Physiotherapy led Palliative Exercise Programme for people with advanced Parkinson's Disease (PEP-PD): a feasibility study

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Candidate Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree Masters of Science by Research, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed

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Date 06/10/15

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SUMMARY

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative condition with an estimated world prevalence of 5 million. People with PD in Ireland cannot consistently avail themselves of specialist palliative care services. A recent cross sectional study by Saleem et al, 2013 examined the palliative care needs of people with PD [1]. The study reported problems with mobility as one of the main symptoms for people with PD.

Aim

The main aim of this thesis was to examine the feasibility of engaging people with advanced Parkinson's disease (Hoehn and Yahr stage 3 to 4) in a group exercise programme in a hospice setting. The secondary aim was to examine if this exercise programme impacted on measures of impairment, activity limitation and participation restrictions in people with advanced PD.

Methods

Two systematic reviews with meta-analysis were completed to examine the totality of evidence for aerobic and progressive resistance exercise for people with PD. The review output informed the design of a feasibility study comprising six weeks of a lower limb, progressive resistance training programme; once weekly supervised in a hospice out-patient setting and twice weekly unsupervised at home. Primary outcome measure was the SMWT. Secondary outcome measures included the p1-RM, MDS-UPDRS and PDQ-39. Assessments took place at pre, post and six month follow up points. Semi-structured interviews were also outlined and took place at the post assessment.

Results

A significant improvement was found in muscle strength ($p < 0.05$) of the lower limbs and non-significant improvement in the SMWT, MDS-UPDRS and PDQ-39. Qualitative interview results reported participants experiencing a perceived improvement in walking capacity and identified and outlined four main themes that impact exercise in people with PD. Further

research is needed to examine the impact of progressive resistance training for advanced stage people with PD in a hospice setting.

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ABBREVIATIONS

AIIHPC	All Ireland Institute of Hospice and Palliative Care
ACSM	American College of Sports Medicine
BDI	Beck Depression Inventory
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DBS	Deep Brain Stimulation
FEM	Fixed Effects Method
FITT	Frequency, Intensity, Time and Type
HR	Heart Rate
HRR	Heart Rate Reserve
HSE	Health Service Executive
H&Y	Hoehn and Yahr
ICC	Intraclass Correlation Coefficient
ICF	International Classification of Functioning, Disability and Health
IHF	Irish Hospice Foundation
MD	Mean Difference
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
NAI	Neurological Alliance of Ireland
NICE	National Institute for Health and Clinical Excellence
Nm	Newton meters
PAR-Q	Physical Activity Readiness Questionnaire
PASE	Physical Activity Scale for the Elderly
PDQL	Parkinson's Disease Quality of Life questionnaire
PD	Parkinson's Disease
PDQ-39	Parkinson's Disease Questionnaire – 39

PEP-PD	Physiotherapy led palliative Exercise Programme for people with advanced Parkinson's Disease
PIMS	Parkinson's Impact Scale
PLQ	Parkinson LebensQualität
PRT	Progressive Resistance Training
PwP	People with PD
p1-RM	Predicted one repetition maximum
RCT	Randomised Controlled Trial
REM	Random Effects Method
SD	Standard Deviation
SMWT	Six minute walk test
SMD	Standardised Mean Difference
UPDRS	Unified Parkinson's Disease Rating Scale
UPDRS – III	Unified Parkinson's Disease Rating Scale Motor subscale

GLOSSARY OF TERMS

Hoehn and Yahr	A five point numerical staging system for disease severity in Parkinson's disease
Wearing off	A term used to describe people with who suffer from regular intervals, ranging from minutes to hours, where their symptoms of PD are not controlled by their medication and is known as an 'off' period or 'wearing off'
VO_2peak	The highest amount of oxygen that an individual utilizes during an intense or maximal exercise test. It is measured as millilitres of oxygen used in one minute per kilogram of body weight.

Introduction

Purpose of this thesis

The main question of this thesis was whether it is feasible to engage people with advanced Parkinson's disease (PD) in a weekly group exercise programme at a hospice out-patient setting. The secondary question is to discover if this strength training programme impacts on impairment, activity limitation and participation restrictions in people with advanced PD. In this study it was decided that advanced stage people with PD would be defined as stage 3 to 5 Hoehn and Yahr (H&Y), according to a cross sectional study looking at palliative care need for people with PD [1].

The objectives of this thesis are therefore:

- To examine the totality of evidence from published literature (systematic review) of potential exercises interventions for patients with advanced stage PD
- To design an appropriate exercise intervention (PEP-PD) for advanced stage PD using the output from the above systematic review
- To evaluate whether PEP-PD is a feasible intervention for people with advanced stage PD through analysis of the impact on the clinical features of PD, specifically on mobility and secondary outcomes of impairment, activity limitation and participation restrictions.

- To evaluate the impact of PEP-PD on people with advanced PD in a smaller nested qualitative evaluation (semi-structured interviews)

Background of this thesis

Parkinson's disease is the second most common neurodegenerative condition with an estimated world prevalence of 5 million [2]. The incidence and prevalence is expected to rise due to longer life spans causing an increase in elderly populations [3]. An expert review of the pathology, aetiology and diagnosis of PD, by MacPhee and Stewart, 2012, found that the incidence rate of people with PD in western countries ranges in reporting from 8.6 to 19 per 100,000 populations.

The term Parkinson's disease can cover a variety of conditions such as: vascular parkinsonism, drug induced parkinsonism, multiple system atrophy and progressive supranuclear palsy. This thesis is concerned with idiopathic Parkinson's disease which will be referred to as Parkinson's disease. Parkinson's disease is primarily described as a condition of the basal ganglia. The dorsal basal ganglia are composed of three nuclei at the base of the cerebral cortex; the caudate, putamen and globus pallidus. The substantia nigra is one of two brain stem nuclei included in the basal ganglia because of the functional relationship between forebrain nuclei. The basal ganglia are involved in motor control mainly as well as motor learning, executive functioning, behavior and emotions [4].

Parkinson's disease is described as idiopathic due to the ongoing attempts to uncover the aetiology at work. Parkinson's is defined most frequently as a disease of the basal ganglia causing the loss of dopaminergic neurons in the substantia nigra, which reduces the level of dopamine in the brain, causing parkinsonian symptoms [5]. The clinical manifestations of PD include bradykinesia, tremor at rest, rigidity and postural instability; however many other motor and non-motor symptoms can occur.

An expert review by Schapira and Jenner, 2011 examined the current evidence and reports that PD is likely as a result of both genetic factors and part of the aging process [6]. Oxidative stress, mitochondrial dysfunction, Lewy body deposits and reactive microgliosis are all mentioned in the article as potential areas of biochemical abnormalities leading to Parkinson's.

The pathology of Parkinson's disease has been most effectively described by Braak et al, 2003 in brains obtained at autopsy; this six point staging system is based on the position of lesions in the brain progressing from the medulla oblongata through to the neocortex [7]. This staging is not possible in living people with PD as of yet but offers an insight into the mechanism and pathology of PD. A clinical staging system which aims to monitor the motor and balance impairments of PD is the H&Y staging system of Parkinson's disease H&Y uses five stages for rating the disease with one being the least symptomatic and five being the most symptomatic. The H&Y staging system has been used extensively in clinical practice and research methods and is recommended as a valid method to describe PD disease stage

and is useful for inclusion and exclusion criteria for research methods [8]. The scale has been outlined in Table 1 below.

**Table 1 - Outline of the Hoehn and Yahr five point staging of Parkinson's disease*

Stage	Description
1	Unilateral involvement only usually with minimal or no functional disability
2	Bilateral or midline involvement without impairment of balance
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
4	Severely disabling disease; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided

*This table is a partial reproduction of 'Table 1. *Comparison between the original and modified Hoehn and Yahr*' scale by Goetz et al, 2004 [8]

People with PD in Ireland can currently not consistently avail of specialist palliative care services within Ireland. A recent jointly commissioned report by the Irish Hospice Foundation (IHF) and the Neurological Alliance of Ireland (NAI) has highlighted the role of palliative care services for neurological conditions [9]. The report by Weafer, 2004 involved a literature review, to examine the potential challenges and issues to introducing a palliative care approach for advancing neurological conditions in Ireland and subsequent qualitative interviews with NAI member organisations. The report recommended that a multi-disciplinary approach be used and that funding be provided to clinicians with expertise in neurological conditions to further develop palliative care for people with advancing neurological conditions. This thesis was funded through a clinical research fellowship from the All Ireland Institute of Hospice and Palliative Care (AIIHPC). The aim of these fellowships is to develop research capacity in palliative and end of life care.

A recent cross sectional study by Saleem et al, 2013 examined the palliative care needs of people with PD using the Palliative Outcome Scale [1]. The study was conducted with 82 people with PD at stage 3 to 5 on the H&Y scale. Results indicated that there was a high burden of symptoms for people with PD and that this increased with a higher disease severity. On analysis over 80% of participants reported four main symptoms; pain, fatigue, day time somnolence and problems with mobility. Owing to the authors aim to engage people with PD in an exercise programme it was decided that the symptom of 'problems with walking' would be examined in this thesis. The author used the H&Y staging examined here of stage 3 to 5 as the main cohort of interest for this thesis. As such a thesis was described by the author to examine the impact of an exercise intervention for people with PD stage 3 to 5 H&Y on the symptom of 'problems with mobility'.

Outline of this thesis

This thesis consists of five chapters. Chapter 1 outlines the methodology and results of a systematic review examining the evidence for aerobic exercise in people with PD. This thesis initially looked at aerobic exercise and found that this was not a feasible intervention for this population group and subsequently examined the evidence for progressive resistance training in Chapter 2. Chapter 2 is a systematic review with meta-analysis updating the evidence of a previous review by Lima et al, 2013 [10] looking at progressive resistance training for people with PD. Chapter 3 describes the methodology of both the quantitative and qualitative sections of this thesis. Chapter 4 reports the results of the quantitative outcomes and discusses the results in the context of the current literature. Chapter 5 outlines the results of the qualitative semi-structured interviews and discuss these finding

with reference to the existing body of evidence. Finally, the conclusion of this thesis summarises the main findings and the dissemination of the results to date as well as any planned dissemination in the future.

Chapter 1 Aerobic Review

1.1 Introduction

The management of the symptoms of Parkinson's disease is twofold, using both pharmacological and non-pharmacological treatments. Pharmacological treatment is the primary medical intervention for the management of Parkinson's disease symptoms. The National Institute for Health and Clinical Excellence (NICE) guidelines recommend that treatment of PD usually starts with a combination of Levodopa and a decarboxylase inhibitor. These pharmacological interventions serve to slow the onset of disease progression and limit the clinical manifestations of the condition. However, side effects include impulse control disorders, daytime somnolence, peripheral edema, nausea and hallucinations [11, 12].

Furthermore, an effect known as 'wearing off' is seen in the more advanced stages of the condition. This is where people with PD suffer from regular intervals, ranging from minutes to hours, where their symptoms of PD are not controlled by their medication and is known as an 'off' period. The term 'on' refers to when a person's medication is working optimally. In the context of research, this is an important concept as the analysis of disease severity is completed by examining the clinical motor impairments of PD. As such, most studies generally specify whether a person is in the 'off' or 'on' phase of medication management. Subsequent assessments should examine participants in a similar manner to ensure

consistency in motor impairments (i.e if at a pre-assessment time point participants are assessed ‘on’ medication, they should be assessed ‘on’ medication for subsequent assessment points).

One of the most effective adjunctive therapies is deep brain stimulation (DBS) which demonstrates a significant improvement in levels of impairment as measured by the Unified Parkinson’s Disease Rating Scale (UPDRS) scores post intervention. A collective review by Chan et al, 2009 of 100 DBS inserted electrodes in 55 patients with PD at a Hong Kong hospital found that DBS was both an effective medical option for people with PD but also a complication-prone surgical procedure [13]. The review categorises three types of complications: operative, hardware and stimulation based. The review found two main operative complications. The first complication was a single subject - of the 55 subjects reviewed - experiencing an intercranial haemorrhage, which resulted in hemiparesis and long term disability. Malposition of the electrodes was found to have occurred in two of the subjects and resulted in intolerable side effects and eventual surgical revision. Hardware related complications occurred in four of the subjects, which included electrode fracture, electrode migration and infection. Three of the participants suffered from stimulation based complications, specifically an acute manic episode within four weeks of the operation. The Health Service Executive (HSE) currently does not offer this intervention and most Irish patients are treated in the United Kingdom, the HSE is an organization of over 100,000 people who organise and manage the public health services of Ireland. These improvements in levels of impairment are reported to be as high as 40%, however DBS remains a last choice for many people with Parkinson’s disease for a variety of reasons including the risks

of brain surgery, as outlined above, such as brain hemorrhaging, infection and incision scarring [14-17].

In terms of non-pharmacological management, exercise has long been used as a treatment technique due to its inherent benefits for cardiovascular fitness [18, 19]. It has also been shown that exercise is not only effective in enhancing physical markers in people with PD, but that it can potentially help to normalize corticomotor excitability[20]. This improvement in motor performance and potential disease modification effects has led to an increase in the number of studies looking at exercise in PD [21-32].

In terms of examining exercise interventions for people with advanced PD, a recent cross sectional survey, as mentioned in the introduction of this thesis, examined eighty two people with PD (H&Y 3 to 5) [1]. 'Problems with mobility' was one of the four main symptoms identified in the study and it is the basis of this thesis to examine the impact of exercise aimed at improving symptoms of poor mobility in people with advanced stage PD. Aerobic exercise has been shown in a previous randomised controlled cross-over study to improve mobility (six minute walk test, p=0.01) in participants with stage 2 to 3 H&Y, but there is a dearth of information for the later stages of PD (H&Y 4 to 5) [33]. To this end, an overview of the totality of evidence relating to aerobic exercise interventions for people with PD was warranted. Therefore the aim of this systematic review with meta-analysis is to determine the effectiveness of aerobic exercise therapy when compared to conventional therapy on outcomes of aerobic capacity in people with PD.

