltd'. Transcripts were not returned to participants for comment and/or correction.

6.2 ANALYSIS AND FINDINGS

Data Analysis: Using a process of inductive thematic analysis (Braun & Clarke, 2006), raw data were manually coded across the data set. Coded data extracts were then collated (this was done by

photocopying the transcript 5 times, then manually cutting extracts and taping them onto index cards- some extracts were included on more than one index card). Codes were sorted by pattern. Analysis was approached from an essentialist position; as such, themes were identified at a semantic level and were based simply on surface meanings, not underlying assumptions or ideologies identified from data (Braun & Clarke, 2006). Once themes began to form, codes were combined and labelled into member-generated themes using the phraseology and concepts of the participants (Fereday & Muir-Cochrane, 2006). Coding criteria were described for each theme- these were written out on separate sheets of cardstock. Index cards (codes) were placed on the cardstock (themes). Themes were reviewed and compared for consistency of coding. Major themes surfaced, but were regarded as provisional and subject to revision throughout analysis. Raw data were frequently returned to so as to ensure inferences accurately reflected the participants' experiences. After refining the themes, two major themes were identified.

Reporting: Quotations from the raw data are presented alongside narrative to blend description and interpretation (Braun & Clarke, 2006; Tuckett, 2005). Their length has been kept to provide some context (Braun & Clarke, 2006). Participants are referred to by an allocated number to preserve anonymity. The major themes that emerged from the focus group discussion are outlined and interpreted below.

6.3. RESULTS AND DISCUSSION

The data revealed two key themes related to the experience of participating in the CARP: 'perceived benefits of taking part in the CARP' and 'social dimensions'.

Perceived benefits of taking part in the CARP

Three sub-themes were identified from the data: 'positive impact', 'self-confidence', and 'returning to normality'.

1. Positive Impact

Data showed that all six participants perceived that taking part in the CARP had a positive impact on both their recovery from cancer and life in general, and expressed that the programme positively impacted their lives in a way that they may not have experienced had they not taken part in the exercise intervention.

> *(6) 'When you're ill and everything that you have to go through, and come to terms with the illness, feeling the effects of the chemo, I know it just puts you off doing anything, but all I would say is just go and do it, if you don't do anything else.... I*

would just encourage anybody to do it, anybody, and I'd just tell them, it doesn't matter what you've got come up, put that off and make this your priority, without this, I don't think that I would be where I am today, to be quite honest'.

Participants repeatedly expressed that the CARP was invaluable. Participant (4) stated *'without a doubt, you can see the difference it (the exercise programme) makes to everybody'* and all others agreed.

(4) 'It's been absolutely, it's a godsend, it really has been for me'.

One participant explained that when she was feeling low or thinking a bit negatively about the future, she told herself to *'do some exercise and take control again'.* Increased perception of control is associated with reduced emotional distress and improved role and social functioning (Bremer *et al.,* 1997; Helgeson *et al.,* 2004).

All six participants agreed that taking part in the programme had helped them with their recovery, both *'physically and mentally'.* To illustrate, one participant attributed his ability to walk again without crutches or a wheelchair to his taking part in the exercise programme. The youngest person in the group said that taking part in the exercise programme gave her the energy to play with her child again. Others expressed that they were now able to return to activities they had enjoyed before diagnosis.

Consistent with the current study, qualitative research have shown exercise improved many facets of life for cancer survivors, including psychosocial and physical outcomes (Luoma *et al.,* 2014, Spence *et al.,* 2011; Stevinson &Fox, 2006); a majority of the focus was on the psychological benefits. The participants in the current study stated that taking part in the exercise programme made them *'feel more positive'* , helped them *'cope'*, and to *'feel better in themselves';* this is consistent with findings from other qualitative studies where cancer survivors expressed exercise improved their mood and overall mental state (Luoma *et al.,* 2014; Stevinson & Fox, 2006).

The findings give preliminary evidence that exercise, in this case an CARP, may be a useful means to improve psychological well-being, particularly social and role functioning. Further research is needed to substantiate these findings.

Self Confidence

Most participants reported taking part in the exercise intervention gave them the confidence to be active; in addition, as they exercised, they were surprised by how much they were capable of accomplishing.'

Participant 4 stated that when he was approached about the programme he thought *'I'm in a wheelchair, how am I going to (participate)...'* but by the end of the intervention he was *'not using sticks or anything'* and he was *'out of the wheelchair a lot quicker than they (the doctors) expected'*. Numerous times this participant attributed his ability to walk again to his participation in the exercise programme; *'the programme motivated me to actually keep pushing forward... gave me the motivation to actually push on... it was just what I needed to actually get me out of the chair'*.

Four participants expressed that the CARP helped them to feel confident in performing healthy activities outside of the programme. One said:

> *(1) 'It's actually, you know, giving you the confidence to step into life again, but you can't just do that by going and exercising on your own... I went back to swimming very quickly, whereas you would have been frightened, you know, you might catch something but, I said to Lisa, and she said, "No, go for it" so I went back to normal really quickly. And, in fact, you know, three months in my case, was fine, you know, I was fine'.*

These results are supported by findings from other qualitative cancer survivor exercise intervention studies where gaining the confidence to be physically active and perform activities of daily living was important to participants (Anderson *et al.*, 2010; Korstjens *et al.*, 2008; Spence *et al.*, 2011; Stevinson & Fox, 2006). Most participants in the current study reported taking part in the CARP gave them the confidence to get back to the activities they did before they were diagnosed with cancer, whether that was playing with their children, swimming, cycling, golfing, or gaining the physical strength to drive an automobile. After taking part in an exercise intervention, cancer survivors had more confidence to return to pre-cancer roles, which is consistent with other qualitative research findings (Spence *et al.*, 2011; Stevinson & Fox, 2006). The quantitative component of the trial showed similar results; functional well-being significantly improved amongst the intervention group after the CARP.

Health promoting behaviours are associated with improved self-confidence and with feelings of increased control over ones' life (Maunsell *et al.*, 2002). A qualitative study of breast cancer survivors reported similar improvements in confidence and control after an exercise intervention; however, authors suggested these benefits were greatly influenced by an all-female intervention group (Luoma *et al.*, 2014). The current study demonstrated that a mix of men and women taking part in the same CARP experienced increased confidence and control as well, thus suggesting that gender exclusive groups are not necessary for improvements in confidence and feelings of control. It could be argued that the current trial was taught on an individual basis and thus gender of other participants was irrelevant, but the participants did cross over and often people of different sexes were exercising in the room at the same time.

Another demonstration of confidence was seen when two women from the group discussed their decision to remove their wigs and scarves during exercise sessions. Without being prompted by the instructors, the two female focus group participants who experienced alopecia articulated the magnitude of this experience by sharing that they had not bared their heads in public before; the removal of their wigs/scarves sounded like a symbol of freedom for them. The significance was reiterated when one female participant described the experience of a fellow exerciser who had removed her scarf for the first time as, 'it was her *moment'*.

> *(1) I remember we, 'B' and I were in and we were talking about hair and 'J' came and said, "Well, if you've all got your headscarves off then," and off came hers, and that was, you know, that 'moment' for her. .. it's a big thing psychologically for people'.*

Hair loss is commonly rated as one of the most feared and traumatic aspects of chemotherapy (Batchelor, 2001); many women disguise baldness with wigs, hats, or scarves. Hair loss has been associated with loss of self or identity (Freedman, 1994; Rosman, 2004; Williams *et al.*, 1999). Changes in appearance can impact ones' ability to fulfil roles and responsibilities and thereby impact quality of life (Luoma & Hakamies-Blomqvist, 2004). The impact of bearing ones head was a unique outcome that was not expected from an exercise intervention. Only one other qualitative study, to the authors' knowledge, has reported that cancer survivors voluntarily removed their wigs during an exercise intervention (Emslie *et al.*, 2007). Emslie and colleagues (2007) thought that the participants removed their wigs because the group consisted of only women. Our findings do not support this suggestion as our participant group was made up of both females and males.

Returning to the overarching theme, the participants who took part in the focus group attributed some level of improved confidence to taking part in the CARP, suggesting they perceived the CARP was beneficial. Improvements in confidence are associated with improvements in HRQoL (defined as satisfaction in relation to ones' health and healthful activities (Center for Disease Control and Prevention, 2000), as the participants expressed how they were more confident in their abilities to take part in other activities. A recent systematic review reported that exercise improves HRQoL amongst post-treatment cancer survivors (Mishra *et al.*, 2012). Although findings should be considered with caution due to limited sample size of the focus group, the improvements, expressed by the participants, support the current trial quantitative findings that the exercise intervention improves HRQoL.

Return to Normality: Transitioning from Patient to Survivor

Although the completion of treatment and the idea of returning to ones previous lifestyle ('normality') is often associated with positive feelings, this transition period from being a patient to a survivor is also associated with feelings of uncertainty, loneliness, and fear of recurrence (Allen *et al.*, 2009; Lethborg *et al.*, 2000). The importance of normality was highlighted by all participants

at some point during the interview; each participant in the focus group stated that the programme made them feel more 'normal'. The consensus from the focus group was that the CARP gave them the *'push'* they needed to return to activities they did before diagnosis, and to leave behind the role of *'patient'*. All participants agreed that the hospital based CARP performed shortly after end of treatment was successful in *'bridging the gap'* between being a patient and feeling *'normal'* again which is consistent with other cancer survivorship studies (Luoma *et al.*, 2014; Stevinson & Fox, 2006).

One participant commented that her life now is as normal as it was before she was diagnosed:

> (6) *'I remember after the first couple of sessions, just afterwards, I just felt, "Oh my goodness, I never thought I could feel like this again," like normal, sort of thing, so I think that was what was really good about it, it really did make you think, oh, gosh, you can feel normal again and you're not feeling the effects of the chemo and, you know, everything else and I would say mentally as well.'*

Stevinson and Fox (2006) found a number of respondents valued the positive focus of their exercising experience and appreciated being treated as 'normal', as the focus was not on their identity as a cancer patient. Taking part in *'normal'* activity reportedly helped some of the participants feel that the cancer was temporary and that they would soon be returning to the life they knew before.

Participants spoke of the intervention as a *'tool'* that helped them to return to pre-morbid lifestyle and activities. Three participants mentioned the programme was more of a stepping stone rather than a 'lifestyle change'; they had no interest in continuing with a formal exercise programme now that the intervention had finished. They described the intervention as a means to an end; it provided the energy and strength they needed to return to the activities they had enjoyed before diagnosis. Participant 4 described how he is now able to return to his previous activities. He expresses how this has improved his QoL:

> *(4) 'I'm back playing golf again. I didn't think I'd ever play golf again..... I'm slow but, you know, I'm doing it, and, again, there's nothing like the joy of being on... I mean, I've worked on golf courses all my life, so for me to be out there, I mean, it's good for the soul. That makes you feel better in yourself.'*

It was clearly expressed during the focus group session that taking part in the CARP made the participants feel 'normal' which in turn helped them to cope better in other areas of life. For example, one participant explains:

> *(1). 'When you're done your exercise and you feel that much better, then you can probably cope with joining everything else'.*

The end of treatment can be quite challenging for cancer patients as they transition into this new phase of life - living with cancer (Allen *et al.,* 2009; Lethborg *et al.,* 2000). Exercise has been found to help with this transition in a number of recent qualitative studies (Hennessy, Stevinson, & Fox, 2005; Luoma *et al.,* 2014; Stevinson & Fox, 2006); however, this outcome is not commonly examined in quantitative research. Role functioning is the closest outcome measured in the current RCT that would relate to this transitioning of roles, but it does not specifically measure one's 'role' in relation to cancer itself. Role functioning improved in the quantitative study but the change was not statistically significant. Other outcomes that have been examined in quantitative research may indirectly measure transition; for example, significant improvements seen in functional well-being and HRQoL may be related to or may be a product of the participants feeling they are returning to 'normality'.

Another interesting finding from the current study was the use of the CARP as a *'stepping stone'*. Much of the exercise specific research focuses on long-term adherence to exercise interventions and amount of activity maintained after the intervention finishes. If participants have continued doing the activity at follow-up, adherence is maintained and can be viewed as success. What was unique in the current trial was that at one year follow-up, many of the participants in the intervention group were not producing the same overall energy output (measured as intensity multiplied by time) as they were at the end of the CARP, thus it was assumed that the participants did not maintain activity and therefore the programme was not successful in terms of adoption of long term exercise behaviour. What may be worth further exploration are what kinds of activities the participants *are* taking part in, and whether they are able to perform activities that they had done before diagnosis. It is possible that although taking part in the CARP did not lead to exercise adherence in the traditional sense, participation helped the cancer survivors return to the activities that they did before diagnosis, which may be more valuable to the participant than just continuing with the exercise they performed in the trial.

Despite the participants view that the exercise intervention helped them feel 'normal' again, it is also plausible that this transition would have occurred regardless of whether they took part in the intervention or not. To explore whether this improvement was common to all survivors or whether these results were specific to taking part in the CARP, it would be useful to have the control group take part in a focus group and compare the findings. Although this was not performed in the current trial, the control group did not experience the same statistically significant increases in functional well-being and HRQoL as the intervention group did in the quantitative study. This indicates that the CARP may have had some part to play in helping participants 'return to normality' and experience improvements in HRQoL and functional well-being.

2. *Social Dimensions*

The second major theme that was prevalent in the focus group was participant perception of improved social dimensions. Improvements in both social support and social functioning were expressed during the focus group. Therefore under the umbrella of social dimensions two sub-themes were identified: 'social support' and social functioning'.

Social support

All participants expressed that belonging to the CARP provided them with social support. Numerous times throughout the focus group, the participants mentioned how they felt supported by the instructors and the 'group'. With regards to instruction, participants were most happy with the way the trainers had encouraged them to do what they could and were accepting of limitations. The traits that seemed to be noted by the participants as most important for an instructor were motivation, acceptance, encouragement, and knowledge.

Participants described themselves as part of 'the group', yet, the exercises were taught and performed independently; participants never actually exercised 'together'. They may have seen each other as sometimes their sessions would cross over (as patient 5 described, *'passing in the night'*); however, they never actually worked as a 'group'. The label *'group'* came directly from the participants themselves.

Most participants commented that knowing others who had the same disease as them were exercising had motivated them and gave them strength to keep pushing themselves to be active. One said;

> *(4) 'just seeing people in the same position, that are doing it, you think well, they can do it, I can do it...motivates you, it really does... you're actually around people doing the same thing, you know, and, again, you can get motivation from other people'.*

Similar to previous research, the majority of participants in the current study suggested the 'group' provided additional motivation to work hard during the exercise sessions (Midtgaard *et al.*, 2006; Stevinson and Fox, 2006; Turner *et al.*, 2004). Vicarious experience, as explained by Bandura's self-efficacy theory, is a powerful motivator; the greater the similarity between the model and the viewer, the greater its influence (Bandura, 1986). This is common in group-based interventions; but, is especially interesting in the current study because of independent instruction. Spence and colleagues (2011) found that participants liked the idea of doing group exercise to increase the aspect of social support; nonetheless, they preferred the one-to-one format as they felt there were greater physical benefits (Spence *et al.*, 2011). The current study provided what participants described as a 'sense of belonging', 'motivation', and 'social support' from simply being part of the intervention 'group', but also gave them the attention and expertise of one-to-one training.

These findings suggest that the format of the current RCT (one-to one training with the instructor, but sharing the room and 'crossing over' of training appointments) might be an alternative to traditional group or personal training.

Beyond just affecting exercise behaviour, participants expressed how the social support gained in the CARP influenced them in their daily lives and improved overall QoL. Similar to findings from previous studies, participants in the current study enjoyed exercising with others who were experiencing the same disease as it gave them a sense of support and solidarity (Stevinson & Fox, 2006).

> *(3) 'It provides a sort of collective or you get a strength from the group, ... there are others who've got, you know, the same disease in different forms and they're getting on with their life, you know, and so, yeah, it does give you a push when you need it, actually, not to wallow too much, which is easy to do'.*

Interestingly, cancer survivor 'support groups' bring about similar benefits to those described in this focus group; cancer survivor support groups provides a sense of belonging, acceptance, encouragement and empowerment (Ussher *et al.,* 2006). When asked if the group would be interested in having an allocated place to meet and talk to one another, two of the current participants adamantly said that they did not want to *'sit around and chat'*, suggesting a formal 'support group' would not appeal to them. Emslie and colleagues (2007) had a similar response in their study; participants rejected the idea of a support group; although, they greatly enjoyed the social support of their exercise group and suggested their main attraction to the exercise intervention was the focus on action rather than emotional burden. Stevinson and Fox (2006) and Adamsen and colleagues (2001) reported that their participants s liked the positive nature of the interaction in their exercise sessions as it did not focus on their status as a cancer patient (Stevinson &Fox, 2006). This is worth exploring in future studies; exercise interventions may be used as a means to enhance feelings of belonging, acceptance and empowerment in the same way as support groups.

Social Functioning

Social functioning is defined as the ability to take part in social activities and family life (Conroy *et al.,* 2000), and is an area of great concern for cancer survivors (Foster *et al.,* 2009; Wyatt & Friedman, 1996). Feelings of worry and doubt are commonly reported by caregivers, in addition to anxiety, fear, stress, sadness, depression, insecurity and injustice/unfairness (Mancini *et al.,* 2011). Researchers have found that the people who are closest to the patient experience lower QoL scores; this has been found in parents (Klassen *et al.,* 2008), partners (Wagner *et al.,* 2006), and children (Kim & Given, 2008) of people with cancer. Family members often take on extra responsibilities when looking after their sick loved one (Thomas & Morris, 2002). Although it was not an aim of

the study, most participants stated that their involvement in the CARP positively impacted their family members. Two male participants said that by exercising, they had gained mobility and could now drive again. Participant 4 said he was able to do more without relying on his wife; *'It takes a bit of pressure off of her a little bit, you know.'*

Participant 3 said that when her family saw her becoming more positive whilst taking part in the CARP it helped them to relax and be more accepting of the cancer:

> *(3) I think there was a positive effect on my family as well, indirectly, in that they saw that I was doing something by going to the exercise and taking the exercises rather than not doing anything ... I think it was worse in some ways for them than it actually was for myself and then, when they saw that I was beginning to get, you know, quite positive about it with the help of the exercises, I think they were able to relax a little bit and accept it a bit more, so, that's, you know, another, sort of, side effect.*

Often the person who is sick is not able to participate in their familial role which can greatly impact the family members. Participant 6 explains how exercise helped her to have more energy to play with her 4 year old daughter:

> *(6) Well, I've got a four year old and I must admit that exercise helped me with her, because, obviously, throughout the time of the chemo I couldn't do a thing with her so, and before I was sick, we used to... I used to take her to the park and stuff and so, when I started the exercises and stuff and she said to me, "Mummy, are you having any more medication?" I said, "No, not anymore". So she goes, "Oh, good, we can go to the park, then". When I first finished, I was thinking, "Not the way I feel". But, then once I started the exercising, you know, I did start to get my energy levels back and stuff, and so I was able to start doing things with her, where I couldn't have, you know, I just didn't literally have the energy or the inspiration or the motivation, whatever you want to call it, to do it, but the exercises definitely helped.*

Literature has shown that exercise improves social functioning amongst cancer survivors (Mishra *et al.*, 2012; Stevinson *et al.*, 2009). The findings from the focus group support the quantitative component of this thesis as social functioning significantly increased amongst the intervention group over the duration of the CARP.

6.4 SUMMARY AND FUTURE RECOMMENDATIONS

The focus group was added to the current trial as a means to explore the impact of the CARP, as experienced from the participants' perspective. Participating in the CARP facilitated the participants' physical and psychological recovery through gains in confidence, social function, and by providing a sense of normality. The findings from the focus group support the quantitative study

in the current trial; both studies resulted in significant improvements in HRQoL, social functioning, emotional, functional, and physical well-being (although PWB also improved in the control group). The participants expressed that involvement in the exercise study brough abundant improvements in psychosocial well-being (described by participants as mental, emotional, and psychological). The qualitative findings, although limited by sample size, are also congruent with other qualitative research done in this field; a majority of the research in this field have reported improvements in QoL and the emotional, physical, social and functional domains of QoL amongst cancer survivors after an exercise intervention (Midtgaard *et al.*, 2006; Chen *et al.*, 2009). The focus group provided many of the benefits associated with support group therapy. If supported with future research, exercise may be a useful optional intervention to improve psychosocial well-being.