1.2 Methods

1.2.1 PROSPERO pre-registration

A draft protocol for the review is registered on a database of systematic reviews. PROSPERO is an international database of prospectively registered systematic reviews in health and social care. The aim of PROSPERO is to reduce the repetition of projects and ensure areas of research are not duplicated. It is also used as a review tool to investigate any changes to a proposed review and the final reported protocol. A draft of the planned literature review was submitted and accepted by PROSPERO under the title 'Interventions for improving aerobic exercise capacity in people with Parkinson's disease (PD)'. The draft protocol outlined in the PROSPERO submission (registration number CRD42014007564) is available on the PROSPERO website (http://www.crd.york.ac.uk/PROSPERO/) and was adhered to throughout the review process (Appendix I).

1.2.2 Study design

A systematic review with meta-analysis was undertaken primarily to examine the impact of aerobic interventions on aerobic capacity (VO_2max, VO_2peak, walking economy) and secondary measures of impairment, activity limitation and participation restriction in people with PD. The PRISMA statement was followed to ensure the appropriate conduct and reporting of this systematic review and meta-analysis [34]. This review included only (cluster) randomised controlled and quasi-randomised controlled trials as they are the reference standard of research methodology for the assessment of a healthcare intervention [35].

1.2.3 Definitions and inclusion criteria

Studies were considered eligible for inclusion if: the population of interest was people with Parkinson's disease of any stage of disease; the intervention included a training component that aimed to increase aerobic capacity in people with Parkinson's disease (see section 1.2.5 for extended definition); the comparison group received either no intervention or a variety of non-aerobic interventions. The types of interventions included are described in detail in Table 1.3. The primary outcome measure of interest was any measure of aerobic capacity, however the review did not exclude studies that had no measure of aerobic capacity to allow for a comprehensive review of the impact of aerobic interventions on people with PD. Secondary outcomes at the level of impairment, activity limitation and participation restriction were also included. The below Table 1.1 outlines the International Classification of Functioning, Disability and Health (ICF) domain, definition, validity and reliability of the outcome measures included in meta-analysis.

Table 1.1 - Validity and reliability of outcome measures included in aerobic studies in people with PD

Measure	ICF domain	Definition	Validity	Reliability
VO_2peak	Activity limitation	VO_2peak refers to the highest amount of oxygen that an individual utilizes during an intense or maximal exercise test. It is measured as millilitres of oxygen used in one minute per kilogram of body weight.	No significant difference in VO_2peak ($p > 0.05$) [36]	ICC of 0.90 [37] (when expressed as ml/kg/min)
SMWT	Activity limitation	The six minute walk test is a pragmatic test of overall mobility and functioning in older adults. It consists of the distance in meters a subject can cover in six minutes on a 25 meter track.	Not reported for PwP	ICC of 0.90 [38]
Gait velocity	Activity limitation	Comfortable walking or self-selected velocity is an accurate measure of gait function in PwP, it is measured as meters per second usually over a ten meter track.	Convergent validity established as ($p<0.01$) [39]	ICC of 0.98 [39]
Cadence	Activity limitation	This is a measure of steps per minute usually calculated over a ten meter track.	Not reported for PwP	Not reported
Double support time	Activity limitation	Is the amount of time in a gait cycle that both limbs are in contact with the floor at the same time, this usually reduces as gait speed increases. Reported below as a percentage of the gait cycle.	Not reported for PwP	Not reported
UPDRS total	Impairment	The UPDRS has four components Part I, Nonmotor Experiences of Daily Living; Part II, Motor Experiences of Daily Living; Part III, Motor Examination; Part IV, Motor Complications. The higher the disease severity the higher the score for UPDRS total	Convergent validity established as $p<0.01$ [40]	ICC of 0.92 [41]
UPDRS III	Impairment	Part III, Motor Examination, of the UPDRS. A higher score is indicative of a higher level of impairment from the motor complications of PD	Relative validity = 37.43 [42]	ICC of 0.90 [41]
PDQ-39	Participation restriction	The health related quality of life tool comprises 39 items representing eight domains (scales).	Significant correlation with H&Y $p<0.01$ [43]	ICC of <0.70 [44]
BDI	Participation restriction	Beck depression inventory is a frequently used generic self-reported depression scale. It consists of 21 items measuring the characteristics attitudes and symptoms of depression.	Correlations ranged from (0.26-0.71) [45]	ICC of 0.89 [45]

VO_2peak – Peak oxygen consumption, SMWT – Six Minute Walk Test, UPDRS – III – Unified Parkinson's Disease Rating Scale Motor subscale, PDQ-39 – Parkinson's Disease Questionnaire 39, BDI – Beck Depression Inventory, ICC - Intraclass Correlation Coefficient, PwP - people with PD

1.2.4 Aerobic intervention working definition

To be considered eligible for inclusion in the review, an 'aerobic' intervention must have included an explicit measure of intensity and have been progressive in nature. A minimal aerobic exercise definition was included and described below to aid screening of exercise trials, based on a review of the literature by the authors and also the American College of Sports Medicine (ACSM) position stand: Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise [46].

1.2.5 Aerobic exercise definition approved for use in this review

Minimal criteria for inclusion in the review were as follows: the aerobic exercise training intervention must specify intensity as % VO_2peak, % peak work, % max predicated HR or % HRR; frequency must be at least two days a week or equal to 150 minutes a week for at least 6 weeks; exercise interventions must be a minimum of 20 minutes per session; the type of exercise must be regular, purposeful exercise that involves major muscle groups and is continuous and rhythmic in nature.

Where studies did not specify what level of aerobic exercise was achieved, the author attempted to contact the author for clarification. All modalities of intervention were included and then analysed collectively.

1.2.6 Literature search

A literature search was performed using the following databases to identify relevant studies published: The Allied and Complementary Medicine Database (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Science Direct, The Cochrane Library, Database of Abstracts of Reviews of Effects (DARE), Physiotherapy Evidence Database (PEDro), Excerpta Medica dataBASE (EMBASE), Web of science and PubMed. The above databases were searched using an adapted search strategy for each database according to the example boolean search below: 'parkinson's disease' OR 'parkinson's' OR 'pd' AND 'physiotherapy' OR 'physiotherapist' OR 'physical therapy' OR 'rehabilitation' OR 'exercise'. A full example of the search strategy is included in the appendices (Appendix II).

1.2.7 Study identification and selection

The author read the titles of studies identified and excluded any studies that did not meet the inclusion criteria. The remaining articles were marked as either relevant or unsure. The author and a second reviewer independently reviewed the unsure and relevant folders and decided on which were included for full text review. Finally, the selected studies were reviewed in full and excluded based on the inclusion criteria by the author and second reviewer. Any disputes or disagreements were resolved between the two reviewers. The authors included all studies that met the inclusion criteria in the meta-analysis with a descriptive explanation of potential bias coupled with a sensitivity analysis to examine the methodological differences between studies. The Cochrane Handbook outlines this strategy as one of three strategies to analysis when taking into account varying levels of risk of bias as present in this review [47].

1.2.8 Methodological quality

Two reviewers independently assessed the methodological quality of the included studies. The Cochrane risk of bias tool was used to assess methodological quality of the included RCTs, in terms of their internal and external validity; see 'Table 1.2 – Cochrane tool risk of bias definitions' for an explanation of the areas of review undertaken [48]. Internal validity refers to the measure by which a study has answered its question correctly or in a manner that is free from bias, as opposed to external validity which refers to the generalisability of the findings from the study. The Cochrane tool uses several headings such as selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias and there are three possible answers: yes, no or unclear. All sections must be rated as a low risk of bias for an overall low risk rating. Any section not meeting low risk criteria will automatically change the overall score to either a high or unclear risk of bias [48].

Table 1.2 - Cochrane tool risk of bias definitions

Bias types	**Definition**
Selection bias	Inadequate generation of a randomised sequence and inadequate concealment of participant group allocations.
Performance bias	Bias due to the knowledge of intervention and control allocation of participants and study personnel
Detection bias	Outcome measure assessors knowledge of participant group allocation
Attrition bias	Bias due to the volume of participant attrition or clear underreporting of outcomes of the study under review
Reporting bias	Selective reporting of outcomes of a study as a bias to reviewers
Other bias	Bias due to any concern not address above

1.2.9 Data extraction

Information extracted from each study included the population of interest characteristics such as number of participants, mean age, disease duration, disease severity (Hoehn and

Yahr) and medication details on testing and assessment. Intervention details included the frequency, intensity, time and type of exercise interventions for all arms of studies included. The comparison intervention and control subject details were also included in data extraction along with the name, definition and results of all outcome measures used in each study. Additional information was obtained by contacting relevant authors where necessary and 20% of all data extraction was independently verified by the second independent reviewer.

1.2.10 Data synthesis and statistical analysis

Cochrane Review Manager Software was used to conduct statistical analyses to determine the treatment effect. *A priori* it was decided that meta-analysis would be based on the main outcome of aerobic capacity (i.e Vo_2max/ VO_2peak) and secondary measures (where sufficient data was available). Secondary outcome measures were assessed based on the ICF classification, specifically in relation to reporting changes in impairment (e.g. UPDRS – section III, representing the motor element), activity limitation (e.g. gait parameters) and participation (e.g. Parkinson's disease questionnaire- 39).

The mean difference (MD) in outcomes between the intervention and control group post-intervention and at follow-up time points was used as the mode of analysis. The impact of sample size was addressed by estimating a weighting factor for each study, and assigning greater effect weights in studies with larger samples. In studies where the mean was not reported, the median was used as a proxy for the mean and the standard deviation was

calculated by multiplying the inter-quartile range by 0.75 or the range by 0.25 [49]. In instances where the studies used different outcomes to assess the same construct (e.g. quality of life) the standardised mean difference (SMD) with 95% confidence interval (CI) was used. Statistical heterogeneity was assessed using the I^2 statistic. For the purposes of this study, an I^2 statistic of ≤50% was the cut-off point for acceptable heterogeneity and the fixed-effects model was applied below this point [47].

1.3 Results

1.3.1 Study identification

The search strategy returned 12,135 records once duplicates were removed. Initial screening by the primary author resulted in 70 records for review by the two main reviewers. The second stage of screening excluded 39 studies due to the study design and 18 studies due to the intensity described not meeting the criteria outlined in the methods section. The flow of studies through the review is displayed in Figure 1.1. The remaining 13 studies were included for review and meta-analysis.

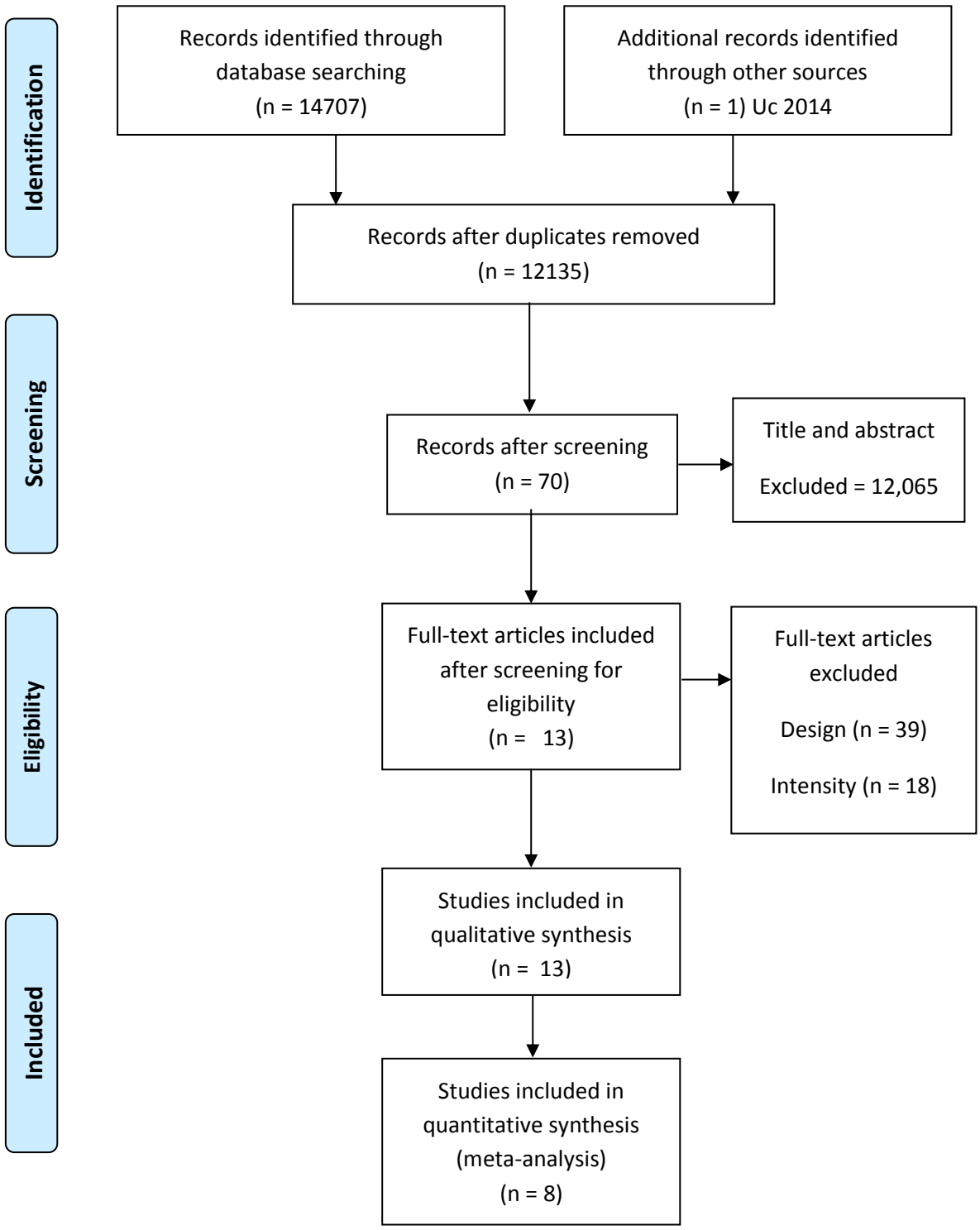

Figure 1.1 - Flow diagram of studies through aerobic systematic review

1.3.2 Study characteristics

A total of 237 participants participated in an aerobic intervention that met the inclusion criteria for the review. These participants had an average age of 63.4 years and mean disease duration of 5.6 years. The majority of studies (n = 7) reported assessing participants while in the 'on' phase of their medication cycle while only two studies reported assessing participants during their medication 'off' phase. Disease severity in the studies included ranged from Hoehn and Yahr stage 1 to 3. The studies' characteristics have been outlined in detail in Table 1.3 below.

Table 1.3 - Characteristics of studies included in the aerobic systematic review

Study	Design	Participants	Aerobic – 1	Aerobic – 2	Control – 1	Control -2	Outcome Measure
Bergen 2002	RCT	N= 4 Age(yr) – 57 (SD-7) H&Y – II DD (yr) – 8 Meds – On	Freq – 3/w x 16 wk Intensity – 60-70% HRR Time – 20-40 min Type – bike+treadmill	N/A	No exercise control	N/A	VO_2peak, Movement Initiation
Bridgewater 1996	RCT	N= 13 Age(yr) – 67.3 (SD-4) H&Y – I-III DD (yr) – 4 (SD-3) Meds – n/r	Freq – 2/w x 12 wk Intensity – 65-85% HRm Time – 20-30 min Type – walking to music	N/A	No exercise control	N/A	Exercise stress test, WRS, NUDS,HAP, Levine-Pilowsky Depression Questionnaire
Burini 2006	RCT (Cross-over)	N= 22 Age(yr) – 65.2 (SD-7) H&Y – II-III DD (yr) – 10.8 (SD-5) Meds – On	Freq – 3/w x 7 wk Intensity – 50-60%HRR Time – 30 min Type – cycle ergometer	N/A	Qigong Freq – 3/w x 7 wk Time – 50 min	N/A	CPET inc. VO_2peak, UPDRS – Sections II and III, Brown Disability Scale, 6MWT, PDQ-39, Beck Depression Inventory
Fisher 2008	RCT	N= 10 Age(yr) – 64 (SD-15) H&Y – I-II DD (yr) – 1.22 (SD-1) Meds –n/r	Freq – 3/w x 8 wk Intensity – MET >3 and/or > 75% AAMHR Time – 45 min Type – BWSTT	Freq – 3pw x 8w Intensity – MET <3 and/or <50% AAMHR Time – 45 min Type – multimodal non-aerobic	Group education classes	N/A	UPDRS 3D Movement Analysis 10 meter walk test Sit-to-stand test Transcranial magnetic stimulation
Kurtais 2008	RCT	N= 12 Age(yr) – 63.8 (SD-11) H&Y – I-III DD (yr) – 5.3 (SD-1) Meds – On	Freq – 3/w x 6 wk Intensity – 70-80% HRm Time – 40 min Type – treadmill	N/A	Home flexibility exercises	N/A	VO_2peak Functional tasks
Nadeau** 2013	RCT	N= 23 Age(yr) – 62.8 (SD-n/a) H&Y – I-II DD (yr) –n/r Meds – n/a	Freq – 3/w x 24 wk Intensity – 75% AAMHR Time – 45 min Type – mixed treadmill	Freq – 3/w x 24 wk Intensity – 75% AAMHR Time – 45 min Type – speed treadmill	Multimodal non-aerobic exercise	N/A	6 min walk test Spatiotemporal parameters of gait PDQ-39, BDI MDS-UPDRS

Park 2014	RCT (delayed start design)	N= 31 Age(yr) – 59.9 (SD-6) H&Y – I-II DD (yr) – n/a Meds – no levodopa therapy	Freq – 3/w x 16 wk Intensity – 75-85% HRmax Time – 20-30 min Type – high intensity interval training	N/A	Delayed start – No exercise controls	N/A	UPDRS Get up and go Walking Test Tinetti Mobility Test PDQ-39 Beck depression inventory
Qutubuddin ł 2013	RCT	N= 13 Age(yr) – 68.2 (SD-9) H&Y – n/r DD (yr) – 7.2 (SD-6.2) Meds – On	Freq – 2/w x 8 wk Intensity – 61–80% AAMHR Time – 30 min Type – Theracycle	N/A	No exercise control	N/A	Berg Balance Scale UPDRS Finger tapping test PDQ-39
Ridgel ** 2009	RCT	N= 10 Age(yr) – 61 (SD-n/r) H&Y – n/r DD (yr) – 6.15 Meds – Off	Freq – 3/w x 8 wk Intensity – 60%-80% AAMHR Time – 40 min Type – Forced stationary bike	Freq – 3/w x 8 wk Intensity – 60%-80% AAMHR Time – 40 min Type – voluntary stationary bike	N/A	N/A	VO_2max UPDRS – III Manual dexterity ax
Ridgel*** 2013	RCT	N= 10 Age(yr) – 61 (SD-n/r) H&Y – n/r DD (yr) – 6.15 Meds – Off	Freq – 3/w x 8 wk Intensity – 60%-80% AAMHR Time – 40 min Type – Forced stationary bike	Freq – 3/w x 8 wk Intensity – 60%-80% AAMHR Time – 40 min Type – voluntary stationary bike	N/A	N/A	UPDRS – III Approximate Entropy Sample Entropy Spectral Entropy
Sage 2009	RCT	N= 13 Age(yr) – 65.1 (SD-9) H&Y – n/a DD (yr) – 3.2 (SD-3) Meds – On	Freq – 3/w x 12 wk Intensity – 60–75% AAMHR Time – 20 min Type – stationary bike	N/A	Freq – 3/w x 12 wk Intensity – n/a Time – 40-60 min Type – SAFEx	No exercise control	UPDRS – III TUG Spatiotemporal parameters of gait
Schenkman 2012	RCT	N = 31 Age(yr) – 63.4 (SD-11) H&Y – I-III DD (yr) – 3.9 (4) Meds – On	Freq – 5-7/w x 68 wk Intensity – 65-80% HRm Time – 30 min Type – treadmill, bike or elliptical	N/A	Freq – 5-7/w x 68 wk Intensity – n/a Time – 45-50 min Type – balance and flexibility in group	Freq – 5-7/w x 68 wk Intensity – n/a Time – 45-50 min Type – strength and flexibility at home	Walking economy [mL/kg/min] Continuous Scale—Physical Functional Performance Functional Reach Test UPDRS –ADL and Motor subscales PDQ-39

Shulman 2013	RCT	N= 45 Age(yr) – 66 (SD-n/r) H&Y – II-III DD (yr) – 6.1 Meds – On	Freq – 3/w x 12 wk Intensity – 40-80% HRR Time – 15-30 min Type – treadmill	Freq – 3/w x 12 wk Intensity – 40-50% HRR Time – 15-50 min Type – treadmill	N/A	Freq – 3/w x 12 wk Intensity – n/a Time – n/a Type – stretch and strengthening	VO_2peak, SMWT, 1-Repitition maximum, Schwab and England Activities of Daily Living Scale TUG, Step Activity Monitor, UPDRS, PDQ-39, Beck Depression Inventory, Parkinson Fatigue Scale, Falls efficacy scale, 10 meter walk

Groups listed are those that were analysed in this systematic review; there may have been other groups in the paper. Participant characteristics are averaged for studies with two of the study arms meeting aerobic intervention criteria.

* = Studies aerobic exercise group also engaged in another form of non-aerobic exercise i.e. resistance training.

** = Studies in which participants from more than one arm of the trial met the aerobic exercise criteria.

*** = Same study sample as 'Ridgel 2009' with some further analysis

ł = 'Qutubuddin 2013' only reported mean age and disease duration for combined aerobic and control groups. These have been used in table as stated that mean age and mean time of onset did not differ between the control and experimental groups.

Key: N = Number of PD aerobic exercisers, yr = year, H&Y = Hoehn and Yahr Scale, Avg. = Average, DD = Disease Duration, Meds = ON or OFF PD meds at assessment, n/r = not reported, ax = assessment, exe = Exercise, HRR = Heart Rate Reserve, HRm = Heart Rate max, pw = per week, w = week, time = time spent on aerobic training not including warmup and cool downs, Con = control group, UPDRS = Unified Parkinson's Disease Rating Scale, 6MWT = six minute walk test, PDQ-39 = Parkinson's Disease Questionnaire – 39, CPET = CardioPulmonary Exercise Test, AAMHR – age adjusted maximal heart rate, MET – metabolic equivalent, BWSTT – body weight supported treadmill training, TUG – Timed up and go

1.3.3 Risk of bias

The 13 studies included in the systematic review were assessed for risk of bias by the author and a second independent reviewer. Overall, five of the studies included had a high risk of bias as determined by the Cochrane risk of bias tool. The main reason for a high risk of bias was the attrition bias scoring high in each of the five studies. An attrition score of ≥ 20% of participants between pre assessment and primary assessment end point was seen as a high risk of attrition bias. The eight remaining studies had an unclear risk of bias, due mainly to unclear reporting of performance bias in their description of blinding of participants and personnel. No study had a low risk of bias on assessment by the two reviewers. Only two studies did not score a low risk of bias for detection bias and one study scored unclear for reporting bias. The results of this review are detailed below in Table 1.4.

Table 1.4 - Cochrane risk of bias tool results from studies included in the aerobic review

Authors	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**	**Risk of bias**
	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall risk of bias
Bergen et al (2002)	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Bridgewater et al (1996)	Unclear	Unclear	Unclear	No	No	Unclear	Unclear	High
Burini (2006)	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear
Fisher et al (2008)	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear
Kurtais (2008)	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Nadeau (2013)	Yes	Yes	Unclear	Yes	No	Yes	Unclear	High
Park (2014)	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Qutubuddin	Unclear	Yes	Unclear	Yes	No	Yes	Unclear	High

(2013)								
Ridgel et al (2009)	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear
Ridgel et al (2013)	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear
Sage (2009)	Unclear	Unclear	Unclear	Yes	No	Yes	Yes	High
Schenkman (2012)	Yes	Yes	Unclear	Yes	No	Yes	Yes	High
Shulman (2013)	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear

1.3.4 Retention rates /attrition

Attrition ranged from 0% [20, 25, 30] to 36.7% [50] in the included studies. The three studies that exceeded the 20% attrition rate were among the studies of longest duration, with a range of 12-68 weeks for intervention duration and 3-7 times a week for frequency.

1.3.5 Primary outcome measure – aerobic capacity

Four studies used VO_2peak (ml/kg/min) to assess aerobic capacity [25, 33, 51, 52]. Two of the studies, Bergen at al, 2002 and Burini et al 2006, did not provide sufficient data to allow for meta-analysis. Burini et al, 2006 did not include the results of the VO_2peak assessments in their published study and Bergen et al, 2002 did not include standard deviations for baseline and post intervention for either intervention or control groups. Both authors were contacted via their published contact details, however neither author was available to elaborate on their study's results.

Two studies provided adequate data for meta-analysis of VO_2peak levels post intervention (n=72). There was no significant difference between the aerobic group and the control group in levels of VO_2peak post intervention (FEM, -0.46, 95% CI -1.01 to 0.09, I^2=0%, p=0.10). See below Figure 1.2 for details of analysis, studies included and forest plot.

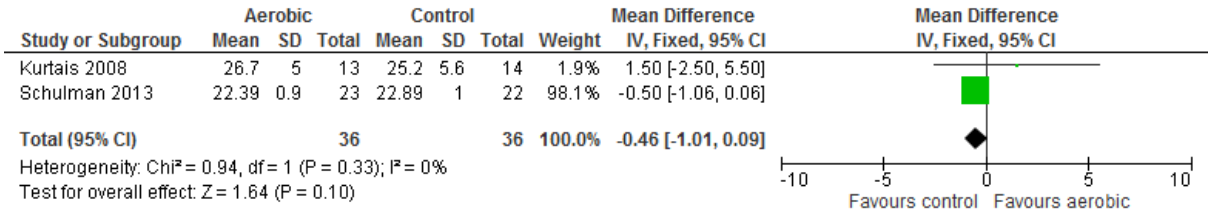

Figure 1.2 - Pooled results of aerobic review for VO_2peak post intervention

1.3.6 Secondary outcome measures

Secondary outcome measures results are presented using the ICF framework of impairment, activity limitation and participation restriction.

1.3.6.1 Impairment

Three studies provided adequate data for meta-analysis of UPDRS total score post intervention (n=129). There was no significant difference between the aerobic group and the control group in UPDRS total score post intervention (REM, 1.27, 95% CI -3.86 to 6.40, I^2=89%, p=0.63). See below Figure 1.3 for details of analysis, studies included and forest plot.

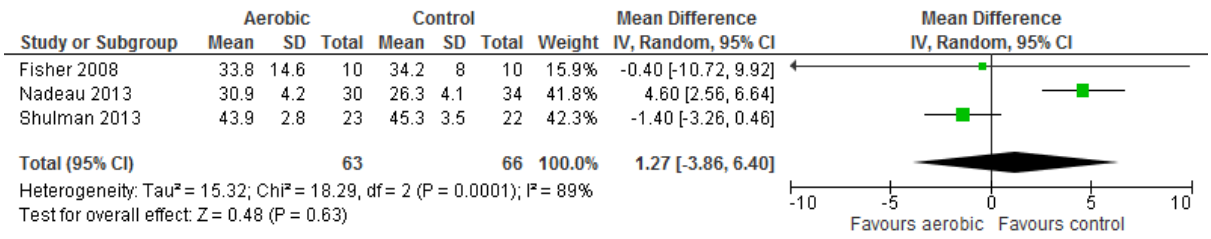

Figure 1.3 - Pooled results of aerobic review for unified Parkinson's disease rating scale total post intervention

Seven studies provided sufficient data for meta-analysis of UPDRS motor subscale post intervention (n=289). There was no significant difference between the aerobic group and the control group in UPDRS motor scores post intervention (REM, 0.15, 95% CI -1.55 to 1.85, I^2=72%, p=0.86). See below Figure 1.4 for details of analysis, studies included and forest plot.