One finding from the current study that is worthy of note was the participants' perception that the CARP facilitated in their transition from the role of patient to survivor, The impact of exercise on this transition to normality has recently been reported in a handful of qualitative studies in the field (Emslie *et al.*, 2007; Hennessy, Stevinson, & Fox, 2005; Luoma *et al.*, 2014; Stevinson & Fox, 2006). As well, participants also reported being very interested in returning to their pre-cancer activities (i.e. swimming and golfing) than in continuing to follow a traditional exercise format (similar to the intervention) as the intervention was just a 'stepping stone'. Qualitative literature in the field supports the current trial in terms of the importance of returning to pre-cancer roles (Spence *et al.*, 2011; Stevinson &Fox, 2006), but this has not been previously examined as the 'goal' of exercise interventions (to date, the 'goal' is adherence to the training programme over time). Further research should be done to explore how exercise influences this transition process, as the need for quality survivorship care during the transition period from the completion of treatment to re-entry into ones 'normal' lifestyle has been identified in previous literature (Costanzo *et al.*, 2007; Rowland, Hewitt, & Ganz, 2006). If supported with further research, exercise could be identified as a non-pharmacological tool to help cancer patients with the challenge of returning to 'normality' once treatment is finished.

Another novel finding from the current study was that social support improved during one-to-one exercise training. Whilst maintaining the benefit of individual attention received with one-to-one training, participants expressed significant improvements in social support, just by having some interaction with other participants (even if just crossing over between exercise sessions). This has not been reported in previous research using one-to-one training sessions. It would be useful to explore whether these findings are maintained in larger studies with more participants, as the feeling of belonging to the 'elite' group may have been due to the small size of the intervention group (n=20); a larger group would make involvement less distinctive.

6.5 LIMITATIONS

A limitation of the current study was the size of this representative sample, thus generalisability of the findings are limited. Participants who took part in the focus group were representative of the intervention group in terms of sex and mean age; however, all participants in the focus group were married compared to only 65% of the participants in the intervention group. Married participants may have differed from unmarried in terms of impact on family or support, and being married is associated with reduced time spent exercising (Nomaguchi & Bianchi, 2004). Furthermore, half of the participants were retired compared to only one third of the intervention group. Those who were retired may not have had difficulty scheduling in the exercise whereas those who were working may have found it hard to juggle both work and exercise (as lack of time is reported as the greatest barrier keeping people from exercising (Chinn *et al.*, 1999). Equally, those who were working may have found the transition into 'normality' easier when distracted by the demands and roles associated with work, whereas those who were not working full-time (as seen in five of the six participants in the focus group) may have had a harder time with this transition. It is also important to note that the focus group took place on a weekday morning which may have excluded participants who were working or in school. These factors limits generalisability of the findings as those intervention participants with different demographics and associated commitments may have perceived the CARP differently than those who were interviewed in the focus group, let alone the differences between this small group and cancer survivors in general.

Participants who took part in the focus group had a markedly positive opinion about the CARP. Although questions were designed to elicit both positive and negative feedback about the programme and participant' experiences, very few negative comments were made. While this is common to a number of exercise studies for cancer survivors (Korstjens *et al.*, 2008; Spence *et al.*, 2011; Stevinson & Fox, 2006), this may be a result of the participants who chose to attend. .As attendance at the focus group was optional; it may be possible that the focus group was comprised of only those participants who had enjoyed the CARP. It is plausible that the improvements that are expressed in the focus group may be more positive than they would have been if some of the other participants from the intervention had attended the focus group.

The focus group participants may have been impacted by the influence of social processes and may not be expressing their own thoughts but may be influenced by those around them. While listening to others stories, participants in the current trial were self-reflective and, when agreeing with others, often provided a story or comment which suggested that they meant what they were saying. Nonetheless, this does not mean participants were not influenced by the group, particularly because social support was valued in this group. To reduce this, subjects could have been

interviewed one to one, or transcripts could have been sent to the group afterwards to confirm that the notes properly described what they meant.

In summary, the focus group session did what it was set out to do. Although the findings are limited due to sample size, the current focus group brought forward participants' views that taking part in the CARP was a positive experience and produced improvements in physical and psychological well-being. The improvements were expressed as improvements in confidence and social functioning whilst providing social support and assisting with the transition from patient to cancer survivor. These findings were congruent with those from the qualitative component of the current trial.

Chapter 7.
DISCUSSION

7.0 INTRODUCTION

There is considerable evidence supporting the positive effects of exercise amongst cancer survivors, but the research has primarily examined solid tumour cancers, namely breast and prostate. Thus, a gap in the literature was evident in that few studies had examined exercise effects amongst haematological cancers, and at the time the current study began, no studies had examined exercise response in lymphoma survivors, despite only one quarter of lymphoma survivors being physically active. The impetus for the present study was to explore the use of exercise in reducing the negative side effects associated with lymphoma survivorship and to examine the impact of exercise on immune function in this cohort who often are immune compromised.

Research evidence suggests: 1) Exercise improves indices of QoL and positively impacts physical and psychosocial well-being in solid tumour cancer survivors; 2) Hodgkin's (HL) and Non-Hodgkin's lymphoma (NHL) survivors are often burdened with debilitating side effects of treatment and post-treatment, significant reductions in QoL, HRQoL, psychosocial and physical health (cardiovascular and muscle function); 3) Only one quarter of lymphoma survivors were performing the minimal amount of exercise required to meet public health guidelines; and 4) no highly regarded RCTs had examined lymphoma survivors at the commencement of this thesis.

Based on these statements, a RCT was constructed that explored the efficacy of a 12-week combined aerobic and resistance exercise training programme (CARP) on: 1) QoL in HL and NHL survivors post- treatment; 2) cardiorespiratory fitness and muscle function in HL and NHL survivors post- treatment; and 3) immune function in HL and NHL survivors post- treatment. A second component to this study examined the determinants of exercise intention and exercise behaviour of in HL and NHL survivors' post- treatment using the *Theory of Planned Behaviour* (TPB).

This thesis offers the first exercise investigation of a 12-week combined exercise (aerobic and resistance) training programme (CARP) on overall quality of life (QoL) in addition to psychological, physiological and immunological outcome measures in Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL) survivors. This chapter interprets the present thesis findings with reference to the available literature and consideration to the thesis hypotheses, generalisablility of these findings and study limitations.

7.1 SUMMARY OF THE STUDIES MAIN FINDINGS

Randomised Control Trial

Combined aerobic and resistance training was found to be useful for improving health-related quality of life (HRQoL) (p=0.044) in lymphoma survivors within 6 months of completing treatment. This is particularly relevant because previous research has shown that lymphoma survivors exhibit a reduction in HRQoL after treatment (Roper *et al.*, 2009), as seen in the control group in the current study (they experienced a slight decrease in HRQoL at T1). Thus, exercise not only prevented decline in HRQoL but also brought about improvement. The current findings suggest that whilst taking part in exercise, the negative psychosocial and functional side effects associated with lymphoma are reduced. Statistically significant and clinically relevant improvements were indicated in emotional well-being (EWB) (p=0.029), functional well-being (FWB) (p=0.025), lymphoma subscale (examining lymphoma related concerns (LymS) (p=0.034), and social function (SF) (p=0.020), and clinically relevant improvements in fatigue amongst the exercise group. Physical functioning did not make any significant contribution to the improvements in HRQoL. Physical improvements were seen in the exercise group, but only resting heart rate (RHR) (p=0.041) and abdominal endurance (p=0.018) were statistically significant. Surprisingly, pulmonary function (% predicted forced vital capacity (FVC), (p=0.013) and an interaction between % predicted (FVC) and % predicted forced expiratory volume in one second (FEV1), (p=0.017)) significantly decreased in the intervention group. Both groups showed no change in immune markers.

The TPB was found to be an effectual model to predict intention and behaviour at T0, but only intention, by group, at T1. The primary finding is that the TPB is an effectual model to predict intention to exercise. With both groups collapsed at baseline, the model predicts 68.6% (r^2=0.723; p=0.000) of the variation in intention, and 36.2% (r^2=0.458; p=0.003) of the variation in actual behaviour. The model predicts 77.0% (r^2=0.831; p=0.000) of the variation in intention at post-testing amongst the control group, and 61.5% (r^2=0.701; p=0.001) of the variation in intention in the intervention group, but prediction of actual behaviour at post-testing was insignificant in both groups. Self-efficacy (β=0.495) and social support (β=0.469) predict intention to exercise among lymphoma survivors and self-efficacy (β=0.609) alone predicts actual behaviour (shortly after treatment cessation) whereas for lymphoma survivors who are already exercising, social support (β=0.800) predicts intention to exercise. At three months post-treatment, attitude (β=0.864) predicted intention to behave, but nothing significantly predicted actual behaviour in the control group.

Because randomization was stratified by tumour type (HL and NHL), the group were fairly matched by type (75% NHL in intervention and 71.4% NHL in control). Mean age was similar

(intervention 52 years, control 56 years), but the intervention was made up of more females (60%); versus 43% in the CON group. Both groups had equal days since end of treatment, but the majority of the intervention group were married; only 5% of the intervention group were divorced or separated compared to 19% of the control group. More of the controls had completed higher educational levels, were working in some capacity (38% of controls compared to 30% of the intervention group), and 4.8% smoked, compared to 25% of the intervention group.

Focus Group.

The small representative group (n=6) of intervention participants perceived that the intervention was beneficial, primarily expressed in terms of having a positive impact, improving self-confidence, and assisting with the return to 'normality' after treatment; the second theme was regarding perceived impact on social dimensions of SF and social support.

Follow-Up at 12 months intervention.

At 12-months post intervention, many of the positive changes experienced by the intervention group had subsided although significant improvement in HRQoL remained. A number of outcomes had regressed or remained unchanged. However, it is important to appreciate that the sample size at follow-up (n=15) was less than half (36.6%) of the RCT and is almost certainly underpowered. Clinically relevant reductions in EWB and role function (RF), along with increased confusion, anxiety, insomnia and pain were seen in the intervention group (increased anxiety (p<0.001), insomnia (p=0.045), and pain (p=0.043) were significantly worsened). Overall QoL scores continued to rise in both groups, but only clinically relevant in the control group. The control group showed statistically significant improvement in anxiety (p=0.002) and lymphoma concerns (p=0.048) (both clinically and statistically), as well as clinical improvements in QoL, SF, emotional function (EF), FWB, vigour, fatigue, and symptoms.

Both groups showed statistical and clinical improvements in HRQoL (intervention, p<0.001, control, p<0.001) and Lymphoma Trial Outcome Index (TOI) (intervention, p<0.001, control, p<0.001), as well as clinically relevant reductions in depression. Both groups reported a decrease in the total amount of time spent exercising, particularly in the control group, who displayed clinically relevant decline in exercise participation at follow up.

Comparing groups from baseline to follow-up, it appeared that taking part in the exercise intervention made no long-term difference to a number of psychosocial outcomes, despite increases in their time being physically active. Statistically significant effects were evident across both groups suggesting normal improvement from end of medical treatment. The findings suggest that taking part in the exercise intervention prevented improvements in many symptoms and functional

domains of lymphoma in this population of lymphoma survivors, although it is important to keep in mind that the sample size at follow-up (n=15) thus RCT and is underpowered.

Tolerance and adherence to exercise in HL and NHL survivors

Adherence to the CARP was high at 90.8%. Recruitment for the study was efficacious; of the eligible lymphoma survivors invited to take part (n=76), 47 participants were pre-tested, and 41 completed the main 12-week study (53.9%) which is higher than other lymphoma exercise trials; (Courneya *et al.*, (2009) and Streckmann *et al.*, (2014) had recruitment rates of approximately 25%). The significance of this finding suggests that exercise is well-tolerated in the sample of HL and NHL survivors and that their adherence to an exercise intervention is equal to, if not slightly superior to other similar sized cancer related studies.

7.2 GENERAL DISCUSSION

This thesis is novel in its investigation of a combined exercise (aerobic and resistance) training programme (CARP) on overall QoL and other health-related outcomes in an understudied population, lymphoma survivors. Due to the uniqueness of the research, few published studies on lymphoma survivors are available for comparison. As such, a comparison is made with exercise randomised controlled trials (RCT) and systematic reviews in other cancer survivorship groups as well.

7.2.1 THE IMPACT OF A 12-WEEK CARP ON QoL AND DOMAINS OF QoL IN LYMPHOMA SURVIVORS

The present research highlights the efficacy of a 12-week CARP in improving HRQoL, EWB and FWB amongst HL and NHL survivors. HRQoL improvements continue to increase into 12 month follow-up. The findings are supported by a recent systematic review of the HRQoL benefits of exercise for cancer survivors; HRQoL scores significantly improved both within subjects from baseline to 12-weeks (SMD 0.33; 95% CI 0.12 to 0.55) and compared to a control group at 12-weeks (SMD 0.47; 95% CI 0.16 to 0.79) (Mishra *et al.*, 2012). The relationship between exercise and HRQoL in lymphoma is corroborated by Bellizzi and colleagues (2009) whose research suggests exercise of any intensity is associated with improvements in HRQoL. Normally, HRQoL decreases post-treatment (Loge *et al.*, 1999), consistent with the present control group, thus the exercise intervention not only improved HRQoL but also prevented decline.

Changes in HRQoL in the exercise group were primarily a result of improvements in psychosocial and mental health; significant improvements were seen solely in the intervention group on outcomes of EWB (p=0.029), FWB (p=0.025), SF (p=0.020) and relief of lymphoma

related concerns (LymS) (p=0.034) (LymS is made up of questions relevant to lymphoma and include all domains of HRQoL). The author of the current study had suggested, in the introduction of this thesis, that improvements in HRQoL would be initiated by improvements in physical outcomes. Conversely, the present findings suggest HRQoL may occur independently of physical improvements. Improvements in subjectively measured PF and PWB were seen in mean scores, but PF was not statistically significant and PWB was statistically but not clinically relevant. Furthermore, the improvements in PWB were seen in both the intervention and control groups suggesting improvements were not related to the exercise intervention. Concomitantly, the exercise intensity was not enough to produce significant physiological change in aerobic capacity, but despite this, the exercise intervention produced improved psychosocial scores and HRQoL. Thus, the load of the exercise needed to increase HRQoL may not need to be high enough to produce physical change. In the current trial, the intervention was of moderate intensity, but was also adjusted to meet generally low initial fitness levels, sedentariness during treatment and exercise capabilities of participants. This provides explanation of why the intervention group showed a significant change in HRQoL despite seeing significant increases in fitness indices.

The findings are promising for new exercisers or lymphoma survivors who may not be able to work under high load when they begin exercising. In practice, this can be very useful as oncology care providers can prescribe lower levels of activity for those survivors who may be unable to perform higher loads of exercise, and HRQoL benefits can still occur. This may increase exercise behaviour as it is more obtainable than the public health guidelines, and may be daunting for people who are sedentary, particularly after having had cancer treatment which makes even daily tasks exigent. The findings seem to corroborate research by Bellizzi and colleagues (2009); HRQoL improved in lymphoma survivors even when they were exercising below the recommended guidelines. This is not to suggest that higher load should be avoided; the current trial did not examine different exercise loads, but Belizzi and colleagues (2009) had reported a dose response relationship between exercise load and HRQoL. Therefore, although HRQoL and psychological improvements were seen with moderate exercise three times per week, it would be useful to examine how increasing the load (intensity, duration, or sessions per week) may further influence findings.

The focus group added insight into what the participants perceived was the most significant benefits from taking part in exercise; in the current trial the psychological (described by participants as mental, emotional, and psychological) benefits were abundant. The representative sample of intervention participants suggested that the CARP greatly impacted their lives, both emotionally and socially.

Supporting the current findings, exercise has been found to reduce emotional distress amongst breast cancer patients taking part in strength and aerobic exercise (Kolden *et al.*, 2002),

patients of all tumour types taking part in aerobic exercise during treatment (Dimeo *et al.*, 1999), and colon and breast cancer survivors participating in aerobic exercise (Burnham and Wilcox, 2002). Thus, the current trial adds to previous literature in that statistically significant improvements in EWB (P=0.029) came from a mixed component exercise intervention amongst a haematological tumour group which has not been previously been reported. Functional well-being (FWB) statistically (p=0.025) and clinically significantly improved with the current exercise regimen. Functional well-being has improved in various types of exercise interventions for cancer patients and survivors (Dimeo *et al.*, 1998; Schneider *et al.*, 2003). The moderate intensity of the current trial did not bring about statistically significant changes in cardiovascular fitness and muscle function, but improvements in FWB suggest that the exercise was enough to make activities of daily functioning easier to perform.

To explain and incorporate the present findings it is possible that by feeling they were doing something positive for their health, the lymphoma survivors began to experience increased self-efficacy (McAuley & Blissmer, 2000) which was found to be the strongest predictor of intention to exercise in the current study. Thus, increasing self-efficacy would likely increase exercise behaviour (Courneya *et al.*, 2003) therefore supporting the high attendance to the intervention (90.8%), and self-efficacy may encourage participants to increase the effort they put into their exercise sessions. Feeling better about themselves and their abilities (supported by the focus group findings as participants said they were surprised with how much they could do in their exercise sessions), participants may have felt more capable and more positive about the exercise session. Concomitantly, fear of relapse, reported in 80% of HL survivors (Ford *et al.*, 2008), may be reduced with increased exercise behaviour; a recent study reported cancer survivors believed that by exercising they were keeping the cancer away (Midtgaard *et al.*, 2011). A normal response to exercise is increased cardiovascular and muscular endurance which was seen in the current trial (although only abdominal endurance was statistically significant); improved cardiovascular and muscular endurance should make daily activities easier to perform, increasing their capability to do functional daily activities (thus increasing FWB) (Penedo & Dahn, 2005). As a result of increased functional ability, reduced fear, and self-efficacy, the participants may feel less anxious about their disease allowing the maintenance of independence and improved coping (Pinto *et al.*, 1999), resulting in demonstrable improvements in their perceived EWB. In turn they are more able to take part in daily activities with family and friends (SF), thus bringing about improved satisfaction with health (HRQoL). As this is speculatory, and this aspect is lacking in qualitative research, further examination is warranted.

The clinically relevant improvements in QoL as a result of exercise are consistent with previous literature, although dissimilar to the present findings, most findings are also statistically significant (Courneya *et al.*, 2009; Ferrer *et al.*, 2011) and many of the studies reporting these improvements are not controlled (Ferrer *et al.*, 2011; Knobf *et al.*, 2007). The increased QoL seen

in the control group opposes the majority of research that has examined QoL after lymphoma; previous literature suggests that QoL significantly decreases post-treatment (Stein *et al.,* 2008; Vallance *et al.,* 2005) and this is widely documented to last for months or even year's post-treatment (Bellizzi *et al.,* 2009; Fernsler and Fanuele, 1998; Jerkeman *et al.* 2001; Sitzia *et al.* 1997; Bellizzi *et al.* 2007; Demierre *et al.,* 2006; Mols *et al.,* 2007). In light of this, it is encouraging that both groups showed improvements in QoL. It is possible that by being involved in an exercise study, even as a control, the participants were motivated to exercise. Most of the recent research examining exercise amongst lymphoma survivors that report levels of activity and associated QoL have been cross-sectional (excluding Courneya's RCT), so it is likely that they did not impact behaviour. Subjective reporting of physical activity finds that both groups were reasonably active, therefore, the physical activity they were performing may have brought about improvements in QoL in both groups.

One reason that the current participants did not follow the normal pattern may be due to the timing of the intervention. The current study began shortly after the end of treatment (mean 36.1 days after last chemotherapy/ radiation treatment), whereas the majority of survivorship studies examine a greater range in the time that has passed since the end of treatment (Wolin & Colditz, 2011); for example, Oldervolls study included lymphoma survivors who were 0-10 years from the end of treatment (Oldervoll *et al.,* 2003). It is possible that, being so close to the end of treatment, participants were still experiencing the initial euphoria associated with having completed treatment (Little & Sayers, 2004), and the appreciation for life that comes with knowing you won't be needing further treatment, at least not in the near future. Although the literature shows that after treatment, lymphoma survivors and cancer survivors in general experience reduced QoL and psychosocial well-being, there is a short window where the participants feel relief and gratitude that treatment is complete (Weiss & Weiss, 2010). Shortly after treatment ends, participants may be beginning to feel better in themselves as the short term negative effects of chemotherapy begin to improve, as is evident in the improvement in LymS scores and cancer symptoms of both groups in the current study., This may provide temporary improvements in QoL, although this is short lived (Little & Sayers, 2004). As previously mentioned, 42% of NHL survivors at 5 years post treatment reported low or worsening QoL scores compared to 3-5 years earlier (Smith *et al.,* 2013). It is possible that these participants had not yet begun to see a decline in QoL so soon after treatment had ended.