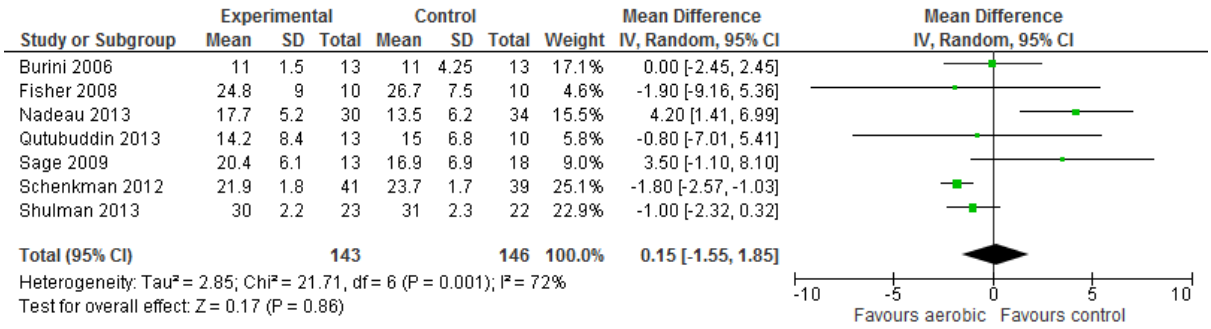

Figure 1.4 - Pooled results of aerobic review for unified Parkinson's disease rating scale motor subscale post intervention

The poor heterogeneity (I^2=72%) of the seven studies was subsequently examined in a sensitivity analysis. Due to the weighting and methodological quality of the trial by Nadeau et al, 2013, it was excluded in the sensitivity analysis. The between study heterogeneity fell within acceptable levels (I^2=29%), and results demonstrated a significant difference in favour of the aerobic intervention, mean improvement -1.04 points (FEM, -1.04, 95% CI -2.06 to -0.02, I^2=29%, p=0.05) (Appendix III).

1.3.6.2 Activity limitation

Three studies provided adequate data for meta-analysis of the SMWT post intervention (n=134). There was no significant difference between the aerobic group and the control group in metres walked post intervention (REM, 19.70 metres, 95% CI -26.63 to 66.02, I^2=83%, p=0.40). See below Figure 1.5 for details of analysis, studies included and forest plot.

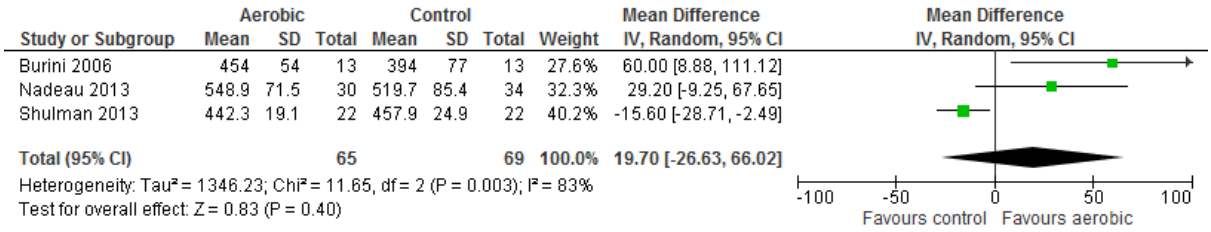

Figure 1.5 - Pooled results of aerobic review for six minute walk test post intervention

A sensitivity analysis indicates that when Shulman et al, 2013 is excluded heterogeneity drops below 50% (I^2=0%) and the revised analysis demonstrates that there is a significant difference among the groups post-intervention, favouring the aerobic intervention (FEM, 40.33 metres, 95% CI 9.60 to 71.06, I^2=0%, p=0.01) (Appendix IV). Shulman et al, 2013 was given the highest weighting of the studies included at 40.2% and there was no significant improvement in walking distance in the studies high intensity aerobic group. However, there was a second group, in the Shulman et al, 2013 study, of lower intensity intervention that showed a significant improvement in walking capacity (p=0.01). This low intensity group was not included for comparison owing to a methodological flaw in the prescription of exercises

with the high intensity (30 minute exercise sessions) and low intensity (50 minute exercise sessions) groups.

Two studies provided adequate data for meta-analysis of self-selected velocity post intervention (n=51). There was no significant difference between the aerobic group and the control group in self-selected velocity post intervention (REM, 0.01, 95% CI -0.16 to 0.17, I^2=63%, p=0.92). See below Figure 1.6 for details of analysis, studies included and forest plot.

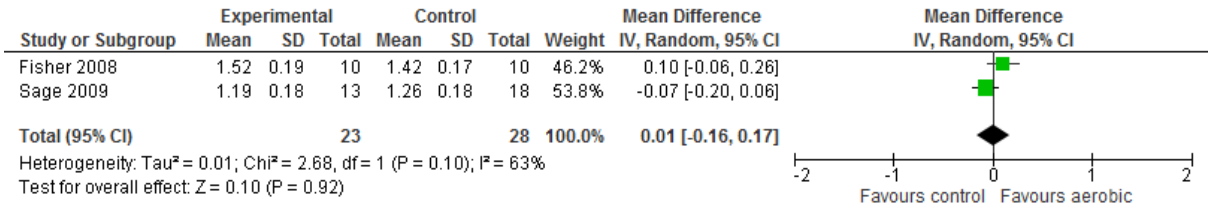

Figure 1.6 - Pooled results of aerobic review for self-selected velocity post intervention

Other measures of gait function, cadence (n=124) and double support time (n=84), provided suitable data for meta-analysis post intervention. Both measures showed no significant difference between the aerobic group and the control group in either cadence post intervention (FEM, -1.00, 95% CI -3.36 to 1.36, I^2=33%, p=0.41) or double support time post intervention (FEM, -0.34, 95% CI -1.78 to 1.10, I^2=0%, p=0.64). See below Figure 1.7 and Figure 1.8 for details of analysis, studies included and forest plot.

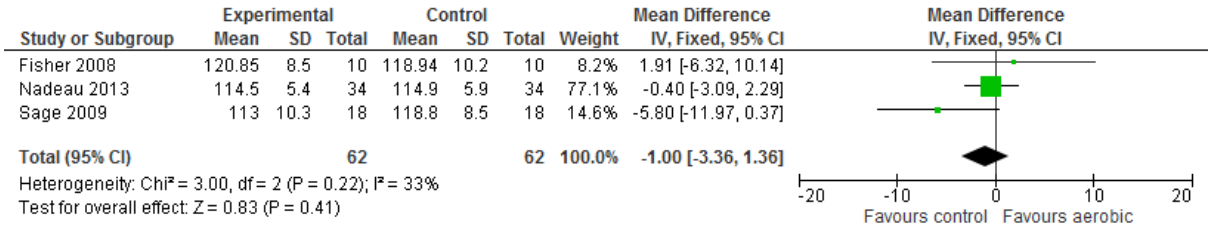

Figure 1.7 - Pooled results of aerobic review for cadence post intervention

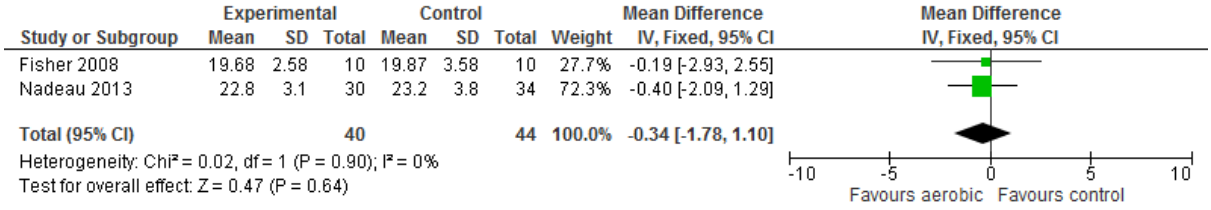

Figure 1.8 - Pooled results of aerobic review for double support time post intervention

1.3.6.3 Participation restriction

Five studies had sufficient data for meta-analysis of PDQ-39 scores post intervention (n=237). There was no significant difference between the aerobic group and the control group in PDQ-39 score post intervention (FEM, -0.97, 95% CI -3.02 to 1.09, I^2=53%, p=0.36). Heterogeneity of I^2=53% was deemed acceptable for fixed effects model analysis. See below Figure 1.9 for details of analysis, studies included and forest plot.

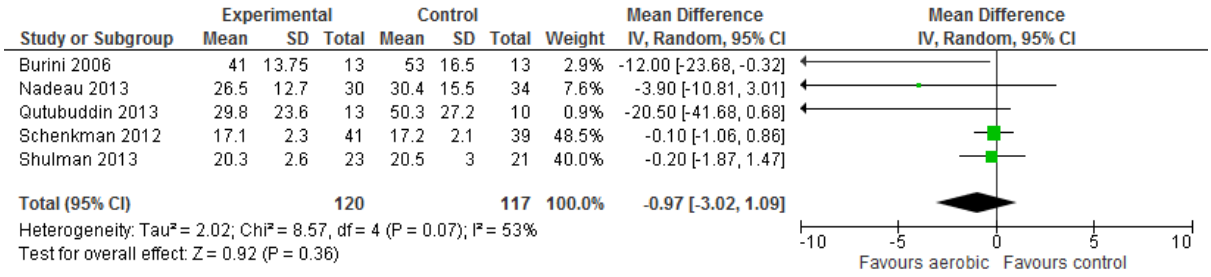

Figure 1.9 - Pooled results of aerobic review for Parkinson's disease questionnaire - 39 post intervention

Three studies were include in meta-analysis for Beck depression inventory score post intervention (n=135). There was no significant difference between the aerobic group and the control group in Beck depression inventory scores post intervention (REM, -0.31, 95% CI -4.13 to 3.50, I^2=88%, p=0.87). The heterogeneity between studies is high (I^2=88%) for the Beck depression inventory score post intervention. See below Figure 1.10 for details of analysis, studies included and forest plot.

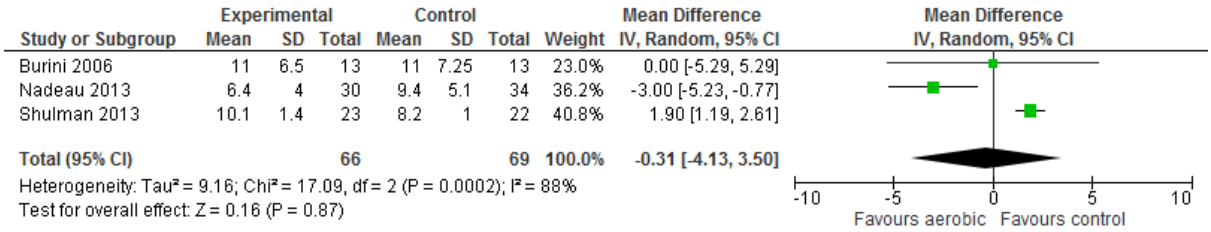

Figure 1.10 - Pooled results of aerobic review for Beck depression inventory score post intervention

On sensitivity analysis, the study by Shulman et al, 2013 is removed (n=90) and heterogeneity reduces to acceptable levels (I^2=5%). These output of the sensitivity analysis demonstrates a significant improvement in favour of the aerobic intervention (FEM, -2.50, 95% CI -4.69 to -0.31, I^2=5%, p=0.03) (Appendix V). The Shulman et al, 2013 study was removed here for similar methodological reasons as outlined in the six minute walk test analysis section.

1.4 Discussion

1.4.1 Statement of principal findings

This review combines the results of 13 studies to examine the impact of aerobic interventions for measures of impairment, activity limitation and participation restriction in people with PD. Despite promising results in some of the individual studies, there was no significant improvement of aerobic capacity, as measured by VO_2peak, following aerobic intervention in the pooled analysis of two studies (p=0.10). Secondary outcome measures of impairment (UPDRS motor), activity limitation (SMWT) and participation restriction (Beck depression inventory) showed significant results in favour of the intervention group with PD stage 1 to 3 H&Y (p<0.05) after sensitivity analysis controlled for heterogeneity (I^2<50%) through the exclusion of two studies Nadeau et al, 2013 and Shulman et al, 2013 for a variety of methodological reasons as outlined in the above results section.

1.4.2 Current literature

In spite of the authors' aim to explore the impact of aerobic exercise interventions on later stage PD (H&Y 3 to 5), there were few studies (n=5) that included stage 3 H&Y and no studies including any participants with advanced stage PD (H&Y 4 to 5). The lack of evidence for aerobic interventions for people with PD at later stages of the disease limits the ability to justify an aerobic intervention within a palliative setting. This section outlines the results in the context of the current literature considering the primary outcome measure and the secondary outcome measures using the ICF domains.

1.4.3 Primary OCM

The primary outcome measure of VO_2peak did not show a significant improvement after meta-analysis (p=0.10). It may be that the lack of studies adequately reporting data for meta-analysis impacted on the findings. However, after review of the frequency, intervention, time and type of exercise programs used by Kurtais et al, 2008 and Shulman et al, 2013 the author found several areas of interest for review. The frequency of the Kurtais et al, 2008 exercise intervention was three times weekly over six weeks; six weeks of intervention is the lowest study duration included in this review. The majority of studies (n=9) were between 8-16 weeks in duration, while one study lasted 68 weeks. Despite Kurtais et al, 2008 demonstrating a significant improvement in VO_2peak within their original study, the short trial duration provides the minimal potential for cardiorespiratory improvements.

Similarly, in the study by Shulman et al (2013), the time spent per exercise session was low at 15-30 minutes per session and this may have resulted in the minimal level to elicit an improvement in aerobic capacity. The majority of studies included in the review (n=8) prescribed exercise session of between 30-45 minutes to allow for a significant improvement in aerobic capacity.