As QoL examines a variety of domains in life, improvements could come from any external aspect of life. Role function, for example may be impacted outside of just exercise alone. Although this is often by chance in a RCT, it can be noted that amongst the control group, twice the amount of participants were working full-time when the study began, whereas the intervention group had four times the number of unemployed people than in the control group. It would be beneficial to consider employment status prior to randomisation. It is possible that, by returning to

work, the participants had been able to 'leave behind' the role of cancer patient and became immersed in their 'pre-morbid' life easier than those who were not working, therefore increasing RF scores (the control group showed clinically relevant increases in RF, whereas the intervention group did not). A study by Mols and colleagues (2007) found that amongst NHL survivors, those who returned to work reported better mental well-being scores than those who were not working (Mols *et al.,* 2007). Similarly, significant increases in PF (p=0.049) seen only in the control group, may have been due to external factors. By not taking part in the exercise intervention, the controls had more time to take part in other activities, possibly returning to pre-morbid lifestyle activities (which can be explained with the improvement seen in RF), such as work, hobbies, exercise routine, and playing with children, grandchildren, or friends. These activities may increase PF and impact other subscales of QoL outside of outcomes related to only HRQoL, as the focus was not on health *per se*.

Finally, it is relevant to comment upon the location of the current trial in relation to previous lymphoma studies. Availability of sidewalks and infrastructure to support daily activity can impact physical activity of the community (Sallis *et al.,* 2009). The current study took place in London, England where it is commonplace to commute by walking or taking the train/ tube. The weather is somewhat mild and is conducive to walking outside; walking can be viewed as part of the culture. The closest comparison to the current study is Couneya's trial that took place in Edmonton, Canada. For a majority of the year the snow and ice in conjunction with the terribly low temperature (which can range from -10 to -40°C during the colder winter months) prevent patrons from safely walking outside for long periods of time and thus transportation is often by automobile. It is possible that the control group in the current study performed more general activity (i.e. walking) than the group in Canada due to weather restraints. Tucker and Gilliland (2007), in a systematic review, found weather and season impact level of physical activity performed and suggest that these effects need to be considered in research. It is possible that the reason for increases in QoL in the control group in the current trial is due to increased daily activity, which may not have been performed by the control group in Courneya's trial. This warrants further investigation (Tucker & Gilland, 2007).

Although the increase in QoL exhibited by the control group was inconsistent with previous research, it is plausible that the timing of the intervention, external factors impacting QoL scores, or even the location of the study may have impacted the results. It is also possible that by taking part in an exercise study (that is supported by their oncologist) motivated the lymphoma survivors in the control group to begin exercising. Further research is needed to explore such suggestions.

7.2.2 SOCIAL DIMENSIONS

Exercise is associated with improved social functioning (McAuley *et al.*, 1997) and social support (Alfano *et al.*, 2009). The current study corroborates previous literature that has shown exercise improves SF amongst cancer survivors (Mishra *et al.*, 2012; Stevinson *et al.*, 2009; Courneya *et al.*, 2003), although a majority of this research has been conducted in breast cancer, and many are group-based interventions, therefore likely impacted by group cohesion (Culos-Reed *et al.*, 2005). Interestingly, the current intervention was conducted on an individual basis, therefore the participants worked one-to-one with the trainer. In the present study, improvements in SF were not only seen in the RCT, but the TPB showed that social support and self-efficacy (r^2=0.684) were the main determinants that influenced the lymphoma survivors to exercise, and at the end of the exercise session, social support (r^2=0.641) was the only significant predictor of exercise intention amongst the exercise group. Finally, the representative group involved in the focus group also reported improvements in social dimensions. The participants said that the intervention provided them with increased social support from the group and instructor, and improved social functioning with their family. The present findings suggest that the format of the current RCT, which was one-to one training with the instructor, can bring about increased social function and support. A factor that may possibly have influenced these results was the (brief) interaction between the participants, as they passed one another in the corridor between sessions, and occasionally shared the exercise space as one person completed their programme before the next began.

The participants in the current study have just recently (a mean of 35.8 ± 38.5 days ago) completed active treatment. During treatment, on-going interaction with medical professionals may provide psychological support (Lobb *et al.*, 2009), but when treatment ends, contact with their oncologist and medical team is reduced, which has been found to reduce social support and may impact social function (Lethborg *et al*, 2000). As mentioned in the focus group, attending a programme at the hospital may help participants maintain contact with, or at least feel as though they are close to their oncology team, even if they do not actually see them. The instructor was described as a mediary between the participants and the medical team; seeing the instructor every week may have increased feelings of support. This is supported by research conducted by Lobb and colleagues (2009) that found haematological cancer survivors report that they would have found it helpful to have a contact in the healthcare field who they could talk to them about their experiences and to assist them with their transition into survivorship. In addition, it is possible that the intervention group participants were more likely to visit with the oncology (Macmillan) nurse being that they were on site, but this was not measured in the current study. Previous literature shows patients who are seen by an oncology nurse exhibit lower distress scores and can increase overall QoL (Swanson & Koch, 2009). It would be worthwhile for future research to quantify the amount of interaction participants in each group had with the oncology team, as this may contribute

to psychosocial well-being and adjustment into survivorship. It is worthwhile examining the impact of the location of the intervention to determine whether these are valid explanations.

7.2.3 THE IMPACT OF A 12-WEEK CARP ON LYMPHOMA SURVIVORS ON MOOD DISTURBANCE, ANXIETY, DEPRESSION, AND FATIGUE

Mood.

Aerobic exercise during treatment has been found to improve mood amongst lymphoma patients on chemotherapy, but no significant change was been seen amongst lymphoma survivors (post-treatment) after taking part in an aerobic exercise intervention (Courneya *et al.*, 2009). The current study found no significant improvements in mood amongst exercising lymphoma survivors as well, despite improvements seen in EWB.

Single bouts of exercise have shown improvements with mood immediately after exercise (Hansen *et al.*, 2001). It is possible that exercise had an acute effect in lymphoma survivors, but may not have brought about chronic changes in mood scores, thus it wasn't seen in our analysis. It is also plausible that additional factors may have contributed to the lack of change in mood. Each of the subscales of mood, as measured with the Profile of Mood States (POMS) questionnaire, will individually affect the overall mood score (Lane & Lovejoy, 2001). Of the POMS subscales, only subscales of anxiety and vigour showed significant change in the present study, no other subscales significantly changed. Previous studies reporting few changes in measures amongst cancer survivors after exercise suggest that lack of significance may be due to reasonably healthy scores before intervention (Adamsen *et al.*, 2003; Grainger and Denehy, 2010). This may apply to the current study, as the participants scores on psychological outcomes were relatively normal at baseline.

Anxiety and Depression.

As observed in previous research, subscales of mood were expected to improve with exercise, particularly anxiety and depression scores (Courneya *et al.*, 2000; MacVicar *et al.*, 1989). Although changes in anxiety scores were insignificant in the current study, the intervention group showed a mean reduction in anxiety and the controls increased anxiety scores. Supporting the direction of change, previous literature reported that mild to moderate resistance training (i.e. 50% 1 repetition maximum), similar to that performed in the current trial, reduced anxiety scores (Focht *et al.*, 1999; Bartholomew and Linder, 1998). Cancer is associated with increased anxiety as seen in the control group of the current trial, and reported in previous research (Thompson *et al.*, 2010; Roper *et al.*, 2009). As such, these findings were not statistically significant, but reduced anxiety scores are relevant because exercise prevented the normal increase in anxiety that was expected

post-treatment. It is possible that with a longer intervention, the trends seen may lead to statistical significant change.

Clinically relevant reductions in depression scores were achieved within both groups thus findings are not likely a response to exercise, but a normal response at the end of treatment. Dissimilar to the present findings, aerobic exercise was found to significantly improve depression scores compared to a control group in exercising lymphoma patients and survivors (Courneya et al., 2009). The control group in the current trial did not follow previous findings; lymphoma survivors tend to experience increased depression after treatment (Massie, 2004). The intervention group started with significantly higher baseline depression scores, and their mean change was almost double the mean change experienced by the control group; thus the exercise group showed more improvement than the control group (although it may be related to the significant difference at baseline). Following this pattern, if the intervention group continued to exercise, it is possible that their depression scores would reach statistical significance. More often than not, research studies have shown that amongst cancer survivors, depressive symptoms decrease with exercise training (Brown *et al.*, 2011; Mutrie *et al.*, 2007; Midtgaard *et al.*, 2005), although some researchers have demonstrated a lack of change in depressive symptoms (although no adverse effects) with exercise (Ohira *et al.*, 2006; Courneya *et al.*, 2007; Dimeo *et al.*, 2008). The severity of depression is known to fluctuate depending on the type of cancer, stage of cancer, treatment choice, as well as stress and coping strategies of the person with cancer (Schneider *et al.*, 2003), therefore it is possible that changes in depression and anxiety were related to factors external to exercise, such as treatment type and stage of cancer.

Fatigue.

Supporting the present findings an inverse relationship exists between physical activity and fatigue amongst people with cancer (Thorsen *et al.*, 2011; Dohnalek, 1997). In the current study, lymphoma survivors who exercised revealed a clinically relevant decrease in fatigue on the POMS scale, whereas both groups showed statistically and clinically relevant decreases in fatigue on the EORTC scale. The EORTC fatigue subscale is made up of three items whereas the POMS measures fatigue with 7 items. The EORTC scale has been found to have a ceiling effect amongst advanced cancer patients (Knobel *et al.*, 2003), so it is not recommended to be used as a single measure (Minton & Stone, 2009). With more items examined using the POMS and a potential ceiling effect with the EORTC, it is likely that the POMS may be the more accurate of the two scales in terms of fatigue scores.

As the intervention took place shortly after the end of treatment, the improvements seen in fatigue scores may be partially due to healing from treatment, but the POMS fatigue scores suggest exercise produced greater reductions in fatigue, compared to usual care. Corroborating with

previous literature, the current findings suggest thta exercise reduces fatigue amongst cancer survivors (Oldervoll *et al.*, 2003; Dimeo *et al.*, 1997a), although previous findings are more prevalent in aerobic exercise studies (Daley *et al.*, 2008; Pinto *et al.*, 2005; Courneya *et al.*, 2003b; Burnham and Wilcox, 2002). Interestingly, recent literature has found that moderate intensity resistance training was useful in reducing fatigue, although subgroup analyses suggest that this is not the case for lymphoma survivors (Brown *et al.*, 2011). The current author believes that of the four studies included in the subgroup analysis, only one study was robust, the other three were of low methodological quality, therefore giving little credence to the subgroup findings. The findings from the current study extend previous research by showing that a mix of moderate intensity resistance with aerobic exercise improves fatigue in lymphoma survivors. As it is not clear whether reduced fatigue in this study was due to aerobic exercise, resistance exercise, or a combination of the two, it may be worth comparing exercise modes in future research.

7.2.4 THE IMPACT OF A 12-WEEK CARP ON LYMPHOMA SURVIVORS ON PHYSICAL OUTCOMES

Objectively measured physical fitness outcomes improved with exercise, in line with current literature. Cardiorespiratory improvements and muscular endurance improved as a result of combined exercise training. The current trial shows that a combination of aerobic and resistance training provided meaningful improvements in physical fitness outcomes, although changes are not statistically significant. We hypothesised that by improving cardiovascular fitness in lymphoma survivors would result in an improved QoL.

Improvements in cardiopulmonary function have been reported in many post-treatment aerobic exercise and cancer studies (Schneider *et al.*, 2007; Sprod et al., 2010; Courneya et al., 2003a; Courneya et al., 2003b), specifically in colorectal and breast cancer. Previous literature on lymphoma cancers supports the current findings. Exercise has reportedly improved cardiorespiratory fitness amongst lymphoma survivors after taking part in a 12 week aerobic exercise programme (Courneya et al., 2009), while aerobic capacity improved amongst chronic fatigued HL survivors who performed 20 weeks of home-based exercise (Oldervoll et al., 2003). It must be noted that both of these studies used an aerobic based intervention, whereas the current studies combined intervention may explain why the results were not statistically significant.

Improvements in these outcomes generally make activities of daily living easier to accomplish (Carter *et al.*, 2003), which is consistent with significant improvements in FWB also reported in the current study. Thus, supporting previous research, exercise training not only counteracts the negative late effects that cancer treatment and the cancer itself have on aerobic capacity (Dimeo, 2002), but can also improve physical aerobic capacity and function (Kolden, *et*

al., 2002; Courneya and Friedenreich, 2001; Mock *et al.*, 2001; Schwartz, 2000; Dimeo *et al.*, 1999; Dimeo *et al.*, 1998) even after high dose chemotherapy which is commonly used for lymphoma (Dimeo *et al.*, 2000). In a meta-analysis by McNeeley and colleagues (2006), pooled results of 3 studies (Courneya *et al.*, 2003; Drouin, 2002) examining peak oxygen consumption (from symptom-limited graded exercise testing) showed improvements in fitness amongst exercising cancer survivors equaled close to one MET (3.39 mL/kg per minute) (McNeeley, 2006). Every 1 MET increment in exercise capacity conferred a 12% improvement in survival in men (Myers *et al.*, 2002); a similar result is expected amongst women (McNeeley *et al.*, 2006). In the current study, the intervention group increased their energy expenditure by 1.0 MET over the duration of the exercise programme thereby potentially improving survival.

Epidemiological data demonstrates that elevated heart rate is an independent risk factor for cardiovascular mortality and morbidity (Mensink and Hoffmeister, 1997; Gillum *et al.*, 1991; Kannel *et al.*, 1987). Cancer survivors have a higher risk of dying from secondary diseases, such as cardiovascular disease (Giovannucci, 2012). In the current study, the intervention group exhibited a significant reduction in resting heart rate ($p<0.05$). In accordance with the current findings, studies examining the impact of exercise for cancer survivors report a significant reduction of resting heart rate (Schneider *et al.*, 2007) suggesting exercise is useful in improving cardiovascular function and reducing risk of cardiovascular disease.

Cardiotoxicity is prevalent amongst lymphoma survivors who were treated with doxorubicin (Limat *et al.*, 2003; Hequet *et al.*, 2004; Haddy *et al.*, 2003; Brusamolino *et al.*, 2006), and cardiovascular concerns are almost always present in disease-free HL survivors treated with chest radiotherapy (Hodgson *et al*, 2007). The control group in the current study exhibited decreases in aerobic capacity at post-testing which is consistent with previous literature. The exercise group revealed improvements in aerobic capacity but not statistically significantly, similar to findings from Wolin and colleagues (2010) who reported weak, but promising evidence of improved cardiorespiratory fitness in haematological cancer patients after taking part in an exercise programme (Wolin *et al.*, 2010). Volume of oxygen (VO2) peak increased amongst lymphoma survivors after taking part in a 12-week aerobic exercise programme (Courneya *et al.*, 2009), while aerobic capacity improved amongst chronic fatigued HL survivors who performed 20 weeks of home-based exercise (Oldervoll *et al.*, 2003). The current findings suggest that, compared to previous research, the combination of aerobic and resistance training did not bring about the same significant increase in aerobic capacity as seen in previous lymphoma based studies, but changes seen in the present study were in the upward direction thus it is likely that with a longer duration or increased intensity, significant improvements may come.

Since CV fitness and PF significantly increased in a previous lymphoma RCT with anaerobic intervention (Courneya *et al.*, 2009), aerobic exercise may be better for improving CV

and PF, thus in future research it may be useful to consider longer aerobic intervals in a mixed programme, or performing all the aerobic work first, followed by resistance training . It is possible in the current trial that the resistance stations were too long in duration and HR did not stay elevated during these intervals. It is also possible that other factors in the intervention design impacted the findings, beyond just amount of aerobic activity. In the trial by Courneya and colleagues, behaviour techniques were used to improve adherence to the programme and the sessions were supervised. As two of the three sessions per week in the current study were not supervised, it is possible that this, along with lack of behavioural techniques being administered, may have impacted the results. As well, the assessment of aerobic capacity used in Courneya's study (ECG maximal treadmill testing) was superior to the current trial and may have provided greater detail in terms of changes that occurred.

Pulmonary Function.

What was not expected was the decrease in pulmonary function exhibited by both groups (FVC predicted % significantly reduced in the INT group). Pulmonary function can be affected by cancer treatment; toxicity can result in abnormal development of the pulmonary tissue and pulmonary fibrosis (De Vita *et al.,* 2005). Toxicity may cause decreased stroke volume (and therefore cardiac output) resulting in decreased oxygen delivery, leading to reduced functional capacity. Disappointingly, the current study found a significant interaction amongst the variables of FVC% predicted and FEV1% predicted between groups over time; showing a decline in pulmonary function over time. Mean values show that the intervention group experienced a greater decline than the control group. Decreased pulmonary function is common to lymphoma patients within the first 3-9 months after radiation treatment (Theuws *et al.,* 1999). Specific to HL, FVC has been seen to decrease over the first 15 months post- treatment and not recover until 36+ months (Horning *et al.,* 1994). It was expected that exercise would reduce the negative effects of treatment on FVC, but unfortunately the current study demonstrated a larger drop in FVC amongst the exercisers than that of the controls suggesting exercise negatively impacted pulmonary function. This result cannot be easily explained as it is unusual to see reduced lung function with exercise. It is possible that the exercise intervention did not offer enough cardiovascular exercise to impact pulmonary function, as it was made up of both aerobic and resistance training. Intensity of exercise in the present study was moderate; it may be beneficial to examine the impact of different exercise intensities as well as compare the current interval exercise format to another type of exercise. It may be useful to examine lung function again at 36 months post-cancer treatment to see if recovery is enhanced amongst lymphoma survivors who exercise.

Another consideration is that 25% of intervention group were smokers versus 5% of control group. This is likely to have impacted respiratory function. It is also possible that the exercise programme was not challenging enough to prevent reductions in pulmonary function. A

previous study with breast cancer survivors reported improved FVC% predicted ($p<0.05$) and FEV1 % predicted ($p<0.05$) with a 'whole body' workout, but the intervention was supervised 2-3 days per week for six months (Schneider *et al.*, 2007). It is possible that by supervising sessions and increasing the duration of the intervention, results may have differed.

A significant association has been reported between pulmonary dysfunction and exercise tolerance in HL survivors (Bonadonna et al, 2004). Reduced pulmonary function heightens the relative workload of activities; therefore, participants may find it more difficult to perform the CARP. This is supported by the lack of statistically significant results seen in the current study on physical function and objectively measured physical indices. It is positive to see the significant improvements in FWB though, because it suggests that exercise is beginning to make some difference in the day-to-day function of the exercise group; with a longer intervention, it is possible PF and objective physical fitness scores may improve.

Muscular Strength and Endurance.

Significant improvements in muscle strength and endurance are common amongst cancer patients taking part in exercise interventions (Wolin *et al.*, 2010; Galvao *et al.*, 2006; Segal *et al.*, 2009, Schneider *et al.*, 2007), and is associated with increases in physical performance (Galvao *et al.*, 2006) and quality of life (Segal *et al.*, 2003). A meta-analysis by Speck and colleagues (2010) reported that physical activity interventions post-treatment improved muscle strength (upper and lower body), and a trend was seen toward improvements in aerobic fitness (Speck et al., 2010), but results are not presented by type of exercise so it is not clear what kind of activity brings about improvements. Another recent meta-analysis that examined only studies of multi-component training or resistance training with cancer survivors have shown improvements in cardiovascular fitness (peak oxygen uptake improvements ranging from 6-39%), and muscle strength (one-repetition maximum increases from 11-110%) with no adverse effects (De Backer et al., 2009), but no significant changes in muscular endurance scores were noted. Similar to the current study, the average duration of the studies in De Backer's meta-analysis were 12 weeks long, but unlike the current thesis, most of the studies examined in the meta-analysis were conducted with breast and prostate cancer survivors.

The clinically relevant improvements in muscle function (particularly in curl-ups) seen in the current trial are similar to findings in other tumour types, predominantly prostate cancer (Galvao et al., 2010; Segal et al., 2003). These findings are meaningful as it has recently been found that muscle is effective in facilitating positive clinical outcomes in cancer survivors (Mourtzakis and Bedbrook, 2009).

Immune Markers.

The current trial was exploring whether immune function could improve with moderate intensity multi-component exercise in a cancer type that patients are often immune-compromised, but preliminary evidence suggests that in this cohort, the exercise intervention did not improve immune function, although no adverse effects occurred either. All subjects, control and intervention, gave absorbance lower than the absorbance produced by the lowest concentration of standard for IL-6 measurements (when the standard concentration was 0ng/ml, the abs was 0.168 (average). Only one subject gave values higher than abs 0.168, therefore the absorbance from the remaining samples were too low.

The current findings differ from the few studies reporting change in immune function amongst cancer survivors. One quality study that had explored changes in CRP reported decreased CRP in postmenopausal breast cancer survivors who took part in exercise training (Fairey et al., 2005). The current study examined exercise in an immune based cancer. Lack of change may be due to small sample size or possibly the exercise prescription was not conducive to changes in immune markers as some studies in the general population have shown increased myokine production during long duration acitivies like marathons (Kasapis & Thompson, 2005); it is also possible that exercise does not improve immune function in lymphoma survivors. Lack of changes in CRP is similar to recent studies amongst the general population (published after the start of the current study) (Campbell *et al.* 2008; Church *et al.* 2010; Nassis *et al.*, 2005; Marcell *et al.*, 2005; Stewart *et al.* 2010). Similar to the current trial, a recent meta-analysis reported no change in immune function amongst cancer survivors who took part in mixed aerobic and resistance training (De Backer et al., 2009). Based on recent literature, future trials should consider longer duration interventions although the population studied may need to be further from the end of treatment.

A study by Thorsen (2005) found both control and intervention groups were performing a similar number of minutes of exercise per week (although intensity was different); it was suggested this may explain their lack of significance. In the current study amount of physical activity being performed per week (measured with the IPAQ) had improved in both groups (although more so in the intervention group). Participants in the control group were given a handout on the benefits of exercise. In addition, it is no secret that exercise may positively affect cancer survivors: healthcare professionals readily recommend exercise and the benefits of exercise (specific to cancer) have often been mentioned in the media. Taking part in an exercise study, albeit as a control, would bring awareness to the use of exercise following treatment. Although this makes interpretation of results a bit more difficult, it is rewarding to see that cancer survivors are taking part in exercise behaviour. An alternative exercise design that may avoid this problem would be a cross-over trial, or a study to compare two different forms of exercise.

7.2.5 CHANGES SEEN IN BOTH THE INTERVENTION AND CONTROL GROUP

In the current study, PWB and vigour significantly increased while fatigue (significantly on the EORTC scale) decreased in both groups from baseline to post-testing in both groups. These changes were expected as a response to exercise, but it was also thought that some degree of improvement may be prevalent in both groups given that the intervention occurred so soon after treatment had ended. Short-term treatmen t induced effects would be diminishing as the body heals. As the survivor begins to feel better and the cells begin to regenerate, vigour and fatigue should improve (Sun *et al.,* 2005). Improvements in PWB were expected more so amongst the exercising group, although the subjective measure of physical activity showed that both groups were doing some level of activity during the intervention period. In the present study, physical functioning, one of the greatest areas of concern for NHL survivors (Oerlemans *et al.,* 2011), significantly improved in the control group only (p=0.049), although the intervention group demonstrated improvement, but it was insignificant. Despite the findings from previous literature that suggests PF decreases post-treatment (Segal *et al.,* 2001), it appears from the current study that PWB and PF improvements seen in both groups are the normal response in lymphoma survivors in the time frame, shortly after treatment ends. It is possible that there is a short improvement as patients finish active treatment. It is also possible that the intervention was not at a sufficient intensity to induce changes in patient rated PF, as a recent systematic review found greater improvements with moderate-vigorous intensity compared to mild -moderate intensities (Mishra *et al.,* 2012). As the current trial showed no known exercise induced adverse events, preliminary findings suggest that moderate intensity exercise may be safe for this cohort. It would be useful for future research to examine the impact of different exercise intensities on lymphoma survivors and explore whether PF may improve following different level of exercise.

A finding to consider when interpreting the results from the current trial was the significant increase in the subjectively reported amount of physical activity performed in both groups (intervention (p=0.029), control (p=0.019). The International Physical Activity Questionnaire (IPAQ) assesses frequency, duration, and intensity of activity over the past week. Interestingly, the objective measure of energy expenditure showed that only the intervention group experienced an increase in metabolic equivalent (MET), while the control group values decreased at post-testing, suggesting one of the measures was inaccurate. Johnson-Kozlow and colleagues (2006) compared the IPAQ to other methods of accessing physical activity and reported that compared to the Physical Activity Recall Questionnaire and to Actigraph accelerometers, the IPAQ over-estimated activity levels (the accelerometer indicated 17% of breast cancer survivors met public health guidelines; whereas the PAR showed 28% and the IPAQ indicated 47% met the same minimum requirement). Thus, in the current trial, it is assumed that the objective results are closer to accurate than the subjective, but subjective will still be considered in terms of the participants perception of exercise performed.

7.2.6 ADHERENCE TO THE EXERCISE INTERVENTION

In the early stages of beginning an exercise programme, participants take on different identities or self-schemas (Burke and Stets, 2009) known as exercise schemas. Exercise schemas are often identified under the labels of exercise schematics (identify themselves as exercisers), non-exercise schematics (identify themselves as a non-exerciser) and aschematics (not concerned with exercise either way, do not identify with exercise) (Lox *et al.*, 2010). Exercise schemata is associated with higher levels of exercise self-efficacy (Yin & Boyd, 2000); beginner exercisers often identify early on with the exercise schemata therefore it is possible that the participants in the exercise intervention began to take on an exercise schemata which brought about feelings of efficacy and thus increased EWB. Enhanced feelings of self-efficacy was a primary motivator in this group (as identified using the TPB), which may explain high adherence to the intervention. An increase in negative life change amongst NHL survivors was significantly associated with decreased mental functioning (Bellizzi *et al.*, 2007); therefore, it is conceivable that an increase in life change, such as beginning an exercise programme and taking on an exercise schema, is associated with increased EWB. The current study did not measure previous activity or perceived exercise schema of the participants, but it may be useful to consider this in future studies as previous experience may affect psychological and physical outcomes, as well as adherence to the intervention.

7.2.7 LONG TERM ADHERENCE; 12 MONTH FOLLOW-UP

Having explored QoL scores and psychological outcomes one year following the completion of the intervention, it appears that the intervention experienced greater psychological distress compared with post-intervention scores and the control group. From baseline, HRQoL improved, but many outcomes showed no significant improvement, whereas the control group did see improvements. Upon further examination, it appears that the improvements in HRQoL were impacted by improvements in lymphoma related symptoms, as those were diminishing as time passed. The exercise group did not maintain the same level of activity at follow-up, providing explanation for their regression in QoL scores. Although this should be treated with caution due to the diminished sample size, it does provide support for maintaining exercise participation following the completion of exercise studies.

Another possible explanation for the reductions in health outcomes seen in the intervention group may be caused by a delay in the participants coping with their cancer and the end of treatment. The end of the exercise pro gramme may have been stressful, as it was the removal of another support system: the exercise and the social support they received from taking part in the programme were taken away. If this is the case, providing on-going support, for example, a drop-in

fitness programme that takes place at the hospital may be useful by providing support as participant's transition to survivorship and back into 'normality'. It may also be beneficial to create a buddy system with family, friends, supporters, or even other participants who took part in the intervention in hopes to increase exercise maintenance at the end of the intervention programme; committing to exercise with someone else improves exercise adherence (Lox *et al.*, 2010).

It is possible that the exercise group experienced reductions in EWB and increased anxiety at follow-up because they were disappointed about quitting exercise, whereas those who were not part of the intervention may not have experienced any inadvertent pressure to exercise so exercise behaviour did not influence their mood. When filling out the questionnaire, the intervention participants who were not exercising were reminded that they had stopped, and this may have affected the way they were feeling whilst completing the questionnaire. This would relate to the idea that the intervention group, during exercise had taken on an exercise schemata (as discussed above) If they had begun to see themselves as exercisers during the intervention but then stopped exercising, they may feel guilt and disappointment more so than if they had not begun exercise in the first instance, as upon reflection (such as during the questionnaire) they realise they may associate more so with non-exercisers. As this was not measured in the current study, this is only a suggestion for what may have occurred.

7.3 STRENGTHS AND LIMITATIONS OF THE PRESENT STUDY

7.3.1 STRENGTHS

The strengths of the current trial include being the first multi-component exercise RCT to focus on lymphoma survivors, the first to examine immune response to exercise in this population, a thorough assessment of important outcomes using validated measures, excellent intervention adherence (90.8%), homogeneity of facility, trainers, testing locations, and meaningful effects on a number of important outcomes. The use of a randomized control group provided a clearer view of the differences between comparable groups which allowed for identification of exercise-induced change.

7.3.2 LIMITATIONS

Study Design

The author examined the effects in the subgroup of participants who adhered to the intervention rather than estimate the effects of allocating the intervention in practice (Streiner & Geddes, 2001). This was because of the large number of participants who withdrew at follow-up. Although this reduced external validity, introduced bias associated with non-random loss of

participants, and decreased robustness, it focused examination on the effects of exercise within the cohort who completed the testing as compared to controls; thus it became more of an efficacy trial than an effectiveness study. The method for dealing with missing data was a limitation that reduced robustness. Data were imputed following the guidelines of the questionnaires, but when normality could not be reached, two variables were removed as they would not meet the requirements of linear mixed models analysis. In future studies, a non-parametric analysis should be used.

A linear mixed methods statistical analysis was used to cope with the lost data at follow-up. By not doing an intention to treat (ITT) analysis, any differences that arose after randomisation (e.g. dropout) could have been due to consequences of the randomized assignment, therefore we have introduced bias due to compliance (increasing type 1 error). The explanatory analysis that was performed (by removing drop-outs from the analysis) really explored the efficacy of the intervention and therefore determined whether the intervention produced the expected results under ideal circumstances rather than under 'real world' settings. As the objective of the current trial was to explore effectiveness of the exercise intervention, an ITT analysis would have been more robust and better suited to the aims. Another reason to use an ITT analysis was the number of participants lost to follow-up; thus the follow-up analysis was underpowered. In future trials with similar objectives an ITT would be used instead of per protocol analysis.

Blinding

The author played a number of roles in the current trial because it was a student-led trial and there was limited funding. Thus, ascertainment bias is possible as the participants and the tester were aware of group allocation. The overlap in roles was discussed by the committee, and it was decided that it was worthwhile running the trial as designed, noting the biases that comes from lack of blinding. In future trials it would be worthwhile to have healthcare providers, data collectors and outcome adjudicators unaware of group allocation to reduce differential bias and increase the integrity and internal validity of the trial.

Hawthorne Effect

It is possible that some of the changes are due to being involved in the study. For example, taking part in an exercise study, regardless of which group to which you are allocated, may increase your interest in exercise and thus motivate you to consider exercising. This may have been the case in the current study. The control group became aware that exercise was being examined post-treatment, suggesting that it may be beneficial, and as well they were given a handout regarding the benefits of exercise post-treatment (Appendix M). These two things combined may have provided

enough incentive to get them to start exercising. It is also possible that the intervention group expects improvements because exercise is known to provide positive results.

In the current study, exercise cross-over during the intervention likely attenuated group differences. It is apparent from the subjective reporting of physical activity that participants in the control group performed exercise during the duration of the intervention. As previous research suggests only a quarter of lymphoma survivors are exercising; the current control group was more active than expected for usual care.

Bias

Information bias may exist as many of the outcomes were patient-rated (despite having used valid and reliable questionnaires), and the objectively measured outcomes were dependent upon human-error. The follow-up questionnaire, although valid and reliable, was completed at home and returned by mail; therefore the conditions in which the participant completed the questionnaire were not controlled for. However, this aspect of the thesis was underpowered and subsequent data should be treated with some caution. High accession may have induced nonresponse bias in our findings. For example, nonresponders at follow-up may have worse health scores and, perhaps, might not be exercising at the same levels of responders. Attrition bias was a significant concern in the current study, particularly at follow-up. The lost participants were not included in the analysis therefore increasing attrition bias and reducing external validity.

Performance bias may exist if participants from either group had strong feelings about exercise either positive feelings or negative feelings. It would have been useful to measure preference before randomisation and possibly consider this in the analysis. It is possible that resentful demoralisation occurred as participants may have been randomized to a group they did not want and may report incorrectly or may allow their feelings about their allocation impact their results. To possibly reduce bias, future trials could be designed so that both groups receive the CARP, but at different times, e.g. a crossover design.

Comparison

Beyond the trial conducted by Courneya and colleagues (2009), direct comparison with other published research was challenging. The exploration of the inflammatory response was novel; therefore, the appropriate exercise dose needed for change to occur was unknown.

7.4 RETURNING TO THE HYPOTHESES

The original intention of the current study was to measure effectiveness of a multi-component CARP, with the potential of finding a protocol that could be generalised in the lymphoma population. The study has not entirely resolved the extent to which exercise effects lymphoma survivors. As the results in the current trial were not analyzed using ITT, external validity is reduced, thus generalisability of the findings may be slightly compromised. The study offers promising preliminary evident that exercise improves HRQoL, SF, EWB, and FWB, and improves cardiovascular fitness and muscular endurance in lymphoma survivors, but due to methodolical weaknesses decreasing robustness of the study as well as limited additional research in this area, the findings require further exploration.

Hypothesis 1. The current study showed significant improvements in HRQoL, a domain of QoL, but positive changes in QoL, the primary aim, were not statistically significant (although were found to be clinically relevant) and were exhibited in both the intervention and control group, suggesting that the improvement was a normal response in this cohort, and not a result of exercise. The null hypothesis is accepted because although clinically relevant improvements were evident in the intervention group, when compared to the control group they were not unique, as the control group exhibited the same improvements (even slightly better in the control group).

Hypothesis 2. Cardiovascular (CV) fitness and muscular strength and endurance (MSE) outcomes showed trends towards improvement and a statistically significant increase in abdominal muscle endurance (p=0.018) in the intervention group. Improvements in aerobic capacity and all muscle function scores compared to their baseline measurements were seen in the intervention group, with the exception of pulmonary function, which significantly decreased (FVC% predicted, p=0.025), and a significant interaction between FVC% predicted and FEV1% predicted (p=0.017) occurred in the intervention group). Thus, the null hypothesis for the second aim in the current study is accepted.

Hypothesis 3. In the current study, no significant changes were produced in either of the serum inflammatory markers examined (IL-6 and CRP), thus the null hypothesis for the third aim of the study is accepted.

Hypothesis 4. The TPB is an effectual model to predict intention to exercise and exercise behaviour (at baseline), therefore the null hypothesis is rejected. With both groups collapsed at baseline, the model predicts 68.6% (r^2=0.723; p=0.000) of the variation in intention, and 36.2% (r^2=0.458; p=0.003) of the variation in actual behaviour. The model predicts 77.0% (r^2=0.831; p=0.000) of the variation in intention at post-testing amongst the control group, and 61.5% (r^2=0.701; p=0.001) of the variation in intention in the intervention group, but prediction of actual behaviour at post-testing was insignificant in both groups.

Chapter 8.
CONCLUSION

8.0 INTRODUCTION

The findings from this exploratory study extend the exercise and cancer literature by examining an understudied tumour type that is unique because it is immune-based, and a mode of exercise that has only recently begun being studied in the literature, and not previously examined in lymphoma survivors. Based on the findings from the current study and relevant literature, this chapter will suggest some implications for practice and future research.

8.1 IMPLICATIONS FOR PRACTICE

The present thesis identifies CARP to be feasible and safe for HL and NHL survivors for participants in the current trial. The level of adherence and lack of accession or injury in the intervention group provides supporting evidence for this. The CARP was effective at improving HRQoL and psychosocial outcomes, most physical outcomes showed improvement as well. The current study showed that HRQoL improvements were evident before physical changes, thus lymphoma survivors do not have to experience physical improvements to experience HRQoL and psychosocial changes. Lymphoma survivors were compliant during the intervention (seen by high adherence rates) and reportedly believed the intervention positively influenced their lives outside of the exercise programme.

Shortly after treatment, lymphoma survivors are most influenced by self-efficacy and social support when it comes to predicting intention to exercise. Appropriate behavioural techniques can be applied to future interventions for this population to assist with behaviour change (Michie *et al.*, 2008), particularly self-efficacy and social support for adoption shortly after the end of treatment, and social support for adherence when participants are already exercising.

Previous research in this field has just begun to be adopted in the exercise industry; a 'knowledge-to-action' process model has recently been examined in exercise and cancer research with the intention of finding ways to bring theory to practice (Wurz *et al.*, 2013). Programmes have begun to emerge that are based on this process of knowledge translation. For example, a research team at the University of Calgary, Canada have implemented research informed exercise programmes in local cancer centres. The practical intention for the current thesis is to provide preliminary evidence that can, with support from future research, lead to the development of an exercise programme for lymphoma survivors that medical professionals could use as an alternative or additional therapy to assist with side effects post treatment.

8.2 IMPLICATIONS FOR FUTURE RESEARCH

What still remains unclear is whether exercise of any type impacts the immune response of lymphoma survivors. The current trial showed that moderate intensity multi-component exercise did not affect CRP and IL-6; results from a recent study suggest that higher intensity and higher minutes of activity per week (above 120 minutes of exercise per week) can improve CRP levels in cancer survivors, although this was conducted on breast cancer survivors (Jones *et al.*, 2012) therefore changing the intensity and duration of the current intervention may produce different results. The current trial included approximately 180 minutes of exercise per week, but only 60 minutes were supervised. Having all three sessions supervised may be beneficial to ensure activity levels are sustained at the appropriate intensity. Another recent study reported that moderate to vigorous exercise, regardless of whether it was resistance training or aerobic exercise, induced larger increases in IL-6 and CRP than when compared to low impact exercise, although this was reported in sedentary, overweight general population (Mendham *et al.*, 2011). It is not clear what exercise dose is best to improve immune function, thus this is an area requiring further investigation. One consideration in terms of intensity was the identification of self-efficacy as one of the determinants of exercise behaviour in lymphoma survivors shortly after treatment ends. If any intervention is too challenging, it may deter participants from continuing as they may experience reduced self-efficacy, therefore intensity must remain low enough for participants to feel a sense accomplishment.

Previous exercise experience, stage of change (using the transtheoretical model of change (Prochaska & DiClemente,1983), or exercise schemata (Yin & Boyd, 2000) would be beneficial to know about each participant as the relationship with exercise may impact results. It would be useful to measure any of these confounding variables as it may change the way participants experience the intervention and perceive benefits of the programme.

To extend the current findings, now that this exploratory study has shown that exercise is feasible and safe in this group of lymphoma survivors, it would be worthwhile performing a larger study with a sample size that allows for the examination of HL and NHL as separate groups. The tumours differ in terms of age distribution, which may influence how cancer and side effects impact life, and some treatment choices differ, thus potentially resulting in different side effects.

What remains to be explored in this field is whether exercise design affects the outcomes, or whether all exercise exhibits a similar response in lymphoma survivors. It would be worth comparing combined exercise to other modalities. Aerobic exercise has been examined (Courneya *et al.*, 2009) to date; not other modes of exercise have been examined in lymphoma, therefore it would be useful to see if another mode of exercise may produce additional results. Although both aerobic and combined exercise have now been examined, it may be worthwhile comparing these in

one study, specific to treatment status (all on or off treatment) as there were many factors that differed between the two trials. Controlling for these external factors, it may be useful to further explore the differences in these formats before moving on to other modes of exercise.

Now that it has been established that multi-component exercise is beneficial for lymphoma survivors in this cohort, it would be useful to examine the optimal time point to begin an exercise programme (during or following treatment; how far out of treatment). It would be advantageous to examine the impact of this form of exercise amongst lymphoma patients to add to the findings from Courneya and colleagues who examined the impact of only aerobic exercise in this population.

From the current study, we learned of the importance of social support for lymphoma survivors. It would be advantageous to examine the impact of training partners; it may be beneficial to create partnership within the group participants because the current findings suggest that the group positively affected social support (primarily in terms of vicarious learning). A challenge with survivor partnerships is proximity; as the current study included participants from London and surrounding areas, it may be difficult for some partner groups to get together outside of exercise sessions due to distance between them, which defeats the purpose as after the programme ends it would be difficult for the participants to exercise together. It may be worthwhile using family or friends (supporters) to be training partners, as it may improve adherence, long term. As the instructor also provides social support, weekly drop-in exercise classes or even phone calls or emails with the trainer may help to improve long-term exercise behaviour. It may be useful to have a tapering plan in place with the intention of creating a sense of independence amongst the intervention participants. By slowing reducing supervision and increasing home-based activity instead of doing one supervised and two home-based for the duration of the intervention, the participants may slowly transition into performing exercise at home as exercise related self-efficacy improves.

8.3 LIMITATIONS OF THE CURRENT STUDY

A per-protocol analysis was used in the current study. This reduced external validity of the current findings. An intention to treat (ITT) analysis would have increased generalisability of findings as all participants, even those lost to withdrawal, would have been included in the findings. Because the participants who withdrew before pre-testing were not included in analysis and those who withdrew before follow-up were not included in the follow-up data, the robustness of the study was reduced. A linear mixed models statistical analysis was used to deal with the lost participants, but performing an ITT analysis would have provided results that were more applicable to real life situation.