In the context of current literature the study results fall broadly within the physical outcomes expected from a previous aerobic exercise review for people with PD, once heterogeneity is controlled for in the sensitivity analysis. A recent systematic review with

meta-analysis by Shu et al, 2014 found similar improvements in Unified Parkinson's Disease Rating Scale III ($p=0.01$) and Six Minute Walk Test ($p=0.03$), however it did not find significant improvements in measures of participation restriction as seen in this review [53]. Shu et al, 2014 examined eighteen studies, with two studies including people with PD stage 4 H&Y. The studies included with participants of stage 4 H&Y were both below the threshold of aerobic exercise as outlined for this review. One was focused on Tai Chi, which was not seen as significantly intense [54], and the other study looked took place over only four weeks [55]. The mean age of 67±3.3 years is comparable to this review (63.4 years) and mean disease duration of 6.4±2.7 years is comparable also (5.6 years). A review by Allen et al, 2011 looked primarily at the impact of exercise on balance related activities and did find similar non-significant results in measures of gait velocity ($p=0.38$) and cadence ($p=0.84$) [56]. Allen et al, 2011 examined nineteen trials with sixteen included for meta-analysis; the cohort of the included studies were described as between mild to moderate PD with no H&Y rating provided reducing the ability to compare the results to an advanced stage PD population. The mean age was 67.97 years which is also comparable to the current review (63.4 years). The main difference in the Allen et al, 2011 review was the broad inclusion of both exercise and motor training interventions which were multifaceted in nature and aimed at improving balance related activities in 50% of the included studies intervention. There are significant improvements in measures from each of the ICF domains ($p<0.05$) as seen in the above results section.

1.4.4 Impairments

A recent systematic review with meta-analysis by Shu et al, 2014 , outlined above, showed similar non-significant results in the UPDRS total scores (p=0.23) when looking at aerobic interventions [53]. This systematic review also found similar significant improvements in UPDRS motor subscale scores (p=0.01). The review by Shu et al, 2014 did not examine the impact of aerobic interventions on aerobic capacity and did not include a minimal definition to classify aerobic interventions. The Shu et al, 2014 review does however support the improvements observed on meta-analysis of motor impairments for people with PD post aerobic intervention in our review.

1.4.5 Activity limitation

This review demonstrated no significant improvements in self-selected velocity, cadence and double support time after meta-analysis. A previous review reported that gait velocity (p=0.01) improved in people with PD post exercise intervention, while another systematic review with meta-analysis found no significant improvement (p=0.38) in gait velocity following exercise intervention [53, 56]. These two previous reviews found no significant improvement in cadence (p=0.28-0.84) and neither looked at double support time during analysis. In Shu et al, 2014 there were a total of twelve studies for meta-analysis of gait velocity, while Allen et al, 2011 included sixteen studies in meta-analysis of gait velocity post intervention. The broad inclusion criteria for Shu et al, 2014 and Allen et al, 2014 facilitated the inclusion of a greater number of studies and participants (Shu n=584, Allen n=562) in the meta-analysis of gait velocity post intervention. Despite the comparatively large sample

sizes, both reviews differ on the significance of improvements in gait velocity. It is not surprising that no significant result was obtained for gait velocity and measures of gait parameters in this review due to the limited number of studies included in the pooled statistical analysis. A significant improvement in walking distance as measured by the SMWT, once heterogeneity was adjusted for, has also been reported in the Shu et al, 2014 review.

1.4.6 Participation restriction

The PDQ-39 did not show a significant improvement following an aerobic intervention, consistent with the findings of a recent systematic review [53]. There was however a significant improvement in Beck depression inventory ($p=0.03$), once heterogeneity was controlled for. The improvement in the Beck depression inventory has not been seen in previous reviews and is a unique finding for this review. An improvement in depression is not surprising owing to the evidence based benefits of exercise on the characteristics of depression in patients with diagnosed depression[57], however the improvement in depression scores for people with PD is a new finding from this review.

1.4.7 Clinical Implications

This study suggests there is evidence for aerobic interventions as a treatment to improve the symptoms of mild to moderate PD (H&Y 1 to 3), specifically motor impairments, walking capacity and depression scores. Interventions should include a measure of intensity to ensure they meet an appropriate level of aerobic intensity, frequency should be at least 2

days a week for at least 6 weeks, exercise interventions should be a minimum of 20 minutes per session and the type of exercise should be regular, purposeful exercise involving major muscle groups and be continuous and rhythmic in nature. It should be noted that if attempting to improve aerobic capacity then the above recommendations are not proven to improve aerobic capacity and clinicians should potentially look at longer duration, higher frequency or higher intensity of interventions. Owing to the higher level of frequency, interventions should look to motivate patients to exercise independently where possible as twice weekly supervised interventions are usually not feasible in clinical practice. Stationary bikes in the home environment coupled with a once weekly supervised intervention via attendance, or potentially using telehealth services, may be a pragmatic intervention to meet the above recommendations in clinical practice.

1.4.8 Strengths and Limitations

This was the first systematic review with meta-analysis to look at the totality of evidence in relation to the impact of aerobic exercise on aerobic capacity in people with PD. The review search strategy was aimed only at randomised controlled trials and quasi-randomised controlled trials to inform current practice. Broad search terms were used to examine the current literature with 12,000+ papers reviewed during this review process. The robust methodology and inclusion and exclusion criteria used identified and selected studies likely to improve aerobic capacity. Quality assurance checks to ensure the accuracy of the data extracted were undertaken throughout the review process with two reviewers reviewing the methodological quality independently using validated criteria.

However, the findings from the review have to be considered in the context of the study limitations. It is important to note that the ACSM guidelines, used in the inclusion and exclusion criteria, have been accepted for use in healthy adults and explicitly state that lower aerobic intensities can be beneficial for deconditioned adults [46]. Physical activity has been established in people with PD as being lower than in age matched controls; therefore, a lower level of exercise intensity could improve aerobic capacity in people with PD. Additionally, the inadequate heart rate increase in response to exercise present in approximately half of people with PD has an unknown effect on heart rate assessed intensity levels. The definition included in this review was therefore a guide only. The population in question was mainly from the early stages of PD (H&Y 1 to 3) and as such limits the generalisability of the results to later stage PD (H&Y 4 to 5) patients. The methodological quality of the studies was variable and no study achieved a low risk of bias rating. The lack of a standardised battery of outcome measures used in aerobic exercise for people with PD limited the ability to statistically pool results. Thirteen studies were included for analysis and only four included VO_2peak as a measure of aerobic capacity. Three measures of aerobic capacity (VO_2peak, n = 4, VO_2max, n = 1, and walking economy, n = 1) were used throughout the studies included and only one measure had an appropriate number of studies to allow for meta-analysis. Five studies had no standard measure of aerobic capacity despite the interventions meeting the criteria for improving cardiorespiratory fitness. Finally, the small numbers included in each study reduces the generalisability of these results to a larger population.

1.4.9 Areas for future research

Future studies should look to explore higher intensity, frequency and duration studies to further examine the minimal level of aerobic intervention needed to elicit a significant improvement in aerobic capacity for people with PD. The lack of a consistently used measure of aerobic capacity in exercise interventions for people with PD limits the ability for comparisons and systematic reviews to examine the relationship between aerobic capacity and aerobic interventions in people with PD. VO_2peak should be used in all interventions which aim to examine aerobic capacity in people with PD. The examination of the impact of aerobic exercise on people with later stage PD is needed to develop the understanding of the safety and feasibility of this potentially beneficial intervention. Aerobic exercise for later stage PD should occur initially in specialised movement disorder clinics, with trained movement disorder staff, owing to the complex nature and treatment of this cohort of patients.

There is a need to assess the quality of life and participation restrictions experienced by people with PD. It was noted by the reviewers that no studies in this review looked at robust qualitative interviews to explore the lived-in experience of patients' aerobic interventions. Park et al, 2014 did include a post intervention survey; however this was reported as a single score of 1-5 looking at 'how they liked the class' overall. Qualitative methods should be used concurrently with quantitative methods to fully explore the impact of exercise for people with PD.

1.4.10 Summary

The systematic review with meta-analysis presents evidence for aerobic interventions as a treatment to improve the symptoms of mild to moderate PD (H&Y 1 to 3), specifically motor impairments, walking capacity and depression scores. There was no significant improvement in aerobic capacity after reviewing the current literature. The lack of later stage PD participants limits the generalisability of these results to all PD populations and clinicians should be conscious of the high frequency, duration and intensities needed to produce significant improvements in measures of PD that may not be feasible for later stage PD participants.

At this stage of the research process, it was deemed necessary to examine another exercise modality as there was insufficient evidence to support or refute aerobic exercise for advanced stage people with PD. Exercise interventions for people with PD can be broadly split into aerobic [20, 31, 58], strength based [52, 59] or balance [60, 61] exercise interventions. To this end, Chapter 2 will explore the impact of strength based interventions in people with PD as a potential modality to improve walking capacity in later stage PD (H&Y 3 to 5).

Chapter 2 Strength Review

2.1 Introduction

Parkinson's disease has been estimated to cost between £449 million to 3.3 billion annually in the United Kingdom [62]. These costs are largely consisting of direct costs of inpatient care and nursing home costs. In the advanced stages of the disease it has been clearly shown that the cost of PD increases significantly as 'off' medication periods increase [63]. Treatments that aim to improve function in the later stages of PD (H&Y 3 to 5) are needed to explore what can maintain the function and independence of people with PD.

In Chapter 1, the impact of aerobic interventions on outcomes for people with PD was explored. Despite promising results ($p < 0.05$) in improving outcome measures of impairment (UPDRS motor), activity limitation (SMWT) and participation restriction (Beck depression inventory), there was a lack of later stage evidence available with no participants included in the studies of stage 4 to 5 H&Y. The lack of later stage PD participants limited the studies ability to recommend aerobic interventions for people with PD stage 3 to 5 H&Y. As such the author conducted a second systematic review of evidence for another exercise modality, progressive strength training.

There is a body of evidence that demonstrates muscular weakness in people with PD is present when compared with healthy age matched controls. Axial musculature and

appendicular musculature are both affected in people with PD. A pre and post medication comparative study assessed 20 people with PD before and after taking their first daily levodopa dosage and then compared with 20 age and sex matched healthy controls [64]. There was a reduction in inspiratory and expiratory muscle strength when compared with controls and a close correlation between perception of dyspnea and inspiratory muscle strength in people with PD ($p < 0.01$). Inspiratory muscle strength is not the only axial muscle group affected by PD. The prevalence of dysphagia is high in people with PD and is often underreported. A systematic review of the literature with meta-analysis examined 12 studies looking at dysphagia in people with PD. A third of people with PD in the community reported difficulties swallowing while 4 in 5 people with PD were found to have difficulty swallowing on assessment. The pooled relative risk was shown as 3.2 for both subjective and objective outcomes [65]. These studies identify that reduced muscle strength for people with PD has an impact on axial musculature. This weakness seen above is present in appendicular musculature as well.

Leg extensor muscles were tested in an Australian based comparative study to examine the difference in muscle strength and muscle power between people with PD ($n = 40$) and healthy age matched controls ($n = 40$) [66]. It was found that on average, 172 N less ($p = 0.02$) was produced during one repetition maximum testing in people with PD when compared with healthy age matched controls. This reduced muscle strength has also been shown in other studies. A comparative study examined the impact of lower limb strength on a functional task (sit to stand). Ten male subjects were compared with ten age and sex matched controls both ‘on’ and ‘off’ medication. Hip torque was correlated to sit to stand

duration ($r = -0.71$, $p < 0.05$) indicating an increase in hip strength to improve sit to stand speed [67]. Finally a study by Nallegowda et al, 2004 examined the correlation between muscle strength and gait measures. Thirty PD subjects and thirty age and sex matched control subjects were included. There was a positive correlation between muscle strength and gait velocity (ON state $r = 0.37$, OFF state $r = 0.56$). The evidence of these studies illustrates the presence of weakened lower limb musculature in people with PD when compared with age matched healthy controls. This muscle weakness not only impacts one repetition maximum and hip torque but also correlates to vital (inspiratory muscle strength) and functional (sit to stand and gait velocity) measures for people with PD.

Progressive muscle strength training has been shown to improve muscle strength in people with PD in several trials. A recent preliminary non-randomised controlled trial compared an intervention ($n = 12$) and control ($n = 12$) group of people with PD with stage 1 to 3 H&Y. This study found that an exercise programme including progressive strength training over 32 weeks improved UPDRS motor score ($p < 0.05$) and muscle strength (arm curls, $p = 0.01$). This study supports the hypothesis that a personal exercise programme can improve motor symptoms in people with PD. There is also evidence to suggest that progressive strength training can improve function in people with PD. A recent study by Prodoehl et al, 2015 was a secondary analysis study looking at a previous prospective, parallel-group, single-center, randomised controlled trial [68]. This study examined the impact of people with PD undertaking a progressive resistance exercise programme ($n = 24$) when compared with a non-progressive multi-modal exercise programme ($n = 24$). The intervention was over 24 months and involved twice weekly exercise. There was a significant improvement in the

measure of walking capacity used (SMWT) 'off' medication after the intervention ($p < 0.01$). It is this improvement in walking capacity (SMWT) that is most interesting to the author of this thesis as this is the symptom of prevalence that the Physiotherapy led Palliative Exercise Programme for people with advanced Parkinson's Disease (PEP-PD) trial is aiming to impact. The Prodoehl et al, 2015 did not report a measure of muscle strength so it did not examine muscle strength in relation to walking capacity.

There is already a review that has looked at progressive strength training and its impact on measures of muscle strength and secondary outcomes of physical performance. The Lima et al, 2013 study examined the totality of literature up to November 2011 in; The Cumulative Index to Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro), Literatura Latino Americana em Ciências da Saúde (LILACS) and Medical Literature Analysis and Retrieval System Online (MEDLINE) [10]. This review found four studies for systematic review and meta-analysis. The results of this review found that progressive resistance strength training improved strength by a standardised mean difference of 0.50 (95% CI 0.05 to 0.95, $I^2 = 0\%$) and also improved walking capacity by a standardised mean difference of 96 metres (95% CI 40 to 152,$I^2 = 0\%$). An improvement of 96 meters is above the minimal detectable change established for the SMWT previously [38]. The participant characteristics of this review however included participants from stage 1 to 3 H&Y. The lack of studies that included stages 4 to 5 H&Y was a limitation of the research explored to date by Lima et al, 2013. Owing to the fact that the author had completed a full systematic review with meta-analysis prior to this second review and the Lima et al, 2013 study provided an appropriate template for review it was decide by the author and their supervisor to update the Lima et al, 2013 review to include the most up to date research

available. As such an update of the Lima et al, 2013 systematic review with meta-analysis was undertaken by the author to explore the most up to date research and has been described below.