A noteworthy limitation of the current trial was accession rates between the completion of the CARP intervention and subsequent 12-month follow-up. This limits the level of interpretation that could be made in the follow up measurements. A majority of the lymphoma survivors in the current trial were lost to follow-up. It may be particular to this group, but as there is very little literature to compare to, lymphoma survivors are low adherers after the end of an intervention, therefore future research is needed to find methods to increase adherence at follow-up. It is important therefore to find methods of maintaining adherence at follow-up. An option to mail out questionnaires that may increase accession rates would be the use of a survey that could be conducted online, by telephone, or even email. It would also be worthwhile considering periodic follow-up sessions or even phone call/email reminders to keep participants interested in the study (and to potentially increase exercise adherence), which would help with loss of contact, which was one reason for a number of lost participants in the current study. New technology have recently become a means to increase adherence (Stevens & Bryan, 2012). It may be worthwhile adding a weekly email or text with a short exercise reminder for cancer survivors in hopes to increase exercise behaviour. It may be worthwhile exploring whether use of internet or media would enhance exercise adherence. By providing participants with a DVD or internet -based exercise programme to follow at home, the `at home' exercise sessions will be more controlled and adherence may improve because the participant could continue to use the resource once the intervention is complete. To gain further information of the perceived benefits of the intervention, telephone interviews, or a one-to-one interview at post-testing could have been used instead of the poorly attended focus group session to ensure a better response rate.

8.4 SUMMARY

The current study provides additional support for the growing evidence that moderate exercise provides some benefits for cancer survivors whilst also presenting novel exploration of a cancer type that has not yet been given much attention in this area.

The findings offer a clearer understanding of the use of exercise as a means to reduce long-term side effects of lymphoma treatment, particularly psychosocial effects. Combined aerobic and resistance exercise of moderate intensity was safe for lymphoma survivors in this cohort; with future research to support these findings, exercise may be used as supplementary therapy for survivors to help improve HRQoL and assist with psychosocial adjustment shortly after treatment ends. These preliminary results may lead to further examination of the impact of exercise amongst lymphoma survivors, and eventually may lead to exercise becoming a useful option for medical professionals to suggest to patients as an alternative means to cope with the long term and late effects of lymphoma and its treatment. Ideally, a hospital based exercise programme would be

available to all survivors and eventually in the community as well. Based on literature to date, exercise programmes informed by research are being implemented in Calgary, Canada; with continued research in this area, it is hopeful that this may be offered in the United Kingdom in the future.

Consideration should be given to the significant determinants of exercise when designing exercise for lymphoma survivors. Specifically strategies should be implemented to enhance self-efficacy and social support to increase the likelihood that lymphoma survivors will exercise, and social support specifically to help with adherence.

According to the ACSM round table (Schmitz *et al.*, 2010), QoL, PF and cancer-related fatigue are the reported benefits of exercise amongst several cancer groups; this was not the case for lymphoma survivors in the current trial. Thus, the current findings highlight the necessity of examining the effects of exercise by tumour type. One unique difference was that psychosocial benefits occurred in the absence of statistically significant physical improvements, which supports the findings of Bellizzi and colleagues (2009), by showing that lymphoma survivors experience benefits in HRQoL when performing exercise that is even below the ACSM recommended health guidelines. Future research conducted on specific tumour types is useful for creating exercise programmes that are specific and beneficial for the participants.

As lymphoma is a disease that people live with rather than die as a result of, health care providers require evidence based options to assist with long-term management of disease. In recent years, exercise has emerged as a non-pharmacological therapy providing substantial improvement in health related outcomes, but clinical trials have often examined solid tumour cancer survivors. The current study found that a CARP was useful in increasing HRQoL, EWB, FWB, and improving fitness outcomes in this cohort of lymphoma survivors; with further research to substantiate these findings, combined exercise may be used as a means to increase psychological well-being in lymphoma survivors, thus providing health care providers a non-pharmacological option to assist the long term management of lymphoma.

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APPENDICES

APPENDIX A. PARTICIPANT INFORMATION SHEET: Feasibility Study

Participant Information Sheet
October 3, 2008

Exercise Training Intervention Programme PILOT study

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information and don't hesitate to ask if there is anything that needs clarification.

What is the purpose of the study?

Exercise has been found to increase well-being and overall quality of life in patients and survivors of cancer. The purpose of this study is to compare the physical, psychological and social effects of exercise activity between a healthy general population, and lymphoma survivors. Your voluntary involvement with this project will help us gain valuable information that may help lymphoma survivors improve their health and well-being.

Do I have to take part?

It is up to you to decide whether to take part. We will describe the study through this information sheet. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason.

What will I have to do?

If you decide to take part in this study, you will be asked to complete questionnaires and undertake some basic physical testing.
Being part of the study involves participating in an exercise programme provided by a certified fitness trainer. The exercise programme will be individually tailored to be safe for you and to suit your health and fitness needs. Your trainer will meet with you weekly to ensure the programme is running smoothly and to update your programme when necessary (at a time that suits you). You will be asked to follow your personal exercise programme three times per week for three months. Testing will occur at the beginning of the programme, and at the end of the exercise study (12 weeks).

Your involvement will last 3 months during which time we would like you to complete a daily exercise logbook (provided to you at the beginning of the study) - it should take no more than a minute or two per day.

Adverse events or reasons to cease involvement will be reviewed at each visit; your health and well-being take precedence over study involvement.

What are the possible benefits of taking part?
We cannot promise the study will help you but the information we get from this study will help improve the treatment and recovery of people with lymphoma. We will follow ethical and legal practice and all information about you will be handled in confidence.

What are the possible disadvantages and risks of taking part?

Taking part will involve your time. Other than this, there are no anticipated disadvantages and risks of taking part.

What if there is a problem?

Any complaint you may have during the study or any possible harm you might suffer will be addressed. If you are harmed by taking part in this research study there are no special compensation arrangements. Your certified trainer is registered and insured with FitPro Public and Teacher Liability Cover. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Your right at law to claim compensation for injury where you can prove negligence is not affected. Copies of these guidelines are available on request.

If you have a concern about any aspect of this study, please ask to speak to your consultant Lisa Cole who will do her best to answer your questions.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. You are guaranteed confidentiality throughout the study, as only the investigators will view the data collected. All information which is collected about you during the course of the research will be kept strictly confidential. Only summary results of this study (i.e., no individual results) will be published or made available.

What happens when the research study stops?
Upon completion of this study, you will receive feedback about your personal results, but these remain confidential and will not be available to anyone besides yourself and the student investigator.

What will happen to the results of the research study?

The results of this study may be published in scientific journals or presented to authorities, but you will not be named or identified in any way. The people analysing the information you supply will not be able to identify you from looking at the questionnaires.

Further information and contact details

You are encouraged to ask questions at any time during the study. If you have a problem or have more questions about the study or your rights as a patient please call: - Principal Investigator: Lisa Daroux-Cole at 020-8547-2000 ext 62876, or at l.cole@kingston.ac.uk.

Thank you for considering taking part in this study.

You are free to ask questions and take as much time as you need to decide whether or not you want to take part.

APPENDIX B. PARTICIPANT INFORMATION SHEET: RCT

Participant Information Sheet
Version 3
October 3, 2009

Exercise Training Intervention Programme for Lymphoma Patients

Protocol number: 08/H0803/188

PART 1

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.
(Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study).
Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
The link between physical activity and well-being has been well documented. Exercise interventions have been found to increase well-being and overall quality of life in patients and survivors of a variety of different forms of cancer. The purpose of this study is to determine the physical and psychosocial effects of exercise activity specifically for lymphoma survivors. Your voluntary involvement with this project will help us gain valuable information that may help other lymphoma survivors improve their health and well-being.

Why have I been invited?
Only participants from the St. Georges Lymphoma clinic will be invited to take part in this study. You have been chosen by the study consultant because you meet the required criteria for this specific study.

Do I have to take part?

It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?
If you decide to take part in this study, you will be asked to complete questionnaires and undertake some basic physiological testing. These measures, along with blood tests will be completed at each of your regular clinic visits (bi-monthly) for six months post-treatment. These testing sessions will follow your routine appointments, so no additional test visits will be necessary for testing.

You will be randomly allocated to one of two groups. We put people into groups and give each group a different treatment- one group will be involved in the exercise programme, the other group will not. The results are compared to see if there are any differences. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly).

What will I have to do? Being in the intervention group involves participating in an exercise programme which is individually tailored and will be provided by an exercise instructor. You will

be given a personal exercise programme that we would like you to perform three times per week for three months. One of the sessions will take place at St. George's Hospital or Kingston University under the supervision of your exercise instructor; the other two sessions are to be completed on your own time. After this, you will progress to the next three month phase. During this time you will continue exercising three times per week, but you will only come in once a month for a supervised session. At every supervised session we will observe your progress and adjust your exercise intervention programme appropriately. There are a total of fifteen exercise sessions for you to attend at St. Georges Outpatient Gym (or Kingston University) during the six month intervention; each session taking approximately one hour. Your initial assessment session will take approximately 1.5 hours so that we have time to create your starting programme to meet your specific requirements.

Being in the control group involves attending your regularly scheduled clinic visits during which time you would also be asked to complete the questionnaires and undertake basic physical measures, a stepping test and muscular testing, during the 6-month study. At the beginning of the study, you will be provided with information about the benefits of exercise for cancer patients and survivors. Once the study has been completed, you will be given the opportunity to meet with an exercise instructor, and may be given an exercise programme for you to use on your own time.

Regardless of group allocation, your involvement in the study will last 6 months during which time we would like you to complete a daily exercise logbook (provided to you at the beginning of the study). We will ask you to attend a follow-up testing session twelve months after the intervention has ceased.

No normal treatment will be withheld at any part of the study- only additional assessment and attention will be provided. Adverse events or reasons to cease involvement will be reviewed at each study visit; your health and well-being take precedence over study involvement.

What are the possible benefits of taking part?
We cannot promise the study will help you but the information we get from this study will help improve the treatment and recovery of people with lymphoma. We will follow ethical and legal practice and all information about you will be handled in confidence.

What happens when the research study stops?
Upon completion of this study, you will receive a synopsis of the findings. All information is confidential, so you will not receive personal feedback, but will get a summary of the study results.

What if there is a problem?
Any complaint you may have during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making a decision.
PART 2

What if relevant new information becomes available?
Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide

not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study she may ask you to sign an updated consent form.
If this happens, your research doctor might consider you should withdraw from the study. She will explain the reasons and arrange for your care to continue.
If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?
You can withdraw from treatment at any time, but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

What if there is a problem?
In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs.

Complaints If you have a concern about any aspect of this study, please ask to speak to the researchers who will do their best to answer your questions (0208 547 2000, ask for Lisa Cole). If you are unhappy and have a complaint or concern, you can do this via the researcher team or through the St. Georges Hospital Research and Development Office. Details can be obtained from the hospital.

Will my taking part in this study be kept confidential?
You are guaranteed confidentiality throughout the study, as only the investigators will view the data collected. All information which is collected about you during the course of the research will be kept strictly confidential and stored in a securely locked fireproof cabinet, and any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised. Only summary results of this study (i.e., no individual results) will be published or made available. All electronic data will be kept on a secure NHS hospital server for the duration of the study (plus 2 years). You have the right to check the accuracy of data held about you and correct any errors.

Involvement of the General Practitioner/Family doctor (GP)
Your doctor (GP or other health care practitioner) needs to be notified of your participation, and we will seek their consent. We will provide them with a copy of this letter and will discuss with them any concerns they may have.

What will happen to any samples I give?
Samples you have provided will be kept for the duration of the study, plus two years. Samples will not be traceable to you- they will be identified by allocated subject numbers.

What will happen to the results of the research study?
The results will be presented as broad scientific results; no results will be reviewed with relevance to individuals. You will not be identified in any report/publication unless you have given consent. As this study is part of an academic qualification, results will be analysed and written up in a report and potentially published.

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Wandsworth Research Ethics Committee.

Further information and contact details
Please contact the student investigator if you have any concerns or would like further details.
Lisa Daroux-Cole can be contacted at 020-8417-2876, or at l.cole@kingston.ac.uk.

Thank you for your time. If you choose to be involved in our study, please complete the attached consent form. We appreciate your commitment to the further development of health and exercise for lymphoma survivors.

Sincerely,

Dr. Ruth Pettengell
020 8672 9944
St. George's University, London

Lisa M. Daroux-Cole
020 8417 2876, or 078 9984 4575 (mob)
Kingston University

St George's
University of London

Exercise Training Intervention Programme for Lymphoma Patients

Participant Invitation Letter
Protocol number: 08/H0803/188

Version 1
February 18, 2010

Dear ___,

I would like to invite you to participate in a focus group for participants who have taken part in the exercise training intervention programme for people who have finished treatment for lymphoma. The purpose of the focus group is to gain information about the impact of the exercise intervention and whether or not it was useful to you. If you decide to participate, you will be asked to meet with a small group of other study participants and an independent interviewer. You will be asked participate in a group discussion about the programme. The meeting will take place in the cardiopulmonary rehabilitation room on Monday, ____ at 11am. The meeting should last about 60 minutes. The session will be audio taped so that we can accurately reflect on what is discussed. The tapes will only be reviewed by members of the research team who will transcribe and analyse them. They will then be destroyed. When transcribed, your name will not be recorded. The results of the study may be published or presented at professional meetings, but your identity will not be revealed.

You do not have to answer any questions that you do not wish to.

Others in the group will hear what you say, and it is possible that they could tell someone else. Because we will be talking in a group, we cannot promise that what you say will remain completely private, but we will ask that you and all other group members respect the privacy of everyone in the group and keep what comes from the discussion to yourselves.

Taking part in the study is your decision. You do not have to be in this study if you do not want to. You may also quit being in the study at any time or decide not to answer any question you are not comfortable answering.

We will be happy to answer any questions you have about the study. You may contact me at
07899844575 or l.cole@kingston.ac.uk or my faculty advisor if you have study related questions or problems.

Please refer to the participant information sheet for further details.

Thank you for your consideration. If you would like to participate, please contact me at the number or email address below.

With kind regards,

Lisa Daroux-Cole

Kingston University
Penrhyn Road, Kingston-upon-Thames
KT1 2EE
07899844575
l.cole@kingston.ac.uk

Participant Information Sheet: *focus group*
Version 1
February 18, 2010

St George's Healthcare NHS
NHS Trust

Exercise Training Intervention Programme for Lymphoma Patients: Focus Group

Protocol number: 08/H0803/188

We would like to invite you to take part in a focus group. Before you decide you need to understand why the focus group is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

(Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study).

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

PART 1

What is the purpose of the focus group?

Exercise has been found to increase well-being and overall quality of life in patients and survivors of cancer. The purpose of this focus group is to explore whether the focus group had any impact on you.

Why have I been invited?

You have taken part in the exercise training intervention programme (intervention arm).

Do I have to take part?

It is up to you to decide whether to take part. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part in this study, you will be asked to meet with a small group of other study participants and an independent interviewer. You will be asked participate in a group discussion about the programme.

What will I have to do?

You will be asked to attend the meeting which will take place in the cardiopulmonary rehabilitation room on Monday, ____ at 11am. The meeting should last about 60 minutes. The group will be asked a few questions by the interviewer and you are invited to discuss if you so wish. You do not have to answer any questions that you do not wish to.

What are the possible benefits of taking part?

Although you probably won't benefit directly from participating in this study, we hope that others in the community/society in general will benefit because we can learn more about what is needed for lymphoma patients after treatment.

What are the possible disadvantages and risks of taking part?

Others in the group will hear what you say, and it is possible that they could tell someone else. Because we will be talking in a group, we cannot promise that what you say will remain completely private, but we will ask that you and all other group members respect the privacy of everyone in the group and keep what comes from the discussion to yourselves.

What happens when the focus group is finished?

Upon completion of this study, you will receive a synopsis of the findings. All information is confidential, so you will not receive personal feedback, but will get a summary of the study results.

What if there is a problem?

You may quit being in the study at any time or decide not to answer any question you are not comfortable answering.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence. The session will be audio taped so that we can accurately reflect on what is discussed. The tapes will only be reviewed by members of the research team who will transcribe and analyse them (you will not be identified by name, instead data will be coded when transcribed). The tapes will then be destroyed.

Although we ask members of the group to keep what is discussed during the focus group confidential, we cannot ensure other participants will keep what is said to themselves.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making a decision.

PART 2

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study she may ask you to sign an updated consent form.

If this happens, your research doctor might consider you should withdraw from the study. She will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

You can withdraw from treatment at any time. The information that you supply will not affect the treatment that you are receiving or any of your legal rights. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

What if there is a problem?

If you are harmed by taking part in this focus group there are no special compensation arrangements, but you do have access to the Macmillan Lymphoma specialist nurse in the lymphoma oncology clinic. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Your right at law to claim compensation for injury where you can prove negligence is not affected. Copies of these guidelines are available on request.

Complaints

If you have a concern about any aspect of this study, please ask to speak to your consultant (Dr Pettengell) the Lymphoma specialist nurse (Debbie Gardiner), or Lisa Cole (07899 844 575) who will do their best to answer your questions. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study the normal National Health Service complaints mechanisms should be available to you. Copies of these guidelines are available on request

Will my taking part in this study be kept confidential?

All information which is collected from this focus group will be kept strictly confidential and is accessible to only the research team. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised. All electronic data will be kept on a secure NHS hospital server for the duration of the study (plus 2 years).

Involvement of the General Practitioner/Family doctor (GP)

Your doctor (GP or other health care practitioner) has been notifed of your participation in the exercise study. We will not be sending them information regarding this portion of the study (the focus group, specifically).

What will happen to the results of the research study?

The results of this study may be published in scientific journals or presented to authorities, but you will not be named or identified in any way. The people analysing the information you supply will not be able to identify you from looking at the transcripts.

Who is organising and funding the research?

Dr Ruth Pettengell at St George's Hospital is leading the research study. Kingston University is the Sponsor of the research, and they have authorized the St George's Hospital Lymphoma Unit to manage the trial on their behalf.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Wandsworth Research Ethics Committee.

Further information and contact details

You are encouraged to ask questions at any time during the study. If you have a problem or have more questions about the study or your rights as a patient please call: -

Principal Investigator: Dr Ruth Pettengell at 0208725 2955 or Lisa Daroux-Cole at 07899 844 575, or at l.cole@kingston.ac.uk.

Research Nurses: Debbie Gardiner 0208725 4953

During the study, if there is an emergency please call the hospital switchboard (02086721255) and ask for the Oncology Registrar on call. One copy of this document will be kept together with research records on this study. A second copy will be given to you to keep.

Thank you for considering taking part in this focus group.

You are free to ask questions and take as much time as you need to decide whether or not you want to take part in this focus group.

APPENDIX E. INFORMED CONSENT: RCT

Version 1

Consent Form

St George's Healthcare NHS
NHS Trust

June 25, 2008

Exercise Training Intervention Programme for Lymphoma Patients

Protocol number

Study Number:

Please initial by each box

- ☐ I confirm that I have read and understand the 'Patient Information Sheet' for the above study.

- ☐ I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

- ☐ 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.

- ☐ I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals involved in this study where it is relevant to my taking part in this research.
- ☐ I give permission for these individuals to have access to my records.

- ☐ I agree to my GP being informed of my participation in the study.

- ☐ I agree to take part in the above study.

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

General Practitioner Letter

St George's Healthcare NHS
NHS Trust

Version 1

August 19, 2008

Exercise Training Intervention Programme for Lymphoma Patients

Protocol number

Patient Details

Name:

Date of Birth:

Hospital Number:

Dear Doctor,

This patient is participating in the above study involving an exercise intervention for lymphoma patients. The study will involve extra investigations in the form of basic physiological testing and psychological questionnaires, but does NOT involve any changes in standard treatment. A copy of the patient information sheet is enclosed.

Sincerely,

Dr. Ruth Pettengell
020 8672 9944
St. George's University, London

Lisa M. Daroux-Cole
0208-547-2000

Kingston University

APPENDIX G. ECOG CRITERIA

ECOG PERFORMANCE STATUS*

Grade	ECOG
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

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am Journal of Clinical Oncology,5:649-655, 1982.

APPENDIX H. QUESTIONNAIRES

Lymphoma Exercise Training Intervention Programme

Participant #: ☐

Date: ☐

Time Since Cancer Diagnosis (months): _____.

Time Since the 'end' of treatment (days, weeks, months) _____.

Type of lymphoma and treatment: _____.

DEMOGRAPHICS (please answer in relation to your CURRENT status):

Please circle/highlight only **ONE** option:

1. Marital status

a) Married/ common law
b) Divorced/ separated
c) Widowed
d) Never Married

2. Education Level (please check highest level attained):

a) Some high school (secondary school)
b) Completed high school (secondary school)
c) Some University/ College
d) Completed University/ College
e) Some OR completed Graduate school

3. Employment Status:

a) Full-time
b) Homemaker
c) Retired
d) Part-time
e) Unemployed
f) Disability/ sick leave

4. Smoker/ Non-smoker

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

(Include *only* about those physical activities that you did for at least 10 minutes at a time).

Think about all the **vigorous** activities that you did in the **last 7 days**.

Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ **days per week**

☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**.

Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ **days per week**

☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Theory of Planned Behaviour

Each question in this section refers to your ***engagement in exercise sessions over the next 3 months.***

SE1. I am *confident* that I could engage in exercise sessions three times per week for the next three months if I wanted to

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

---

*SS2. Most *people who are important to me* think that...

I should 1 2 3 4 5 6 7 **I should not**

...engage in exercise sessions three times per week for the next three months.

INT3. "Over the next three months, *I expect I will* engage in a minimum of three exercise sessions PER WEEK"

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

SS4. It is *expected of me* that I engage in exercise sessions three times per week for the next three months"

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

SE5. "For me to engage in exercise sessions three times per week for the next three months will be ...."

1 2 3 4 5 6 7

Extremely Difficult **Extremely Easy**

INT6. "Over the next three months, *I intend* to engage in a minimum of 3 exercise sessions PER WEEK"

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

SS7. I feel under *social pressure* to engage in exercise sessions three times per week for the next three months"

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

---

*CON8. The decision to engage in exercise sessions three times per week for the next three months is *beyond my control.*

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

INT9. "Over the next three months, *I want* to engage in a minimum of 3 exercise sessions PER WEEK"

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

SS10. People who are important to me *want me to engage* in exercise sessions three times per week for the next three months.

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

CON11. Whether I engage in exercise sessions three times per week for the next three months is *entirely up to me.*

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

EX12. "Over the PAST three months, I engaged in approximately 3 exercise sessions PER WEEK"

1 2 3 4 5 6 7

Strongly Disagree **Strongly Agree**

Please complete the following (circle one number per line):

Example:

" FOR ME TO ENGAGE IN EXERCISE THREE TIMES PER WEEK FOR THE NEXT THREE MONTHS WILL BE....." (please circle one number for each line below)

FUN	**1** extremely fun	**2** quite fun	**3** slightly fun	**4** a bit fun, a bit of a chore	**5** slightly a chore	**6** quite a chore	**7** extremely a chore	CHORE

" FOR ME TO ENGAGE IN EXERCISE THREE TIMES PER WEEK FOR THE NEXT THREE MONTHS WILL BE....." (please circle one number for each line below)

		Extremely 1	**Quite** 2	**Slightly** 3	**A bit of both** 4	**Slightly** 5	**Quite** 6	**Extremely** 7	
1	**WORTHLESS**	1	2	3	4	5	6	7	**USEFUL**
2	**HARMFUL**	1	2	3	4	5	6	7	**BENFICIAL**
3	**UNENJOYABLE**	1	2	3	4	5	6	7	**ENJOYABLE**
4	**NEGATIVE**	1	2	3	4	5	6	7	**POSITIVE**
5	**HEALTHY**	1	2	3	4	5	6	7	**UNHEALTHY**
6	**INTERESTING**	1	2	3	4	5	6	7	**UNINTERESTING**
7	**FUN**	1	2	3	4	5	6	7	**CHORE**

8	**DULL**	1	2	3	4	5	6	7	**STIMULATING**
9	**OBLIGATION**	1	2	3	4	5	6	7	**TREAT**
10	**CONVENIENT**	1	2	3	4	5	6	7	**INCONVENIENT**

Profile of Mood States

Below is a list of words that describe feelings that people have. Please read each one carefully. Then circle **ONE** number corresponding to the adjective phrase which best describes HOW YOU HAVE BEEN FEELING DURING **THE PAST WEEK** INCLUDING TODAY. The numbers refer to the following descriptive phrases

		Not at All	*A Little*	*Moderately*	*Quite a Bit*	*Extremely*
1.	Friendly	0	1	2	3	4
2.	Tense	0	1	2	3	4
3.	Angry	0	1	2	3	4
4.	Worn-out	0	1	2	3	4
5.	Unhappy	0	1	2	3	4
6.	Clear-headed	0	1	2	3	4
7.	Lively	0	1	2	3	4
8.	Confused	0	1	2	3	4
9.	Sorry for things done	0	1	2	3	4
10.	Shaky	0	1	2	3	4
11.	Listless	0	1	2	3	4
12.	Peeved	0	1	2	3	4
13.	Considerate	0	1	2	3	4
14.	Sad	0	1	2	3	4
15.	Active	0	1	2	3	4
16.	On edge	0	1	2	3	4
17.	Grouchy	0	1	2	3	4
18.	Blue	0	1	2	3	4
19.	Energetic	0	1	2	3	4

20.	Panicky	0	1	2	3	4
21.	Hopeless	0	1	2	3	4
22.	Relaxed	0	1	2	3	4
23.	Unworthy	0	1	2	3	4
24.	Spiteful	0	1	2	3	4
25.	Sympathetic	0	1	2	3	4
26.	Uneasy	0	1	2	3	4
27.	Restless	0	1	2	3	4
28.	Unable to concentrate	0	1	2	3	4
29.	Fatigued	0	1	2	3	4
30.	Helpful	0	1	2	3	4

		Not at All	*A Little*	*Moderately*	*Quite a Bit*	*Extremely*
31.	Annoyed	0	1	2	3	4
32.	Discouraged	0	1	2	3	4
33.	Resentful	0	1	2	3	4
34.	Nervous	0	1	2	3	4
35.	Lonely	0	1	2	3	4
36.	Miserable	0	1	2	3	4
37.	Muddled	0	1	2	3	4
38.	Cheerful	0	1	2	3	4
39.	Bitter	0	1	2	3	4
40.	Exhausted	0	1	2	3	4
41.	Anxious	0	1	2	3	4
42.	Ready to fight	0	1	2	3	4
43.	Good-natured	0	1	2	3	4
44.	Gloomy	0	1	2	3	4
45.	Desperate	0	1	2	3	4
46.	Sluggish	0	1	2	3	4
47.	Rebellious	0	1	2	3	4
48.	Helpless	0	1	2	3	4
49.	Weary	0	1	2	3	4
50.	Bewildered	0	1	2	3	4
51.	Alert	0	1	2	3	4
52.	Deceived	0	1	2	3	4

53.	Furious	0	1	2	3	4
54.	Efficient	0	1	2	3	4
55.	Trusting	0	1	2	3	4
56.	Full of pep	0	1	2	3	4
57.	Bad-tempered	0	1	2	3	4
58.	Worthless	0	1	2	3	4
59.	Forgetful	0	1	2	3	4
60.	Carefree	0	1	2	3	4
61.	Terrified	0	1	2	3	4
62.	Guilty	0	1	2	3	4
63.	Vigorous	0	1	2	3	4
64.	Uncertain about things	0	1	2	3	4
65.	Bushed	0	1	2	3	4

FACT-LYM

Below is a list of statements that other people with lymphoma have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
1	I have lack of energy	0	1	2	3	4
2	I have nausea	0	1	2	3	4
3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4	I have pain	0	1	2	3	4
5	I am bothered by side effects of treatment	0	1	2	3	4
6	I feel ill	0	1	2	3	4
7	I am forced to spend time in bed	0	1	2	3	4
	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**

8	I feel close to my friends	0	1	2	3	4
9	I get emotional support from my family	0	1	2	3	4
10	I get support from my friends	0	1	2	3	4
11	My family has accepted my illness	0	1	2	3	4
12	I am satisfied with family communication about my illness	0	1	2	3	4
13	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
14	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* □.					
	I am satisfied with my sex life	0	1	2	3	4
	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
15	I feel sad	0	1	2	3	4
16	I am satisfied with how I am coping with my illness	0	1	2	3	4
17	I am losing hope in the fight against my illness	0	1	2	3	4
18	I feel nervous	0	1	2	3	4
19	I worry about dying	0	1	2	3	4
20	I worry that my condition will get worse	0	1	2	3	4
	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
21	I am able to work (include work at home)	0	1	2	3	4
22	My work (include work at home) is fulfilling	0	1	2	3	4
23	I am able to enjoy life	0	1	2	3	4
24	I have accepted my illness	0	1	2	3	4
		Not at all	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
25	I am sleeping well	0	1	2	3	4
26	I am enjoying the things I usually do for fun	0	1	2	3	4

27	I am content with the quality of my life right now	0	1	2	3	4
	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
28	I feel fatigued	0	1	2	3	4
29	I feel weak all over	0	1	2	3	4
30	I feel listless (washed out)	0	1	2	3	4
31	I feel tired	0	1	2	3	4
32	I have trouble starting things because I am tired	0	1	2	3	4
33	I have trouble finishing things because I am tired	0	1	2	3	4
34	I have energy	0	1	2	3	4
35	I am able to do my usual activities	0	1	2	3	4
36	I need to sleep during the day	0	1	2	3	4
37	I am too tired to eat	0	1	2	3	4
38	I need help doing my usual activities	0	1	2	3	4
39	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
40	I have to limit my social activity because I am tired	0	1	2	3	4
41	P2 I have certain parts of my body where I experience pain	0	1	2	3	4
42	LEU1 I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
43	BRM 3 I am bothered by fevers	0	1	2	3	4
44	ES3 I have night sweats	0	1	2	3	4
45	LYM1 I am bothered by itching	0	1	2	3	4
46	LYM2 I have trouble sleeping at night	0	1	2	3	4
47	BMT6 I get tired easily	0	1	2	3	4
48	C2 I am losing weight	0	1	2	3	4
49	Ga1 I have a loss of appetite	0	1	2	3	4

50	HI8 I have trouble concentrating	0	1	2	3	4
51	N3 I worry about getting infections	0	1	2	3	4
52	LEU6 I worry that I might get new symptoms of my illness	0	1	2	3	4
53	LEU7 I feel isolated from others because of my illness or treatment	0	1	2	3	4
54	BRM 9 I have emotional ups and downs	0	1	2	3	4
55	LEU4 Because of my illness, I have difficulty planning for the future	0	1	2	3	4

The EORTC Quality of Life Questionnaire

Please answer all 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.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous exercises, 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 the house?	1	2	3	4
4. Do you have to stay in bed or a chair for most of the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
6. Are you limited in any way in doing either your work or doing household jobs?	1	2	3	4
7. Are you completely unable to work at a job or to do household jobs?	1	2	3	4
DURING THE PAST WEEK:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
DURING THE PAST WEEK:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhoea?	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 trouble remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your <u>social</u> life?	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 physical condition during the past week?	
	(poor)1 2 3 4 5 6 7 (excellent)	
30.	How would you rate your overall quality of life during the past week?	
	(poor)1 2 3 4 5 6 7 (excellent)	

Hospital Anxiety and Depression Scale (HADS)

Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':		**I feel as if I am slowed down:**	
Most of the time		Nearly all of the time	
A lot of the time		Very often	
Time to time, occasionally		Sometimes	
Not at all		Not at all	
I still enjoy the things I used to enjoy:		**I get a sort of frightened feeling like 'butterflies in the stomach':**	
Definitely as much		Not at all	
Not quite so much		Occasionally	
Only a little		Quite often	
Not at all		Very often	
I get a sort of frightened feeling like something awful is about to happen:		**I have lost interest in my appearance:**	
Very definitely and quite badly		Definitely	
Yes, but not too badly		I don't take as much care as I should	
A little, but it doesn't worry me		I may not take quite as much care	
Not at all	0	I take just as much care as ever	
I can laugh and see the funny side of things:		**I feel restless as if I have to be on the move:**	
As much as I always could		Very much indeed	
Not quite so much now		Quite a lot	
Definitely not so much now		Not very much	
Not at all		Not at all	

Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**		
A great deal of the time			A much as I ever did		
A lot of the time			Rather less than I used to		
From time to time but not too often			Definitely less than I used to		
Only occasionally			Hardly at all		
I feel cheerful:			**I get sudden feelings of panic:**		**A**
Not at all			Very often indeed		
Not often			Quite often		
Sometimes			Not very often		
Most of the time			Not at all		
I can sit at ease and feel relaxed:			**I can enjoy a good book or radioor TV programme:**		
Definitely		0	Often		
Usually			Sometimes		
Not often			Not often		
Not at all			Very seldom		

Thank you for completing this questionnaire.

APPENDIX I. THEORY OF PLANNED BEHAVIOUR QUESTIONNIARE DEVELOPMENT

Table A11.1. Theory of planned behaviour (TPB) Constructs and Questionnaire Design for this thesis.

construct	question	Scale
Attitude	" FOR ME TO ENGAGE IN EXERCISE THREE TIMES PER WEEK FOR THE NEXT THREE MONTHS WILL BE....." : Worthless- useful Harmful- beneficial Unenjoyable- enjoyable Negative-positive Healthy-unhealthy Interesting- uninteresting Fun- chore Dull-stimulating Obligation-treat	Extremely, quite, slightly, a bit of both, slightly, quite, extremely (1-7)
Subjective Norm	Most *people who are important to me* think that... ...engage in exercise sessions three times per week for the next three months.	I should - should not (1-7)
	It is *expected of me* that I engage in exercise sessions three times per week for the next three months"	Strongly agree- strongly disagree (1-7)
	I feel under *social pressure* to engage in exercise sessions three times per week for the next three months"	Strongly agree- strongly disagree (1-7)
	People who are important to me *want me to engage* in exercise sessions three times per week for the next three months.	Strongly agree- strongly disagree (1-7)
PBC: self efficacy	I am *confident* that I could engage in exercise sessions three times per week for the next three months if I wanted to	Strongly agree- strongly disagree (1-7)
	For me to engage in exercise sessions three times per week for the next three months will be ...."	Extremely Difficult-Extremely Easy (1-7)

PBC: control	The decision to engage in exercise sessions three times per week for the next three months is *beyond my control.*	Strongly agree- strongly disagree (1-7)
	Whether I engage in exercise sessions three times per week for the next three months is *entirely up to me.*	Strongly agree- strongly disagree (1-7)
Intention	. "Over the next three months, *I expect I will* engage in a minimum of three exercise sessions PER WEEK"	Strongly agree- strongly disagree (1-7)
	Over the next three months, *I intend* to engage in a minimum of 3 exercise sessions PER WEEK"	Strongly agree- strongly disagree (1-7)
	Over the next three months, *I want* to engage in a minimum of 3 exercise sessions PER WEEK"	Strongly agree- strongly disagree (1-7)
Actual behaviour	"Over the PAST three months, I engaged in approximately 3 exercise sessions PER WEEK"	Strongly agree- strongly disagree (1-7)

*

APPENDIX J. PRELIMINARY TESTING INSTRUCTIONS FOR PARTICIPANTS

1. Dress requirements: come dressed in comfortable clothing and footwear, preferably shorts, short sleeved shirt and running shoes.
2. Food and beverages: please do not eat, or drink caffeinated beverages for at least two hours before taking the appraisal. Do not drink alcohol for six hours prior to appraisal.
3. *Smoking: please do not smoke two hours prior to appraisal.*
4. Exercise: Exercise should be avoided for six hours prior to appraisal.

Pre-Appraisal Screening

1. Par-Q: The PAR-Q must be administered without interpretation, although the following terms may need clarification: heart condition (includes heart attacks, angina, congenital heart disease, heart-valve disease, congestive heart failure, dropsy, and the use of heart medications) ; dizziness (frequently referred to as lightheadedness; associated with the sensation of instability).
2. Consent Form: The consent form should be read, understood, and duly signed prior to the administration of the appraisal.
3. Observations: Although PAR-Q identifies most concerns, which would make a fitness appraisal inappropriate, you must also make some general observations during the screening process. The appraisal should be cancelled or postponed if clients:
    - Are pregnant
    - Demonstrate difficulty breathing at rest
    - Cough persistently
    - Are ill or have a fever
    - Have lower-extremity swelling
    - Are currently on certain medication
    - Have clearly ignored the preliminary instructions
    - For any reason the appraiser feels testing will be a risk

APPENDIX K. WEEKLY EXERCISE LOG

Participant Weekly Exercise & Rating of Perceived Exertion

Logbook

Participant #: _____ **Week Number:** _____

*** Place an asterisks beside the session you did with your exercise trainer.**

Date	Type of Cardio Exercise (ie. walk, run, bike, gardening, etc.)	Duration (time) (minutes)	Exercise Intensity (circle one)	Rating of Perceived Exertion (1-10)	Maximal Heart Rate (taken right at the end of the exercise session)
			Mild Moderate Difficult		
			Mild Moderate Difficult		
			Mild Moderate Difficult		
			Mild Moderate Difficult		
			Mild Moderate Difficult		
			Mild Moderate Difficult		

Any additional notes to record:

Any visit to the physicians/ surgery/ hospital?

Any changes to your medication?

RATING OF PERCEIVED EXERTION

1 = No exertion at all

2 = Extremely light

3 = Very light - (easy walking slowly at a comfortable pace)

4 = Light

5 = Somewhat hard (It is quite an effort; you feel tired but can continue)

6 = Becoming Difficult, but can continue

7 = Hard (heavy)

8 = Very hard (very strenuous, and you are very fatigued)

9 = Extremely hard (You cannot continue for long at this pace)

10 = Maximal exertion

BORG SCALE

6 No exertion at all

7 Extremely light

8 Very light - (easy walking slowly at a comfortable pace)

9

10

11 Light

12

13 Somewhat hard (It is quite an effort; you feel tired but can continue)

14

15 Hard (heavy)

16

17 Very hard (very strenuous, and you are very fatigued)

18

19 Extremely hard (You cannot continue for long at this pace)

20 Maximal exertion

Physical Activity and the Cancer Patient

In the past, people being treated for a chronic illness (an illness a person may live with for a long time, such as cancer or diabetes) were often told by their doctor to rest and reduce their physical activity. This may still be true if movement causes severe pain, rapid heart rate, or shortness of breath.

Newer research has shown that exercise is not only safe and possible during cancer treatment, but it can improve physical functioning and quality of life. Too much rest may result in loss of function, strength, and range of motion in the person with a chronic illness. As a result, many cancer care teams are now urging their patients to be as physically active as possible during cancer treatment. Regular exercise is an effective way to counteract the negative effects of inactivity in chronic illness.

Possible benefits of regular exercise during cancer treatment

- keep or improve your physical abilities
- better balance, lower risk of falls and broken bones
- keep muscles from wasting due to inactivity
- lower risk of heart disease
- less risk of osteoporosis (weak bones that are more likely to break)
- better blood flow to legs and lower risk of blood clots
- less dependence on others to do normal activities of daily living
- improved self-esteem
- lower risk of anxiety and depression
- less nausea
- better ability to keep social contacts
- fewer symptoms of fatigue
- better weight control
- improved quality of life

We still do not know a lot about the effects of exercise and physical activity on recovery from cancer and on the immune system. But regular moderate exercise has been found to have health benefits for the cancer patient. Moderate exercise is defined as activity that takes as much effort as a brisk walk.

Goals of an exercise program

While there are many reasons for being physically active during cancer treatment, each person's exercise program should be based on what is safe, effective, and enjoyable for that person. Your exercises should take into account any exercise program you already follow, what you can do now, and any physical problems or limits you have. You and your doctor should tailor an exercise program to meet your interests and needs.

The type of cancer you have; your cancer treatment; and your stamina, strength, and fitness level

all affect your ability to exercise. What may be of low or moderate intensity for a healthy person may seem like a high intensity activity for some cancer survivors. While some people can safely begin their own exercise program, many will have better results with the help of an exercise specialist, physical therapist, or exercise physiologist. Be sure to get approval from your doctor first, and be sure that the person knows about your diagnosis and limitations. These specially trained professionals can help you find the type, frequency, duration, and intensity of exercise that is right for you.

Exercise safety and precautions for cancer survivors

Always check with your doctor before starting any exercise program. This is especially important if you are taking treatments that affect your lungs (such as bleomycin or radiation to the chest) or your heart (such as doxorubicin or epirubicin) or if you have risk of lung or heart disease.

- Do not exercise if you have anemia (low red blood cell count). Your cancer care team will be checking your blood counts during your treatment, so ask them about the best time to exercise.
- If you have low white blood cell counts or if you take medicines that may reduce your ability to fight infection, avoid public gyms and other public places until you are back at safe levels. Check with your cancer care team about these.
- Do not exercise if the level of minerals in your blood, such as sodium and potassium, are not normal. This can happen if you have had a lot of vomiting or diarrhea. Ask your doctor about your blood tests. If it is ok with your doctor, drink plenty of fluids.
- If you are very tired and don't feel up to exercising, you can try to do 10 minutes of stretching exercises every day. (Later we will discuss fatigue and exercise in more detail.)
- Avoid uneven surfaces or any weight-bearing exercises that could cause a fall and injury.
- Do not use heavy weights or do exercise that puts too much stress on the bones if you have osteoporosis, cancer that has spread to the bone, arthritis, nerve damage, poor vision, poor balance, or weakness. You may be more likely to injure yourself or break bones.
- If you have numbness in your feet or problems with balance, you are at higher risk for falls. You might do better with a stationary reclining bicycle, for example, than a treadmill.
- Watch for swollen ankles, unexplained weight gain, or shortness of breath while at rest or with a small amount of exertion. Let your doctor know if you have any of these problems.
- Watch for bleeding if you are taking blood thinners. Avoid any activity that raises your risk for falls or injury. If you notice swelling, pain, dizziness, or blurred vision, call your doctor right away.
- To avoid irritation, don't expose skin that has had radiation to the chlorine in swimming pools.
- Do not exercise if you have unrelieved pain, nausea/vomiting, or any other symptom that causes you concern. Call your doctor.
- Do not exercise above a moderate level of exertion without talking with your doctor. Remember, moderate exertion is about as much effort as a brisk walk.
- If you still have a catheter (tube that goes into your body), avoid water and other exposures that may cause infections. Also, avoid resistance training that uses muscles in the area of the catheter to avoid dislodging it. Talk with your cancer team about what is safe for you.