2.2 Methods

2.2.1 Study design

A systematic review with meta-analysis was undertaken primarily to examine the impact of strength training on muscle strength and secondary measures of physical performance and activity limitation and participation restriction in people with PD. The PRISMA statement was followed to ensure the appropriate conducting and reporting of this systematic review and meta-analysis [34]. Similar to the rationale outlined in the previous chapter, this review included only randomised controlled and quasi-randomised controlled trials as they are the reference standard of research methodology for the assessment of a healthcare intervention.

2.2.2 Definitions and inclusion criteria

Studies were considered eligible for inclusion if the population of interest was people with Parkinson's disease of any stage of disease and had no previous surgery such as deep brain stimulation; the intervention had to include a training component that included progressive resistance exercise or repetitive effortful muscle contractions; the comparison group received either no intervention or a variety of non-strength based interventions. Studies were also included that combined progressive resistance exercise with another intervention and compared against this intervention alone, the results are outlined in Table 2.2. Studies

included had to have a clear measure of muscle strength such as voluntary force production. Secondary outcome measures of physical performance were included for analysis also. Functional measures of physical performance consisted of the following; sit-to-stand time, fast and comfortable walking speeds, 6-min walk test, stair ascent and descent, the Activities-specific Balance Confidence scale, Timed Up and Go test and the Short Physical Performance Battery. The below table Table 2.1 outlines the ICF domain, definition, validity and reliability of the outcome measures included in meta-analysis.

Table 2.1 - Validity and reliability of outcome measures included in meta-analysis in strength review studies

Measure	ICF domain	Definition	Validity	Reliability
Gait velocity	Activity limitation	Comfortable walking or self-selected velocity is an accurate measure of gait function in PwP, it is measured as meters per second usually over a ten meter track.	Convergent validity established ($p<0.01$) [39]	ICC of 0.98 [39]
Timed up and go	Activity Limitation	Timed test of rising from a chair, walking 3 meters and returning to sitting in the chair. Functional gait task	Convergent validity established ($p < 0.01$) [69]	ICC of 0.80 [70]

ICC - Intraclass Correlation Coefficient, PwP = People with PD

2.2.3 Literature search

A literature search was performed using the following databases to identify relevant studies published; CINAHL, PEDro, LILACS and MEDLINE. The above databases were searched using an adapted search strategy for each database according to the example boolean search

below: ‘parkinson’s disease’ OR ‘parkinson’s’ OR ‘pd’ AND ‘physiotherapy’ OR ’physiotherapist’ OR ‘physical therapy’ OR ‘rehabilitation’ OR ‘exercise’. A full example of the search strategy is included in the appendices, (Appendix VI).

2.2.4 Study identification and selection

Similar to the previous approach in Chapter 1, the author read the titles and/or abstracts of retrieved studies and subsequently excluded any studies that did not meet the inclusion criteria. The remaining articles were marked as either relevant or unsure. The author and a second reviewer independently reviewed the unsure and the relevant folders and decided on which were included for full text review. Finally the selected studies were reviewed in full and excluded based on the inclusion criteria by the author and second reviewer. Any disputes or disagreements were resolved between the two reviewers.

2.2.5 Methodological quality

The author independently assessed the methodological quality of the included studies. The Cochrane risk of bias tool was used to assess methodological quality of the included Randomised Controlled Trial’s (RCT’s), in terms of their internal and external validity, see Table 1.2 for an explanation of the areas of review undertaken [48].

2.2.6 Data extraction

Information extracted from each study included the population of interest characteristics such as number of participants, mean age, disease duration, disease severity (Hoehn and Yahr) and medication details on testing and assessment. Intervention details included the

frequency, intensity, time and type of exercise interventions for all arms of studies included. The comparison intervention and control subject details were also included in data extraction along with the name, definition and results of all outcome measures used in each study. Additional information was obtained by contacting relevant authors where necessary and 20% of all data extraction was independently verified by second independent reviewer.

2.2.7 Data synthesis and statistical analysis

Cochrane Review Manager Software was used to conduct statistical analyses to determine the treatment effect. *A priori* it was decided that meta-analysis would be based on the main outcome of muscle strength. Secondary outcome measures were assessed for meta-analysis as described below. See section 1.2.10 for a description of the statistical approach taken to analysis.

2.3 Results

2.3.1 Study identification

The search strategy returned 85 records once duplicates were removed. Initial screening by the primary author resulted in three records for review by the two main reviewers. The screening excluded 21 studies due to the study design, 15 due to inadequate outcome measures and 46 studies due to the intervention not meeting the criteria outlined in the methods section. The flow of studies through the review is displayed in Figure 2.1. The remaining three studies were included for review and meta-analysis.

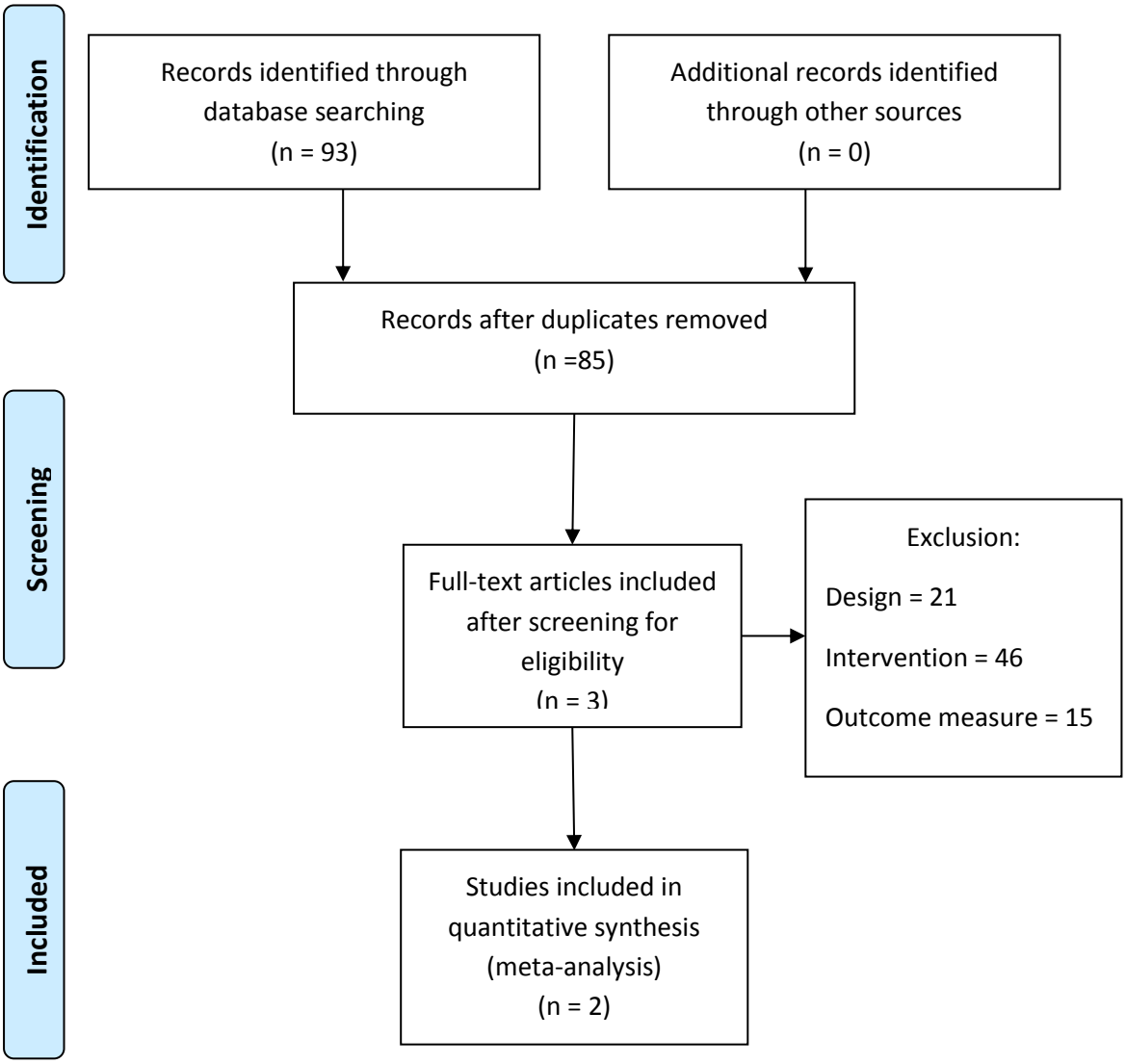

Figure 2.1 - Flow diagram of studies through strength systematic review

2.3.2 Study characteristics

A total of 92 participants took part in a progressive resistance exercise study that met the inclusion criteria for the review. These participants had an average age of 67.0 years and mean disease duration of 8.9 years. All of the included studies (n = 3) reported assessing participants while in the 'on' phase of their medication cycle. Disease severity in the studies included ranged from Hoehn and Yahr stage 1 to 4. The studies characteristics have been outlined in detail in Table 2.2 below.

Table 2.2 - Characteristics of studies included in the strength systematic review

Study	Design	PRT Participants	Aerobic Intervention	Control – 1	Control -2	Outcome Measure
Hass 2012	RCT	N= 9 Age(yr) – 64 (SD-7) H&Y – I-III DD (yr) – 11.1 (SD-10) Meds – On	Progression: volitional fatigue, daily-adjusted progressive resistance exercise protocol as per ACSM F – 2/w x 10wk I – 70% 1RM T – n/a T – 2 x 12–20reps seated leg press, knee extension, knee flexion, abdominal curl, back extension, seated calf raise	No exercise control	N/A	Gait Initiation, 1-RM
Li 2012	RCT	N= 65 Age(yr) – 69(SD 8) H&Y – I-IV DD (yr) – 8(SD-9) Meds – On	Progression: Weighted-vest resistance was initially set at 1% of body weight and was increased until 5%. Ankle weights started at 0.45 kg (1 lb) per limb and were gradually increased to 1.36 kg (3 lb). F – 2/w x 24wks I – 1-5% of body weight T – 60 min T – 1-3 sets x 10-15 reps of 8 to 10 Lower limb exercises	Tai-Chi	Stretching	Computerised dynamic posturography (Maximum excursion, directional control), stride length, gait velocity, Peak torque knee ext and flex, functional reach, TUG, UPDRS III, falls calendar
Paul 2014	RCT	N= 18 Age(yr) – 68.1 (SD 6) H&Y – I-III DD (yr) – 7.8 (SD 5.2) Meds – On	Progression: The first set was performed at 40% of 1-RM, the second set at 50% and the third set at 60%. When participants could perform repetitions with good form and speed, 1-RM was increased by 5%. F – 2/w x 12wks I – 40-60% 1-RM T – 45 mins T – PRT of the leg extensors, knee flexors, hip flexors and hip abductors	F - 2/w x 12wks I – low (non-therapeutic) T – n/a T – Lower limb exercises at home. 2 sets x 10-12 reps	N/A	peak muscle power (1-RM), maximal muscle strength and movement speed of lower limb muscles, 10m walk, TUG, Choice stepping reaction time, maximum balance range, single leg stand, New Freezing of Gait Questionnaire, falls diary,

Key:1-RM = 1 repetition maximum, PRT = Progressive resistance training, N = Number of PD aerobic exercisers, yr = year, H&Y = Hoehn and Yahr Scale, Avg. = Average, DD = Disease Duration, Meds = ON or OFF PD meds at assessment, ax = assessment, exe = Exercise, pw = per week, w = week, time = time spent on resistance training not including warmup and cool downs, Con = control group, UPDRS = Unified Parkinson's Disease Rating Scale, TUG – Timed up and go

2.3.3 Risk of bias

The three studies included in this systematic review were assessed for risk of bias by the author and a second independent reviewer. Overall one of the studies included had an unclear risk of bias as determined by the Cochrane risk of bias tool. There were several areas of an unclear risk of bias such as the reporting of a randomisation method, allocation concealment, blinding of participants, personnel and outcome assessment. There was also no clear intention to treat stated for analysis in Hass et al, 2012. The lack of a clear reporting of several areas of the Cochrane risk of bias tool led to the author scoring Hass et al, 2012 at an unclear risk of bias. The two remaining studies had a low risk of bias and this was due mainly to clear reporting of bias in their description of their studies methodology. The results of this review are detailed below in Table 2.3.

Table 2.3 - Cochrane risk of bias tool results from studies included in the strength review

Authors	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**	**Risk of bias**
	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall risk of bias
Hass 2012	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Li 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Paul 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

2.3.4 Retention rates /attrition

Attrition scores were 0% [71], 5.1% [54] and at the highest 10% [72] in the studies included for systematic review. None of the three studies exceeded the 20% attrition rate agreed *a priori* as the cut off score for attrition bias.

2.3.5 Primary outcome measure – muscle strength

All three studies used a measure of muscle strength such as peak muscle power (Paul et al, 2014), one repetition maximum (Hass et al, 2012) and peak torque (Li et al, 2012). Unfortunately the studies did not provide sufficient data or similar outcome measures to allow for meta-analysis of muscle strength. A review of the results shows that in all of the three studies the measure of muscle strength improved significantly. Li et al, 2012 showed a mean difference of 13.5 Newton meters (Nm) (95% CI 3.4 to 23.6, $p = 0.01$) improvement in peak torgue knee extension and a mean difference of 7.7 Nm (95% CI 1.9 to 13.6, $p = 0.01$). Hass et al, 2012 described a 76% improvement in one repetition maximum ($p < 0.01$) in both knee extension and knee flexion within the progressive resistance group. Finally, Paul et al, showed an improvement in peak muscle power (Watts) for leg extensors ($p < 0.01$), knee flexors ($p = 0.01$), hip flexors ($p < 0.01$) and hip abductors ($p < 0.01$).

2.3.6 Secondary outcome measures

Secondary outcome measures results and sensitivity analysis with forest plot are presented separately below.

Two studies provided adequate data for meta-analysis of Timed Up and Go score post intervention (n = 85). There was no significant difference between the strength group and the control group in Timed Up and Go score post intervention (FEM,-0.64, 95% CI -1.58 to 0.30, I^2=0%, p=0.18). See below Figure 2.2 for details of analysis, studies included and forest plot.