Effective exercise

To make your exercise most effective, it is important that you work your heart. Pay attention to your heart rate, your breathing, and how tired your muscles get. If you get short of breath or very tired,

rest for a few seconds, and start back exercising as you are able. Start slowly at first, and over the next few weeks, increase the length of time you exercise. Be careful if you are taking blood pressure medicine that controls your heart rate. Your heart rate will not go up, but your blood pressure can get high. Ask your doctor, nurse, or pharmacist about this if you are not sure about your medicine.

The best level of exercise for someone with cancer has not been established. But the goal is to have your exercise program help you maintain endurance, muscular strength, flexibility, and level of functioning. The more you exercise, the more your ability to exercise can improve and your ability to function can improve. It is common for people who have exercised before they were diagnosed with cancer to need to reduce their intensity (make it easier and less taxing) and amount of exercise during treatment. Even if planned exercise stops, it is good to continue being active by keeping up your normal activities.

Things to think about when planning an exercise program

- Discuss any exercise with your doctor before starting.
- Start slowly with an exercise program. Even if you can only do an activity for a few minutes a day it will help you. How often and how long you do a simple activity like walking can be slowly increased. Your muscles will tell you when you need to slow down and rest.
- Try short periods of exercise with frequent rest breaks. For example, walk briskly for a few minutes, slow down, and walk briskly again, until you have done 30 minutes of brisk activity. You can divide the activity into three 10-minute sessions, if you need to. You will still get the benefit of the exercise.
- Try to include physical activity that uses large muscle groups. Strength, flexibility, and aerobic fitness are all important parts of an exercise program that works.
- Try to include some exercises that will help you keep lean muscles mass and bone strength, such as exercising with resistance or light weights.
- You might want to include exercises that will increase your flexibility and maintain the range of motion in your joints.
- Always start with warm-up exercises for about 2 to 3 minutes. Examples of warm-up exercises are shoulder shrugs, lifting arms overhead, toe tapping, marching, and knee lifts. End your session with stretching or flexibility exercises. Hold the stretch for about 15 to 30 seconds and relax. Remember to breathe when you stretch. Examples of stretching are reaching overhead, deep breathing, and bending over to touch your toes so that you relax all the muscle groups.
- Exercise moderately.

Too tired to exercise -- Fatigue in cancer

Most cancer patients notice a loss of energy. During chemotherapy and radiation, about 70% of patients have fatigue. For many, fatigue is severe and limits their activity. Inactivity leads to muscle wasting and loss of function.

An aerobic training program can help break this cycle. In research studies, regular exercise has been linked to reduced fatigue. It is also linked to being able to do normal daily activities without major limitations. An aerobic exercise program can be prescribed as treatment for fatigue in cancer patients. Talk with your doctor about this.

Tips to reduce fatigue:

- Set up a daily routine that allows activity when you are feeling your best.
- Exercise regularly at light to moderate intensity.
- Get fresh air.
- Unless you are told otherwise, eat a balanced diet that includes protein (meat, milk, eggs, and legumes such as peas or beans) and drink about 8 to 10 glasses of water a day.
- Keep your symptoms such as pain, nausea, or depression controlled.
- To save energy, keep things you use often within easy reach.
- Enjoy your hobbies and other activities that give you pleasure.
- Use relaxation and visualization techniques to reduce stress.
- Balance activity with rest that does not interfere with nighttime sleep.
- Ask for help when you need it.

Keep it fun

The key is to keep your exercise program simple and fun. Exercise and relaxation techniques are great ways to relieve stress. Reducing your stress is a vital element in maintaining health.

Tips to enhance your interest in your exercise program

- Set short-term and long-term goals.
- Focus on having fun.
- Do something different to keep it fresh. Try yoga, dancing, or tai chi.
- Ask for support from others, or get friends, family, and co-workers involved in your exercise program.
- Use charts to record your exercise progress.
- Recognize and reward your achievements.

Beginning an exercise program can be a big task, even for a healthy person. It may be even harder for you if you have a chronic illness, more so if you were not used to exercising before your diagnosis. Start slowly and build up as you are able. If you were exercising regularly before you were diagnosed with cancer, you may need to reduce your intensity and length of exercise sessions.

Let exercise provide you with its benefits.

- helping prevent muscle wasting
- reducing the side effects of treatment
- improving your fitness
- improving your quality of life

Ways to add physical activity to your daily routine

Remember, only do what you feel up to doing.

- Take a walk around your neighborhood after dinner.
- Ride your bike.
- Mow the grass or rake the leaves instead of using the blower.
- Scrub your bathroom.
- Wash and wax the car.
- Play active games with the kids, like freeze tag, jump rope, and the games you loved to play when you were a kid.

- Walk a dog (one that can be controlled enough that you don't trip or get pulled off balance.)
- Weed your garden by hand.
- Take a friend dancing, or dance in your own living room.
- Use an exercise bike or treadmill or do arm curls, squats, lunges, and sit ups while watching TV.
- Walk to lunch.
- Park your car in the farthest parking space at work and walk to the building.
- Use the stairs instead of the elevator or escalator.
- Get off the bus several stops early and walk the rest of the way to work. .
- Form a walking club of co-workers to help you stay motivated to walk during the workday.

Cancer survivors may need to exercise less intensely and increase their workout at a slower rate than people who are not getting cancer treatment. Remember, the goal is to keep up as much activity as possible. Keep it safe, keep it effective, and keep it fun.

Additional resources

We have selected some related information that may also be helpful to you. These materials may be ordered from our toll-free number, 1-800-ACS-2345.

- American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention
- Guidelines for the Early Detection of Cancer
- Nutrition and Physical Activity During and After Cancer Treatment: Answers to Common Questions

Contact us anytime, day or night, for information and support. Call us at **1-800-ACS-2345** or visit www.cancer.org.

References

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Doyle C, Kushi LH, Byers T, et al. Nutrition and Physical Activity During and After Cancer Treatment: An American Cancer Society Guide for Informed Choices. CA Cancer J Clin 2006; 56:323-353

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APPENDIX N. PSYCHOLOGICAL DATA: MEAN (SD), AND ALL MIXED MODEL *RESULTS*

Table AN1. Psychological Results: Mean Scores and Mixed Model Analysis

		Time 1 Pre Mean (SD)	**n**	**Time 2 Post Mean (SD)**	**n**	**Time 3 Follow-Up Mean (SD)**	**n**	**Mixed Model Analysis**
Anxiety (HADS)	**Intervention**	2.33 (0.9)	20	1.93 (1.1)	19	4.43 (0.5)	7	Time: F 2(22.345)=0.333,p=0.720 Group: F 1(23.808) =35.530, p=0.000** Time X Group: F2(22.345)= 19.088, p=0.000**
	Control	1.76 (1.1)	20	2.09 (0.9)	18	0.17 (0.4)	6	
Depression (HADS) [1]	**Intervention**	5.55 (4.1)	19	3.67 (3.5)	18	2.29 (2.3)	7	Time: F3(27.925)=2.963, p=0.049 Group: F 1(58.494=3.210, p=0.078 Time X Group: F3(27.925)=0.754, p=0.529
	Control	3.41 (2.7)	17	2.87 (2.3)	18	2.17 (1.9)	6	
Vigour/ Inertia (POMS)	**Intervention**	13.87 (3.7)	20	17.56 (4.7)	20	16.38 (8.3)	8	Time: F 2 (23.546)=6.311,p=0.006** Group: F 1(20.655)=4.285, p=0.051 Time X Group: F2(23.546)= 0.159, p=0.854
	Control	16.30 (6.1)	20	19.82 (1.7)	14	21.00 (7.0)	7	
Anger/ Hostility (POMS)	**Intervention**	2.29 (1.4)	19	1.96 (1.2)	18	2.53 (1.5)	8	Time: F 2 (26.041)=0.539,p=0.590 Group: F 1(29.217)=2.038, p=0.164 Time X Group: F2(26.041)= 0.952, p=0.399
	Control	2.15 (1.0)	18	1.94 (1.1)	17	1.33 (1.4)	7	
Confusion/ Bewilderment (POMS)	**Intervention**	6.02 (3.4)	18	5.52 (2.8)	19	8.38 (6.5)	8	Time: F 2 (23.546)=0.521,p=0.601 Group: F 1(18.627)=2.157, p=0.159 Time X Group: F2(22.957)= 0.353, p=0.706
	Control	5.13 (2.9)	20	4.84 (2.9)	19	5.00 (5.2)	7	
Depression/ Dejection (POMS) [1]	**Intervention**	7.50 (6.5)	20	9.68 (12.24)	19	12.86 (12.8)	7	Time: F 2 (23.546)=0.521,p=0.601 Group: F 1(18.627)=2.157, p=0.159 Time X Group: F2(22.957)= 0.353, p=0.706
	Control	8.44 (12.5)	16	9.89 (13.7)	18	3.71 (5.2)	7	
Tension/ Anxiety	**Intervention**	8.94(1.1)		8.05(1.1)		17.44(6.9)		Time: F 3 (16.671)=1.423,p=0.271

(POMS)[1]	**Control**	5.33(1.2)		6.50(1.1)		7.5(14.6)		Group: F 1(9.637)=0.936, p=0.357 Time X Group: F3(16.671)= 0.555, p=0.652
Fatigue (POMS)	**Intervention**	2.98 (1.1)	18	2.34 (0.6)	18	2.25 (1.8)	7	Time: F 2 (22.594)=2.259,p=0.128 Group: F 1(21.216)=2.048, p=0.167
	Control	2.38 (1.3)	19	2.253 (1.3)	20	1.73 (1.4)	7	Time X Group: F2(22.594)= 0.176, p=0.840
Total Mood Disturbance (POMS)	**Intervention**	7.15 (2.1)	20	6.40 (2.1)	20	7.53 (3.1)	7	Time: F 2 (22.634)=0.448,p=0.645 Group: F 1(20.969)=0.853, p=0.042**
	Control	6.11 (1.8)	18	6.00 (2.1)	19	5.01 (2.8)	7	Time X Group: F2(22.634)= 0.861, p=0.451
Global QoL (EORTC)	**Intervention**	62.50 (22.4)	20	68.54 (18.3)	20	69.80 (19.4)	8	Time: F 2 (29.484)=2.611,p=0.090* Group: F 1(37.611)=0.049, p=0.826
	Control	58.03 (25.1)	21	69.68 (16.7)	21	76.19 (20.7)	7	Time X Group: F2(29.484)= 0.392, p=0.679
Physical Function (EORTC)	**Intervention**	83.46 (11.6)	18	90.57 (10.2)	19	82.50 (20.1)	8	Time: F 2 (27.248)=,2.896, p=0.072* Group: F 1(31.404)=0.237, p=0.630
	Control	79.53 (22.4)	21	89.14 (12.6)	19	93.33 (12.8)	7	Time X Group: F2(27.248)= 1.016, p=0.375
Emotional Function (EORTC)	**Intervention**	78.07 (21.0)	19	73.80 (24.7)	20	77.08 (27.0)	8	Time: F 2 (28.715)=0.870,p=0.430 Group: F 1(36.707)=8.180, p=0.007**
	Control	86.75 (15.6)		84.46 (18.9)	20	97.62 (6.3)	7	Time X Group: F2(28.715)= 0.487, p=0.619
Role Function (EORTC)	**Intervention**	91.03 (8.7)	17	94.44 (11.4)	18	85.42 (24.3)	8	*Difficulty getting normality** p>.05 with non-parametric tests* Time: F 2 (22.862)=2.446,p=0.109 Group: F 1(19.792)=3.457, p=0.078 Time X Group: F2(22.862)= 1.055, p=0.365
	Control	86.74 (15.6)	19	98.26 (4.4)	16	100.00 (0.0)	7	
Social Function (EORTC)	**Intervention**	66.67 (35.5)	20	84.45 (21.9)	19	81.25 (31.4)	8	Time: F 2 (29.236)=4.285,p=0.023** Group: F 1(36.086)=6.016, p=0.019**
	Control	80.34 (14.7)	19	91.21 (14.1)	19	100.00 (0.0)	7	Time X Group: F2(29.236)= , p=0.611
Cognitive Function	**Intervention**	85.00 (19.4)	20	89.20 (9.8)	18	85.42 (16.5)	8	*Time: F 2 (27.767)=0.756, p=0.479

(EORTC)	**Control**	87.87 (13.0)	20	91.43 (11.5)	19	92.86 (13.1)	7	Group: F 1(32.883)=1.568, p=0.219 Time X Group: F2(27.767)= 0.186, p=0.831
Fatigue (EORTC)	**Intervention**	40.44 (19.5)	20	25.15 (18.3)	20	20.63 (14.9)	7	Time: F 2 (32.575)=10.682,p=0.000** Group: F 1(49.164)= 0.278, p=0.600 Time X Group: F2(32.575)=0.558, p=0.578
	Control	44.86 (31.1)	21	21.48 (20.3)	19	12.70 (18.6)	7	
Pain (EORTC)	**Intervention**	10.19 (13.0)	18	5.68 (8.3)	15	31.25 (41.2)	8	Time: F 2 (20.399)=2.822,p=0.083* Group: F 1(16.273)=1.059, p=0.318 Time X Group: F2(20.399)= 2.95, p=0.099*
	Control	19.69 (22.4)	19	8.50 (10.7)	16	0.00 (6.3)	6	
Insomnia (EORTC)	**Intervention**	35.00 (29.6)	20	24.26 (21.2)	20	50.00 (39.8)	8	Time: F 2 (26.748)=2.883,p=0.073* Group: F 1(29.473)=4.822, p=0.036** Time X Group: F2(26.748)= 2.532, p=0.098*
	Control	36.51 (34.8)	21	19.01 (19.5)	20	9.52 (16.3)	7	
Appetite Loss (EORTC)	**Intervention**	13.33 (25.1)	20	17.04 (29.4)	20	12.50 (35.4)	8	Time: F 2 (29.565)=1.204,p=0.314 Group: F 1(39.065)=0.117, p=0.734 Time X Group: F2(29.565)= 1.319, p=0.283
	Control	24.16 (31.4)	21	12.50 (24.2)	21	0.00 (0.0)	7	
Constipation (EORTC)	**Intervention**	15.00 (27.5)	20	11.85 (22.3)	20	8.33 (15.4)	8	Time: F 2 (59.815)=2.769,p=0.071* Group: F 1(78.861)=0.514, p=0.476 Time X Group: F2(59.815)= 0.610, p=0.547
	Control	18.87 (32.2)	21	7.24 (17.0)	21	0.00 (0.0)	7	
Financial Difficulty (EORTC)	**Intervention**	30.00 (35.7)	20	28.06 (37.9)	20	20.83 (35.4)	8	Time: F 2 (34.797)=3.312,p=0.048** Group: F 1(54.853)=1.108, p=0.297 Time X Group: F2(34.797)= 1.204, p=0.312
	Control	36.68 (39.3)	21	20.50 (25.1)	19	0.00 (0.0)	7	
Dyspnea (EORTC)	**Intervention**	12.28 (16.5)	19	10.00 (21.9)	20	8.33 (23.6)	8	Time: F 2 (28.505)=1.468,p=0.247 Group: F 1(36.832)=0.826, p=0.369 Time X Group: F2(28.505)= 0.577, p=0.568
	Control	22.84 (24.8)	18	11.11 (16.2)	18	9.52 (16.3)	7	
Physical Activity (IPAQ)	**Intervention**	1122.18 (1146.8)	19	2168.67 (1567.7)	17	1905.71 (578.5)		Time: F 2 (40.81)=5.509,*p=0.008*** Group: F 1(60804)=0.094, p=0.760 Time X Group: F2(40.806)= 0.802, p=0.455
	Control	1391.35 (1205.3)	20	2513.11 (1576.9)	17	1533.25 (950.4)		

Physical Well-being (FACT)	**Intervention**	22.61 (3.5)	18	24.93 (1.7)	18	22.14 (5.8)	7	Time: F 2 (19.307)=6.269,p=0.007** Group: F 1(19.307)=2.481, p=0.131 Time X Group: F2(20.676)= 1.661, p=0.214
	Control	22.39 (3.0)	19	25.03 (3.0)	17	26.67 ()	6	
Social/ Family Well-being (FACT)	**Intervention**	22.611 (1.3)	15	21.24 (2.3)	19	21.86 (3.2)	7	Time: F 2 (22.681)=3.059,p=0.067* Group: F 1(22.408)=3.866, p=0.062* Time X Group: F2(22.681)= 0.244, p=0.786
	Control	21.51 (1.3)	20	20.13 (4.3)	21	19.29 (4.4)	7	
Emotional Well-being (FACT)	**Intervention**	18.41 (5.3)	19	20.96 (1.9)	18	17.00 (7.0)	7	Time: F 2 (22.341)=0.378,p=0.690 Group: F 1(20.463)=4.874, p=0.039** Time X Group: F2(22.341)= 4.542, p=0.022**
	Control	21.10 (2.4)	20	19.86 (3.4)	19	22.57 (2.5)	7	
Functional Well-being (FACT)	**Intervention**	18.72 (3.8)	20	21.83 (2.8)	18	20.00 (7.3)	7	Time: F 2 (22.968)=4.969,p=0.016** Group: F 1(21.676)=0.000, p=0.985 Time X Group: F2(22.968)= 1.473, p=0.250
	Control	17.30 (5.5)	21	19.62 (4.3)	21	23.57 (4.0)	7	
HRQoL Lymphoma Total (FACT)	**Intervention**	93.29 (5.8)	14	98.87 (7.0)	15	137.00 (17.0)	6	Time: F 2 (18.786)=62.107,p=0.000** Group: F 1(16.351)=0.255, p=0.620 Time X Group: F2(18.786)= 2.156, p=0.144
	Control	93.44 (5.4)	9	93.00 (10.2)	14	147.43 (13.5)	7	
Lymphoma Total Outcome Index (FACT)	**Intervention**	53.60 (5.5)	15	55.06 (5.3)	16	96.17 (14.0)	6	Time: F 2 (19.215)=112.65,p=0.000** Group: F 1(17.231)=0.165, p=0.689 Time X Group: F2(19.215)= 1.962, p=0.168
	Control	50.50 (6.0)	10	51.60 (6.7)	15	105.57 (8.1)	7	

[1] baseline means were significantly different

APPENDIX O. PHYSICAL ANALYSIS: ALL ANOVA AND MANOVA RESULTS

Table AO1. ANOVA Results: Systolic and Diastolic blood pressure

Source	DF	F-ratio	p-value
Multivariate			
Time	2,29	0.165	0.848
Time * Group	2,29	0.451	0.641
Time Pre * Group	2,29	0.880	0.426
Time Post * Group	2,29	2.662	0.087*
Intervention group	2,29	0.152	0.860
Control group	2,29	0.415	0.664
Systolic			
Time	1,30	0.338	0.565
Group	1,30	1.091	0.305
Time* group	1,30	0.332	0.569
Intervention group * time	Mean Diff 0.018	Std Error 4.314	0.997
Control group * time	Mean Diff 3.918	Std Error 5.215	0.458
Time pre * group	1,30 Mean Diff 7.247	1.320 Std Error 6.308	0.260
Time post * group	1,30 Mean Diff 3.346	0.324 Std Error 5.878	0.573
Diastolic			
Time	1,30	0.043	0.837
Group	1,30	4.075	0.053*
Time* group	1,30	0.187	0.669
Intervention group * time	Mean Diff 1.316	Std Error 2.620	0.610
Control group * time	Mean Diff -0.462	Std Error 3.167	0.885

Time pre * group	1,30 Mean Diff 5.680	1.766 Std Error 4.274	0.194
Time post * group	1,30 Mean Diff 7.457	4.897 Std Error 3.370	0.035**