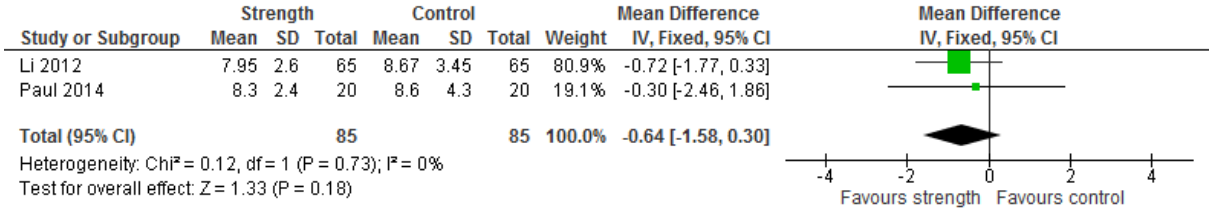

Figure 2.2 - Pooled results of strength review for the timed up and go test post-intervention

Two studies provided adequate data for meta-analysis of gait velocity score post intervention (n = 85). There was a significant difference between the strength group and the control group in gait velocity score post intervention (FEM, 0.13, 95% CI 0.06 to 0.20, I^2=0%, p<0.01). See below Figure 2.3 for details of analysis, studies included and forest plot.

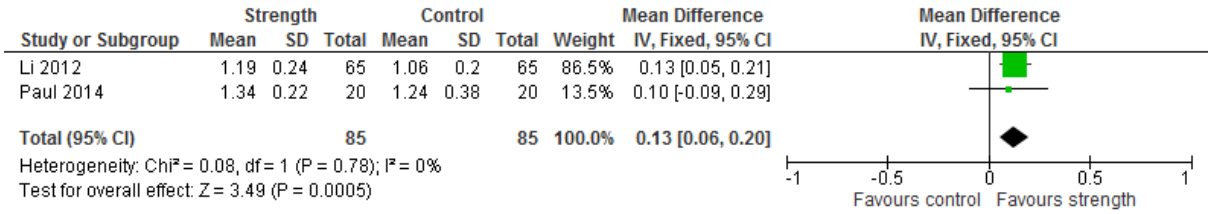

Figure 2.3 - Pooled results of strength review for gait velocity post-intervention

2.4 Discussion

2.4.1 Statement of principal findings

This review is an update of the Lima et al, 2013 systematic review and examines the results of three additional studies to explore the impact of progressive strength training on measures of muscle strength and secondary outcomes of physical performance in people with PD. Despite promising results in some of the individual studies, meta-analysis was not possible to examine the impact on measures of muscle strength owing to the variety of measures of muscle strength used in the three studies. Secondary outcome measures of the Timed Up and Go and gait velocity were examined also. There was a significant improvement in gait velocity ($p < 0.01$) in favour of the strength group following sensitivity analysis. There was no significant improvement in Timed Up and Go ($p = 0.18$) in favour of the strength group following sensitivity analysis. This review adds to the previous results of the Lima et al, 2013 systematic review in two clear outcomes. Firstly, gait velocity can increase as a result of progressive resistance training when compared with controls. Secondly, stage 4 H&Y participants can take part in and benefit from progressive resistance strength training as seen in Li at al, 2012.

2.4.2 Current literature

The update of the Lima et al, 2013 systematic review was a key component of the justification of an exercise intervention for advanced stage people with PD. The authors hoped to capture the impact of progressive strength training on both early and later stage PD (H&Y 3 to 5). There was only one study (Li et al, 2012) that included people with PD of

stage 4 H&Y. It is not surprising that stage 5 H&Y has yet to be included in strength reviews owing to the low level of function of this predominately bed bound cohort of people with PD. The inclusion of people with PD at later stages, in this case stage 3 to 4 H&Y, supported the author to justify a progressive strength training programme within a palliative setting. This section outlines the results in the context of the current literature considering the primary outcome measure and the secondary outcome measures separately.

2.4.3 Primary OCM

The primary outcome of muscle strength was not pooled for analysis owing to the variety of outcome measures of muscle strength in the included studies. The review by Lima et al, 2013 did find that muscle strength increase was as a result of progressive resistance training with a standardised mean difference of 0.50 kilograms (95% CI 0.05 to 0.95, I2 = 0%). The significant improvements in measures of muscle strength, seen in Lima et al, 2013, are in line with the studies included in this review. All three studies Li et al, 2012 ($p = 0.01$), Hass et al, 2012 ($p < 0.01$) and Paul et al, 2014 ($p < 0.01$) showed significant improvements in their respective measure of muscle strength or muscle power in people with PD. This has also been confirmed by a recent systematic review with meta-analysis by Tillman et al, 2015. Tillman et al, 2015 had significantly different inclusion and exclusion criteria to this review, most notably was the inclusion of studies that did not specifically have a measure of muscle strength but could have a measure of balance or gait speed instead [73]. The main aim of the Tillman et al, 2015 review was to examine the impact of progressive resistance training on measures of gait and balance in people with PD. 359 studies were identified in the review and seven were included in meta-analysis. The participants of the studies included ranged in

H&Y from stage 1 to 3, mean age was 66 ± 3.5 years and mean duration of PD was 7.1 ± 1.8 years. Measuring muscle strength was seen by the author as a key method to examine the effectiveness of progressive resistance training in people with PD. Despite this six of the seven studies review by Tillman et al, 2015 included a measure of leg strength. Overall a significant improvement similar to Lima et al, 2013 was found across the trials in improving leg strength ($p < 0.01$). The results of this review, as with Lima et al, 2013, are limited to people with PD at stage 1 to 3 H&Y. The individual result of this review, the previous Lima et al, 2013 review and the more recent Tillman et al, 2015 systematic review support the statement that 'progressive resistance strength training improves muscle strength in people with mild to moderate (H&Y 1 to 3) PD' [10, 73]

2.4.4 Secondary outcome measures

The lack of improvement in measures of physical performance is in line with current literature in strength training for people with PD. A study by Goodwin et al, 2011 examined a multi-modal exercise programme to reduce falls (n = 64) when compared with usual care (n = 66) in people with PD (H&Y 1 to 4). The authors included the Timed Up and Go in the battery of secondary outcome measures [74]. After a ten week once weekly group exercise programme with twice weekly home exercise there was no significant improvement in Timed Up and Go scores for the cohort of patients at either the post intervention ($p = 0.95$) or follow up ($p = 0.72$) time points. The Goodwin et al, 2011 study did not have a robust method of assessing muscle strength and the progressions of the strength training were not well reported, however the results are also consistent with the non-significant result of this review.

The improvement in gait velocity ($p < 0.01$), as described in the results section, is the main original finding of this review when compared with Lima et al, 2013. Despite Lima et al, 2013 finding an improvement in fast walking speed (0.13 metres per second) this was found to be non-significant on analysis. The Tillman et al 2015 systematic review did not confirm these findings and found that there was no significant improvement after progressive resistance training programme on gait speed (SMD 0.418, 95% CI -0.219 to 1.055).

2.4.5 Clinical Implications

This study, coupled with the results of the original Lima et al, 2013 review, suggests there is evidence for progressive resistance training interventions as a treatment to improve the symptoms of people with PD (H&Y 1 to 4), specifically muscle strength, walking capacity and most recently gait velocity. Interventions should include a measure of muscle strength to ensure they meet an appropriate level of progression in training. Based on the current available evidence, the frequency should be at least two days a week for 10 weeks although it should be noted that this is mainly generalisable for mild to moderate people with PD and lower frequency levels may be applicable for people with later stage PD. Interventions should be progressive in nature and the type of exercise should target the muscle groups that relate to improvements in function in, i.e. lower limb exercise if the overall aim is to improve walking.

2.4.6 Strengths and Limitations

This systematic review with meta-analysis further explored the impact of progressive resistance training on people with PD and contributed with original findings in improving gait velocity and the inclusion of stage 4 H&Y people with PD. The review search strategy was aimed only at randomised controlled trials and quasi-randomised controlled trials to inform current practice. The search terms used were previously used successfully by Lima et al, 2013 to examine the current literature with 85 papers reviewed during this review process. The robust methodology and inclusion and exclusion criteria used identified and selected studies likely to impact muscle strength. Quality assurance checks to ensure the accuracy of the data extracted were undertaken throughout the review process with two reviewers reviewing the methodological quality independently using validated criteria.

However, the findings from the review have to be considered in light of the study limitations. It is important to note that the low number of studies (n = 3) is a clear limitation in the generalisability of these results. Despite Li et al, 2012 including stage 4 H&Y people with PD the population in question was mainly from the early stages of PD (H&Y 1 to 3) and as such limits the generalisability of the results to later stage PD patients. The methodological quality of the studies was variable with two studies scoring a low risk and one study an unclear risk of bias. The lack of a standardised battery of outcome measures used for muscle strength in people with PD limited the ability to statistically pool results. Three studies were included for analysis and all included a measure of strength but it was not possible to pool their results for meta-analysis. Finally the small numbers included in two of the studies Hass et al, 2012 (n = 9) and Paul et al, 2014 (n = 18) meant that the Li et

al, 2012 was given a high weighting when completing sensitivity analysis (80.9-86.5%). The high weighting reduces the impact of this reviews meta-analysis as it relies highly on the Li et al, 2012 study.

2.4.7 Areas for future research

Future studies should look to explore the impact of progressive resistance training on the later stages of PD (3 to 5 H&Y). Studies should also look to explore what minimal level of progressive resistance training is required to elicit an improvement in muscle strength in people with PD and secondary measures of physical performance. The lack of a consistently used measure of muscle strength in progressive resistance interventions for people with PD limits the ability for comparisons and systematic reviews to examine the relationship between muscle strength and progressive resistance training in people with PD.

There is a need to assess the impact on quality of life and participation restrictions experienced by people with PD who take part in progressive resistance training. To this end, qualitative methods should be used concurrently with quantitative methods to fully explore the impact of exercise for people with PD.

2.4.8 Summary

The systematic review with meta-analysis presents evidence for progressive resistance training interventions as a treatment to improve the symptoms of PD (H&Y 1 to 4),

specifically improving walking velocity. When coupled with the results of the previous review by Lima et al, 2013 the improvement of symptoms is noted in people with PD for muscle strength and walking capacity also. The low level of later stage PD participants in this study limits the generalisability of these results to all PD populations. Clinicians should be conscious that the frequency and duration needed to produce significant improvements in measures of PD has not been explored fully in later stage PD (3 to 5 H&Y) and potentially shorter duration trials (6-8 weeks) may elicit improvements in this more vulnerable population. To this end, Chapter 3 will outline the methodology to examine a hospice based, lower limb progressive resistance training programme for people with later stage PD.

Chapter 3 Methodology

3.1 Introduction

PD is a progressive neurological disorder. The prevalence of PD in Europe, estimated at 1.2 million in 2005, is expected to double by 2030 [75, 76]. The incidence of PD in men is approximately 1.5 times higher than in women [77]. PD has an estimated annual economic cost of €13.9 billion throughout Europe with most costs incurred through inpatient and nursing home care [62, 78]. The main clinical features of PD are bradykinesia, tremor, postural instability and rigidity, however a range of motor and non-motor symptoms can occur [79]. PD is usually classified using the H&Y scale of 1 to 5, with one being the least symptomatic and five being the most symptomatic [8].

Pharmacological therapy is the primary treatment modality for PD and serves to limit the clinical manifestations of the condition [80, 81]. Exercise and physical activity is a significant component of the non-pharmacological management of PD [82]. The management of patients with non-pharmacological therapies is particularly important in the later stages of this disease as symptoms become more challenging to manage with medication alone. In recent years research has demonstrated that there is a role for specialist palliative care services for PD patients [83, 84]. The need for palliative care has been identified between H&Y stage 3 to 5 or after approximately 12 years since PD diagnosis [83, 85]. A cross sectional survey of 82 people with PD found that 80% of advanced stage PD patients (3 to 5 H&Y), reported symptoms including pain, fatigue, day time somnolence and difficulty with

their mobility [1]. Mobility issues are one of the most frequently reported debilitating symptoms in this patient cohort.

The previous chapters have explored, through systematic review and meta-analysis of the totality of evidence, exercise interventions aimed at people with PD. It was shown in Chapter 1 that despite promising results in measures of impairment (UPDRS motor, $p = 0.05$), activity limitation (SMWT, $p = 0.01$) and participation restriction (Beck depression inventory, $p = 0.03$) post aerobic exercise interventions, there was a lack of research focusing on individuals at later stage PD (H&Y 4 to 5). To this end, an aerobic intervention was not considered appropriate for this population owing to the lack of current research, the high level of aerobic intensity and treatment duration needed to elicit improvements in symptoms of PD. The author was also concerned with prescribing high intensity aerobic exercise for an advanced stage PD cohort due to the well documented cardiovascular dysautonomia at all stages of PD [86] coupled with the inherent increased risk of ischemic stroke for people with PD as seen in a population-based propensity score-matched longitudinal follow-up study of PD patients ($n = 2204$) which showed a hazard ratio of stroke for people with PD when compared to a non-PD population ($n = 44080$) of 2.37 ($p < 0.01$) [87]. These risks were deemed by the author to be excessive for a pilot study to look at aerobic exercise, especially in more advanced stage PD within an out-patient hospice setting.

Chapter 2 focused on strength training as a potential modality for exercise intervention for later stage people with PD. Several studies to date have shown that strength based exercise interventions can positively affect gait parameters in people with PD [10, 19, 88]. The systematic review by Lima et al, 2013 concluded that progressive resistance strength training should be used, in particular when improving walking capacity in people with mild to moderate Parkinson's disease [10]. The literature presented in Chapter 2 expanded on this previous review by Lima et al, 2013 and found that progressive resistance strength training can impact positively on the gait parameters of people with PD (gait velocity, $p < 0.01$) at stage 1 to 4 H&Y. The results from the systematic reviews with meta-analysis, in Chapters 1 and 2, is that both modalities have shown improvement in outcome measures of PD, however only in Chapter 2 were any participants of an advanced disease stage (H&Y 4) included in meta-analysis. There is still a dearth of research examining the impact of strength training programmes on outcomes in people with advanced PD. Therefore the aim of this pilot study is to examine the feasibility of a lower limb strength-based progressive exercise programme for people with PD H&Y Stage 3 or 4 in a hospice out-patient setting.