*Significant at p<0.05** (trends towards significance at p<0.1*)*

Table AO.2. ANOVA Results: Weight, Waist to Hip Ratio, BMI

Source	**DF**	**F-ratio**	**p-value**
Multivariate			
Time	3,25	1.497	0.240
Group	3,25	1.728	0.187
Time * Group	3,25	0.718	0.550
Time Pre * Group	3,25	2.003	0.139
Time Post * Group	3,25	1.367	0.276
Intervention group	3,25	1.612	0.212
Control group	3,25	0.637	0.598
Weight (kg)			
Time	1,27	0.999	0.326
Group	1,27	0.250	0.621
Time* group	1,27	0.332	0.569
Intervention group * time	Mean Diff 0.053	Std Error 0.831	0.949
Control group * time	Mean Diff 1.143	Std Error 0.861	0.195
Time pre * group	1,27 Mean Diff 2.489	0.168 Std Error 6.070	0.685
Time post * group	1,27 Mean Diff 3.579	0.341 Std Error 6.130	0.564
Waist to Hip Ratio			
Time	1,27	1.475	0.235

Group	1,27	0.267	0.610
Time* group	1,27	1.278	0.268
Intervention group * time	Mean Diff 0.020	Std Error 0.012	0.103
Control group * time	Mean Diff 0.001	Std Error 0.012	0.954
Time pre * group	1,27 Mean Diff 0.024	0.652 Std Error 0.030	0.426
Time post * group	1,27 Mean Diff 0.005	0.028 Std Error 0.029	0.867
BMI (kg/m^2)			
Time	1,27	0.100	0.754
Group	1,27	0.404	0.530
Time* group	1,27	0.852	0.364
Intervention group * time	Mean Diff 0.147	Std Error 0.336	0.666
Control group * time	Mean Diff 0.300	Std Error 0.348	0.396
Time pre * group	1,27 Mean Diff 1.118	0.587 Std Error 1.458	0.450
Time post * group	1,27 Mean Diff 0.671	0.231 Std Error 1.395	0.635

*Significant at $p<0.05$** (trends towards significance at $p<0.1$*)*

Table AO.3. ANOVA Results: Sit-Up, Push-Up, Grip Strength

Source	DF	F-ratio	p-value
Multivariate			
Time	3,29	2.036	0.440
Group	3,29	.928	0.131
Time * Group	3,29	1.073	0.376
Time Pre * Group	3,29	1.314	0.289
Time Post * Group	3,29	1.144	0.348
Intervention group	3,29	2.878	0.053*
Control group	3,29	0.580	0.633
Sit-Up			
Time	1,31	1.999	0.167
Group	1,31	1.224	0.277
Time* group	1,31	3.363	0.076*
Intervention group * time	Mean Diff 6.079	Std Error 2.438	0.018**
Control group * time	Mean Diff 0.786	Std Error 2.840	0.784
Time pre * group	1,31 Mean Diff 7.650	2.872 Std Error 4.514	0.100
Time post * group	1,31 Mean Diff 0.786	0.039 Std Error 3.961	0.844
Push-Up			
Time	1,31	1.495	0.231
Group	1,31	2.230	0.145
Time* group	1,31	0.364	0.551
Intervention group * time	Mean Diff 2.105	Std Error 1.502	0.171
Control group * time	Mean Diff 0.714	Std Error 1.750	0.686

Time pre * group	1,31 Mean Diff 6.880	3.005 Std Error 3.969	0.093*
Time post * group	1,31 Mean Diff 5.489	1.420 Std Error 4.606	0.242
Grip Strength			
Time	1,31	4.185	0.049**
Group	1,31	1.900	0.178
Time* group	1,31	0.201	0.657
Intervention group * time	Mean Diff 4.237	Std Error 2.213	0.065*
Control group * time	Mean Diff 2.714	Std Error 2.578	0.301
Time pre * group	1,31 Mean Diff 13.175	1.891 Std Error 9.582	0.179
Time post * group	1,31 Mean Diff 11.652	1.782 Std Error 8.729	0.192

*Significant at p<0.05** (trends towards significance at p<0.1*)*

Table AO.4. ANOVA Results: FVC% predicted and Fev1% predicted

Source	DF	F-ratio	p-value
Multivariate			
Time	2,28	4.241	0.025**
Group	2,28	0.840	0.442
Time * Group	2,28	0.679	0.515
Time Pre * Group	2,28	0.712	0.499
Time Post * Group	2,28	0.505	0.609
Intervention group	2,28	4.745	0.017**
Control group	2,28	0.809	0.455
FVC% predicted			

Time	1,29	7.031	0.013**
Group	1,29	0.016	0.902
Time* group	1,29	1.406	0.245
Intervention group * time	Mean Diff 0.096	Std Error 0.033	0.006**
Control group * time	Mean Diff 0.037	Std Error 0.038	0.344
Time pre * group	1,29 Mean Diff 0.024	0.276 Std Error 0.045	0.604
Time post * group	1,29 Mean Diff 0.036	0.341 Std Error 0.061	0.564
Fev1% predicted			
Time	1,29	2.144	0.154
Group	1,29	0.385	0.540
Time* group	1,29	0.967	0.334
Intervention group * time	Mean Diff 0.075	Std Error 0.040	0.069*
Control group * time	Mean Diff 0.015	Std Error 0.047	0.775
Time pre * group	1,29 Mean Diff 0.006	0.014 Std Error 0.052	0.907
Time post * group	1,29 Mean Diff 0.067	0.730 Std Error 0.078	0.400

*Significant at p<0.05** (trends towards significance at p<0.1*)*

Table AO.5. ANOVA Results: Metabolic Equivalent (METS)

Source	DF	F	probability
Time	1,14	0.150	0.705
Group	1,14	1.149	0.302
Time * Group	1,14	2.010	0.178
Time Pre * Group	1,14	2.535	0.134

	Mean Diff 1.651	Std Error *1.037*	
Time Post * Group	1,14 Mean Diff 0.079	0.007 Std Error 0.918	0.932
Intervention group	1,14 Mean Diff 1.000	1.861 Std Error 0.733	0.194
Control group	1,14 Mean Diff 0.571	0.473 Std Error 0.831	0.503

*Significant at p<0.05** (trends towards significance at p<0.1*)*

Table AO.6. ANOVA Results: Resting Heart Rate

Source	**DF**	**F**	**probability**
Time	1,26	2.172	0.153
Group	1,26	1.435	0.242
Time * Group	1,26	1.801	0.191
Time Pre * Group	1,26 Mean Diff 8,167	3.101 Std Error 4.637	0.090*
Time Post * Group	1,26 Mean Diff 1.375	0.082 Std Error 4.799	0.777
Intervention group	1,26 Mean Diff 7.125	4.625 Std Error 3.313	0.041**
Control group	1,26 Mean Diff 0.333	0.008 Std Error 3.826	0.931

*Significant at p<0.05** (trends towards significance at p<0.1*)*

Table AO.7. ANOVA Results: Body Composition

Source	**DF**	**F**	**probability**
Time	1,34	1.784	0.191

Group	1,34	1.146	0.292
Time * Group	1,34	0.393	0.535
Time Pre * Group	1,34 Mean Diff 4.279	1.297 Std Error 3.758	0.263
Time Post * Group	1,34 Mean Diff 3.302	0.896 Std Error 3.487	0.350
Intervention group	1,34 Mean Diff 0.553	0.266 Std Error 1.071	0.609
Control group	1,34 Mean Diff 1.529	1.823 Std Error 1.133	0.186

Table AO.8. ANOVA Results: Sit and Reach

Source	**DF**	**F**	**probability**
Time	1,25	0.113	0.740
Group	1,25	0.837	0.369
Time * Group	1,25	0.093	0.763
Time Pre * Group	1,25 Mean Diff 2.963	0.406 Std Error 4.649	0.530
Time Post * Group	1,25 Mean Diff 4.173	1.042 Std Error 4.089	0.317
Intervention group	1,25 Mean Diff 0.062	0.001 Std Error 2.537	0.981
Control group	1,25 Mean Diff 1.273	0.173 Std Error 3.060	0.681

*Significant at p<0.05** (trends towards significance at p<0.1*)*

Table AO.9. Physical Assessments: Summmary of All Significant ANOVA and MANOVA Results

Variable	Interaction (time)	F	Std Error	Df	Probability
Diastolic	Time 2* group	4.897	3.370	1(30)	0.035**
Sit Up	Intervention (1-2)	Mean Diff 6.079	2.438		0.018*
Grip Strength	Time	4.185		1,31	0.049**
FVC% predicted and Fev1% predicted	Time	4.241		2,28	0.025**
FVC% predicted and Fev1% predicted	Intervention (1-2)	4.745		2,28	0.017**
FVC % predicted	Time	7.031		1,29	0.013**
	Intervention (1-2)	Mean Diff 0.096	0.033		0.006**
Resting Heart Rate	Intervention (1-2)	4.625 Mean Diff 7.125	3.313	1,26	0.041**

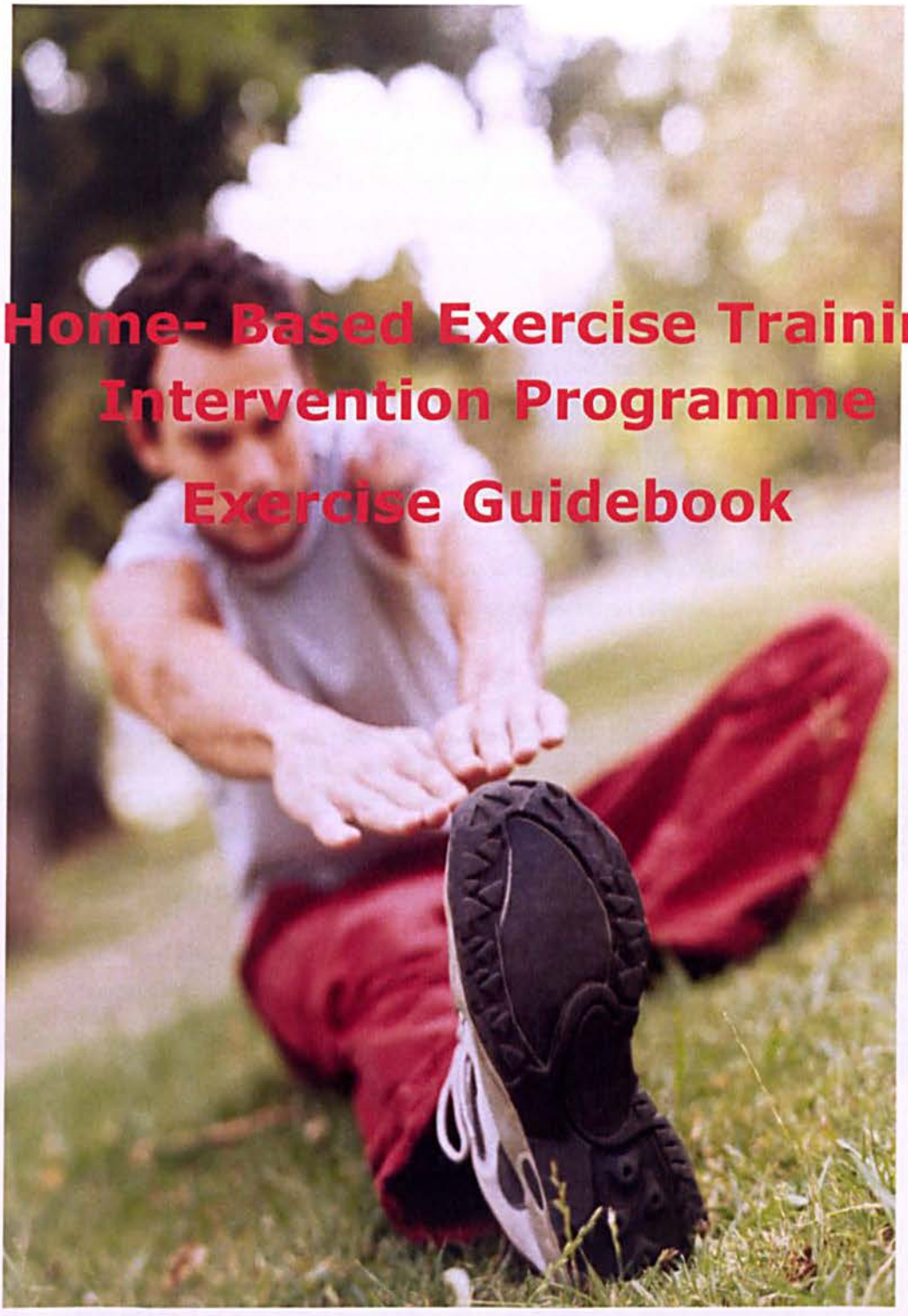
APPENDIX.P. FOCUS GROUP: PARTICIPANT DEMOGRAPHIC DATA

Table AP.1. Focus Group: Participant demographic data are presented for each subject, n=6

ID	Age	Sex	Lymphoma	Time since End Treatment	Marital Status	Education Completed	Employment	Smoker
1	45	Female	NHL (aggressive)	94 days	married	post-graduate	part-time	non
2	70	Male	NHL (aggressive)	35 days	married	secondary	retired	non
3	68	Female	NHL (indolent)	21 days	married	secondary	retired	non
4	42	Male	HL	49 days	married	some university/ college	sick leave	smoker
5	66	Male	NHL (aggressive)	11 days	married	university/ college	retired	non
6	40	Female	HL	17days	married	university/ college	full time	smoker

HL: Hodgkin Lymphoma

NHL: Non-Hodgkin Lymphoma



Home- Based Exercise Training Intervention Programme

Exercise Guidebook

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Home Exercises

1a. Four Point Balance

a. Begin by placing your hands on the physioball and your feet on the floor.
b. Roll the physioball forward and place you knees on the physioball.
c. Use your four points for balance (left and right hand and left and right knees)
d. Focus on a point on the floor out in front of you to help steady the physioball.
e. Hold the position for a desired amount of time, relax, and then repeat.

1b. Two Point Balance

a. Begin by placing your hands on the physioball and your feet on the floor.
b. Roll the physioball forward and place your knees on the physioball.
c. Start with all four points for balance (left and right hand and left and right knees)
d. When you feel comfortable, remove your hands from the physioball and align your knees, hips and shoulders.
e. Focus on a point on the floor out in front of you to help steady the physioball.
f. Hold the position for a desired amount of time, relax, and then repeat.

2a. Wall Squat:

Level 1: With your back against a wall, and your feet about 2 feet away from the wall, slide down until your knees are at a 90 degree angle. Make sure your knees are directly above your heels. Hold the position as long as you can (ideally aim for 30 seconds).

2b. Wall Squats (with ball)

Start with your feet shoulder width apart and your feet out in front of your hips.
b. Place the physioball behind your middle back against the wall.
c. Slowly lower yourself down into a 90 ° squat, while keeping your feet flat on the floor.
d. Do not allow your knees to go past your feet

2c. Single Leg Wall Squats

Start with your feet shoulder width apart and your feet out in front of your hips.
b. Place the physioball behind your middle back against the wall.
c. Lift one leg and slowly lower yourself down into a squat position while keeping your foot flat on the floor.
d. Keep your opposite foot off the floor.

Level 2: same as level 1, but without support. Transfer your weight into your heels and slowly lower your buttocks downwards, to a position whereby your thighs are parallel to the floor, keeping your back straight. Concentrate on keeping your back straight and head up, focusing on preventing your knees from extending over your toes. Exhale as you return

back up from your lowered position, keeping your feet firmly on the floor throughout the exercise.

3. Lunges: (partial or full; stationary or walking; walk holding railing for assistance or independently), Stand tall with your feet shoulder width apart, with your hands by your sides, or placed out horizontally to aid your balance. Lunge forward with one leg, so that your thigh is parallel to the floor, with your knee over your heels, keeping your back straight and head up throughout the movement. Your rear heel should naturally rise off the floor, with that knee resting close to the floor when you extend forward.

Keeping your abdominal muscle contracted, push down on your front foot in order to push yourself back to your starting position, whereby you can then repeat the exercise, working either the same leg (harder) or alternate your legs.

3b. Lunges (with band)

Stand with right leg forward, left leg back and band positioned under right leg. Keeping tension on the band by bending elbows, lower into a lunge until both knees are at 90 degrees, front knee behind the toe. Return to start and repeat.

4a. Triceps Extensions

Hold the band in both hands at shoulder level with right arm bent so that it's in front of the chest, left arm straight out. Keeping the left arm straight to hold tension on the hand, contract the triceps to straighten the right arm. Return to start and repeat before switching sides.

4b. Tricep Dips (option)

Level 1: Place both hands either side of your hips on a **secure** bench or chair, keeping your fingers pointed forward to reduce the stress on your wrist joint. Extend your feet out to your front, the further your feet are away from the bench, the harder the exercise, however always aim to keep a slight bend in the leg to reduce the stress on the knee joint.Focus throughout the movement to extend your elbows back behind you, lower your buttocks downwards by bending the arms, rather than taking your buttocks towards your feet. Bend the arm to help isolate the tricep muscle, keeping your buttocks close to the bench throughout the movement.

4c. Tricep Band Kickback

Attach band to sturdy object in front of you in a split stance, bent at the waist with abs in. Hold handle in one hand, elbow bent. Straighten the arm, contracting the back of the arm.

4d. One-Armed Lateral Raise

Sit (or stand) with one end of tube under foot and the other end in one hand. Keeping elbow slightly bent and fixed, lift the arm out to side, to *shoulder level.*

4e. Cross-Body Bicep

Place left foot on band and hold the handle in right hand. Begin the move with palm facing in and bend the elbow, curling hand up towards the shoulder, going across the body.

5. Push-Ups

Level 1: wall push-up: Stand straight with your feet about 2-4 feet from a wall. Now lean forwards and place your hands on the wall with bent elbows. Then push your body back to starting position using your hands.

Level 2: box push-up: Place your hands underneath your shoulders with fingers facing forward. Your knees and feet should be resting on the floor- aim to make a box shape with your arms, trunk, thighs and the floor. Bend at your elbows, lowering your chest down, no lower than 2 inches from the floor. Aim to make a right angle with your arms. Keep a straight line through your spine (flat back), and avoid forcing your bottom into the air, and arching of the back.

Level 3: from knees (modified push-up): Same as full push-up, but from the knees instead of toes.

Level 4: full push- up: Keep a tight core throughout the entire push up. Slowly lower body towards floor, keeping body in one line (flat) and not bending. Inhale as you slowly bend your elbows and lower yourself until your elbows are at a 90 degree angle. Exhale as you begin pushing back up to the start position. Don't lock out the elbows; keep them slightly bent.

6a. Back Raises

Level 1: simple lift

Keep your feet on the floor when doing this exercise to avoid excessive pressure on the lower back.
Smoothly lift your head and shoulders only 4 to 6 inches off the floor, holding in the upper phase for 2 - 3 seconds prior to slowly returning back down to repeat.

Level 2: lift and twist

Place your hands under your forehead, palms facing down, with your elbows out wide to your sides.
Keeping one elbow on the floor, smoothly raise your upper body and one elbow off the floor, aiming to raise the lifted elbow 10 - 14 inches off the floor.
Focus on using the muscles of your lower back to initiate the lift, then those of your stomach to aid the rotational movement. Hold in the upper phase for 2 - 3 seconds prior to slowly returning back down to repeat.

6b. Supermans Lie on your stomach with your arms and legs stretched out. Raise your arms and legs off the ground a few inches, hold a few seconds, and then lower. Alternate arms and legs as an option.

APPENDIX R. FOCUS GROUP TOPIC GUIDE

Topic guide for Focus group of Lymphoma patients

Welcome and thank them for attending the focus group with the project. Introduce people running the discussion group (myself and Rachel).

You have all been doing the exercise programme for the last few months. Whilst Lisa has been doing the study she has realised that you have opinions about the study and how you have been affected by the physical exercise programme which may not have been captured by the questionnaires you complete. We are aware that you don't have much time to talk in the gym have some valuable opinions about your experiences in this study, and this is why we decided to organise this discussion group.

Confidentiality. As we mentioned in the participant information sheet this discussion will be recorded but any information we use will be made anonymous. Is this all ok with everyone?

As previously mentioned this should take no longer than one hour. There are no right or wrong answers, any feedback is useful for us. The aim of this group is to have a discussion together.

All that I want to say about recording the discussion today is that can we try not to have people talking at the same time as it is difficult for the recording? I will try to get to allow every one to say exactly what they would like but if I do miss someone please remind me?

Experiences of the study

How did the exercise programme affect you – in general?

How has the programme affected your ability/motivation/interest in activity?

We want to know if you are still doing any activity

What aspects of the exercise programme have you enjoyed?

What aspects of the exercise programme have you found difficult?

How has the programme affected you in your every day life?

Commitment to the programme

Why do you keep attending?

(Altruism/makes me feel better/something to do/enjoyment, enjoyed meeting fellow sufferers)

How have you found the difference between attending weekly and monthly?

The future

Do you intend to keep doing the exercises after the study had finished?

Do you have any suggestions for changing/running a similar study?