3.2 Quantitative Methods

3.2.1 Design overview

A group based feasibility study was conducted using mixed methods in the form of quantitative outcome measures and qualitative semi-structured interviews. The modified CONSORT guidelines were followed to ensure the standardized conduct and reporting of this research [35]. The CONSORT 2010 statement includes a 25 item check list with a flow diagram template for participants included in a study. The CONSORT 2010 statement primarily aims to improve completeness, clarity and transparency of reporting of randomised controlled trials. In the absence of standardised guidelines for pre-test post-test intervention studies, we modified the CONSORT statement to consider our study. The methodology for the semi-structured interviews will be explored further later in this chapter.

3.2.2 Setting and participants

The study was conducted in a hospice out-patient physiotherapy department. It was agreed by the multidisciplinary team initially that the participants with PD would not be integrated with the 'usual' population of this hospice which consists primarily of end stage motor neuron, chronic cardiac and chronic respiratory disease as well as palliative stage cancer patients. The reason for this was to expose people with PD to a specialist palliative care environment rather than a specialist palliative care service as it was deemed ethically inadvisable to provide and then withdraw this comprehensive and supportive service and not in keeping with the mission statement and principles of the hospice in question.

Participants engaged with hospice based staff from the physiotherapy service, administration staff and volunteer drivers on a regular basis throughout the study. The HSE describe the aim of palliative care as 'to enhance quality of life and, wherever possible to positively influence the course of illness' as outlined in the National Clinical Programme for Palliative Care [89]. All staff received training by the hospice in the palliative care approach as outlined in the National Clinical Programme for Palliative Care.

3.2.3 Referrals

Patients were referred from the Neurology and Physiotherapy departments of specialist hospitals and from community physiotherapists. The main author engaged with referring departments through formal presentations, one to one education and via phone conversation where appropriate. Referring clinicians were also provided with an information leaflet (Appendix VII) on the PEP-PD study and the inclusion and exclusion criteria. During this process it was highlighted by referring clinicians that several cognitive screening tools were in use across sites and in some cases no screening tool was in use. It was agreed by the author and referring clinicians that clinician opinion of cognition was sufficient as a screening tool for engagement in an exercise programme. The use of clinician opinion was not seen as a definitive indicator of the presence or lack of cognitive impairment but rather the participants' ability to engage in the PEP-PD programme. The following are the inclusion and exclusion criteria agreed by the author and referring clinicians for the PEP-PD study.

3.2.4 Inclusion and exclusion criteria

Participants were considered eligible for inclusion if they had been diagnosed with idiopathic Parkinson's disease by a neurologist, were over 18 years of age, residing in the hospice catchment area to allow for volunteer transport, at an advanced stage of PD (H&Y stage 3 to 4), able to walk with or without an aid for at least ten meters and cognitively able to take part in a rehabilitation programme based on the referring clinician's opinion. Individuals with stage 5 H&Y were not included in this study as these patients are primarily immobile at this stage of disease and the proposed intervention was not appropriate for this cohort.

Participants were excluded if they had engaged in regular exercise over the last six months. For the purposes of this study, regular exercise was defined as 30 minutes formal exercise (gym, swimming, exercise class) three times per week any time over the past six months. A previous study looking at exercise interventions for people with PD, by Shulman et al, 2013, had also excluded participants who had undertaken an exercise programme prior to recruitment to avoid a prior training effect [52].

3.2.5 Participant flow through PEP-PD

Potential participants were provided with an information leaflet (Appendix VIII) by the treating clinician at the community or hospital department where the participant attended. If agreeable, participants were then referred to the hospice by the clinicians at each site. Referrals (Appendix IX) were received by the primary author. Once referrals were received, participants were contacted via telephone to confirm eligibility criteria and to facilitate any questions from participants. If eligible, participants were invited to attend for an initial

assessment where written informed consent (Appendix X) was obtained from all participants.

The revised Physical Activity Readiness Questionnaire (PAR-Q) (Appendix XI) was completed as recommended by the ACSM to aid in identifying the contributing factors that can increase the risks of cardiovascular disease events during and after exercise [46]. Two separate comparative studies by Thomas et al, 1992 and Cardinal et al, 1996, examined this revised version of the PAR-Q. Thomas et al, 1992 examined a cohort of healthy older adults (n = 399) and found that there was a significant reduction in unnecessary exclusions while maintaining safe preliminary screening of exercise participants [90]. Cardinal et al, 1996 examined a cohort of 60-69 year old adults (mean age = 64.82yrs), a similar significant reduction in exclusions was seen ($p < 0.01$) which also supports the concurrent validity of the revised PAR-Q [91]. The patient's general practitioner or consultant neurologist was contacted to discuss the patient's suitability to engage with the exercise programme if the patient answered 'no' to one or more of the questions on the revised PAR-Q.

3.2.6 Predicted one repetition maximum

Participants' lower limb strength was assessed at baseline to determine their predicted one repetition maximum (p1-RM) using the Wathen equation as reported by Mc Nair et al, 2011 [92]. The McNair et al, 2011 comparative study involved patients (n = 18) diagnosed with osteoarthritis of the knee joint attending three separate gym sessions, one familiarisation session, one session to assess one repetition maximum of knee extension and one session where participants performed knee extension with a weight they could lift for approximately ten repetitions. Twelve predictive equations were compared to calculate one

repetition maximum and actual one repetition maximum. Seven of the equations showed the highest levels of predictive accuracy for knee extension (ICC 0.96-0.99). The Wathen equation was one of the seven studies of high predictive accuracy and was chosen as it was one of the least complex equations (Weight (in kilograms) x multiplication factor (based on reps) = p1-RM). An example scenario is as follows: if a patient lifts a 10 kilogram weight five times successfully, and then cannot achieve the sixth repetition. The multiplication factor would be 1.17, which equates to five repetitions. The formula would then consist of 10 x 1.17 = 11.7 kilograms as their p1-RM. Table 3.1 outlines the Wathen equation multiplication factors and is included below.

Table 3.1 – Predicted one repetition maximum Wathen equation multiplication factors for assessment of PEP-PD participants

Repetitions	2	3	4	5	6	7	8	9	10
Multiplications factor (Wathen)	1.05	1.09	1.13	1.17	1.20	1.24	1.28	1.31	1.35

The p1-RM was used as both an outcome measure of muscle strength and to establish a baseline training weight for participants tailored exercise programme. The p1-RM was established bilaterally for the following movements: knee extension, knee flexion, hip extension, hip flexion and hip abduction. These exercises were based on the systematic review of the literature in Chapter 2, specifically the Paul et al, 2014 study found exercises targeting the leg extensors, knee flexors, hip flexors and hip abductors resulted in increased leg muscle strength ($p < 0.01$) [72]. The Paul et al, 2014 study was used in the selection of exercises for this study as ankle weights are prevalent anecdotally in Irish physiotherapy

whereas weighted vest rehabilitation is not commonly used as a treatment technique as seen in Li et al, 2012 [54]. This was decided by the author to ensure a pragmatic and clinically relevant intervention was implemented.

3.2.7 Intensity

Patients' training weight was between 40-70% of the p1-RM [46]. The Garber et al, 2011 position stand 'Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise' from the ACSM was used as the basis of the progression and prescription of weights for the PEP-PD study. In the position stand the resistance exercise frequency and intensity recommendations are outline in 'Table 3.2: Evidence statements and summary of recommendations for the individualized exercise prescription'. The position stand used a four point rating scale for the quality of the evidence supporting recommendations. The rating scale was from A to D with A representing the highest quality (endpoints from well-designed randomised controlled trials) and D the lowest (consensus of the position stand expert panel). The position stand found A category evidence to support the targeting of between 40-50% of 1-RM for older persons beginning to improve strength and similar evidence for 60-70% of 1-RM for novice to intermediate exercisers to improve strength. It was decided by the author to combine these results and recommend the 40-70% of p1-RM as the training level for PEP-PD participants to allow for individualisation of exercise programmes.

Training weights were adjusted based on the clinical judgement of the physiotherapist facilitating the exercise class. Clinical judgement was supported by several objective and

subjective areas of assessment and review when participants were training, such as; equipment used, body position before and during the exercise performance, starting and ending point of motion, cadence of motion, use or non-use of pause points during set, performing technique of exercise, clothing worn for exercise, time of day of exercise, energy level of client, motivation of client towards exercise and adequate rest between repetitions. Based on the above clinical judgement, participant's weights were either increased or maintained at current level by the prescribing therapists. The weights used varied from between two to 12.5 kilograms. Each weighted ankle cuff was fitted with five removable weighted pouches of 0.5 kilogram with higher weighted pouches available of 1 kilogram as needed. If participants exceeded the amount that one ankle cuff could support a second ankle cuff was attached to the same leg to provide increased weighted resistance. Participants were trained in their initial treatment in the management and application of the ankle weights used, including safe techniques on transporting the ankle weights to and from the hospice and home setting.

3.2.8 Frequency

The PEP-PD programme consisted of one exercise session per week, for six weeks that was completed at the hospice under supervision of a physiotherapist. Volunteer drivers supported the transport of participants to and from the hospice setting as part of the PEP-PD programme, this is a standard service for all patients attending the same hospice. Participants also completed two independent sessions per week at home during the programme. The use of a once weekly supervised exercise session with subsequent home based and unsupervised exercise has been used previously in a pragmatic randomised

controlled trail by Goodwin et al, 2011. Adherence was monitored with a weekly phone call by the lead author or at weekly hospice based sessions.

The reduced duration of the study (6 weeks) in comparison to the literature recommendations in Chapter 2 (10 weeks) was decided by the author as the majority of research previously undertaken is aimed at people with early stage PD and the Garber et al, 2011 statement states clearly that lower levels of exercise can improve function in more sedentary older adults that recommended in the position stand [46]. A systematic review with meta-analysis looking at resistance training for older adults by Peterson et al, 2010 included 47 studies with 1079 participants in total and a mean age of 67.4 years [93]. Peterson et al, 2010 found a strong association between resistance training and increased muscle strength ($p < 0.01$). The review reported trial durations, for included studies, of between 6 to 52 weeks. The findings of the Peterson systematic review coupled with the pragmatic approach towards service provision by the study author led to the six week intervention duration.

3.2.9 Type

The ankle weights used were portable, and taken home by participants to do home based exercises, as mentioned above participants were show the correct technique to transport these weights. The exercise programme both supervised and unsupervised consisted of five exercises, with three sets of eight repetitions for each exercise with a three second hold during each repetition at the end of range. Three sets of eight repetitions has been shown in previous studies to be an appropriate number of repetitions to promote muscle strength in people with PD; one randomised controlled trial that saw an improvement in muscle

strength ($p \leq 0.01$) prescribed three sets of eight repetitions [72]. Three sets with eight repetitions were also recommended by Garber et al, 2011.

The exercises were performed with parallel bars for hand support and chairs with arm rests for breaks between sets while in the out-patients department of the hospice. Participants were advised to replicate the exercise programme at home by using a firm surface (chair, table, sink…etc) for support when performing exercises at home and having a chair nearby for regular rests between sets.

3.2.10 Time

Supervised exercise sessions lasted 40-60 minutes, mostly the programme was 40 minutes in duration however the initial two weeks were often longer (50-60 minutes) to allow participants to discuss the application and management of the ankle weights. Participants were provided with a written individualised home exercise programme (Appendix XII) on a weekly basis and asked to complete and return the programme for the author to review.

3.2.11 Education sessions and refreshments

Participants were provided with water throughout the exercise programme. Immediately after the exercise session participants were provided with light refreshments consisting of tea, coffee, water and biscuits. During this time, an informal education session took place to allow participant to discuss any challenges or queries they had with the programme. Participants were supported by the therapist in any topic of interest they had questions on and regularly the treating therapist conducted informal education sessions based on topics of interest to the participants present. Topics that were discussed included; falls prevention

at home, tips and tricks to improving handwriting, identifying the role of different PD medications and finally the benefits of exercise in people with PD.

3.2.12 Outcomes

The categories or classifications of functioning outlined below are reported in the International Classification of Functioning, Disability and Health outlined by the World Health Organisation; the ICF is an internationally recognised method of classification of disability and has been applied previously in a cross sectional study of people with PD (n = 96) which showed that the impact on bodily functions has a direct effect on activity and participation in people with PD [94]. Participants completed a baseline assessment with a blinded assessor using outcome measures of impairment, activity limitation and participation restrictions in line with ICF classifications. Owing to the advanced stage of participants and the impact of medication halting for 12 hours to ensure a true 'Off' medication period participants were assessed in the 'On' phase of medication for pre, post and six month follow up assessments.

3.2.12.1 Primary outcome measure

As mentioned previously the main symptom of interest for this thesis is 'problems with mobility' as this has been identified by late stage people with PD as one of four most reported symptoms of PD in a recent cross sectional study by Saleem et al, 2013 [1]. The primary outcome measure of this study was the six minute walk test (SMWT). The SMWT has been used previously in a large cross sectional study (n = 515) of older people in Australia. The study found that the SMWT is dependent on several variables factors such as physiologic, psychologic, and health factors and as such is an appropriate measure of overall

mobility and functioning [95]. The Lima et al, 2013 systematic review found that progressive resistance strength training could significantly improve the SMWT by standardised mean difference of 96 metres when compared to control groups, however this was only in mild to moderate people with PD (H&Y 1 to 3) [10]. A cross sectional study looking at the test re-rest reliability of the 36 item short form health survey and UPDRS found that upon testing a cohort of community dwelling people with PD (n = 37), the reliability score was of above 0.90, and minimal detectable change was 82 meters [38]. The large minimal detectable change is attributed to the varying severity of H&Y stages in people with PD.

3.2.12.2 Secondary outcome measures

Secondary outcome measures included the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and the Parkinson's Disease Questionaire-39 (PDQ-39). The MDS-UPDRS is the revised version of the UPDRS and is the gold standard measure of disease severity and impairment for PD. Upon revision of the UPDRS (55 items) there were an additional ten items for assessment in the new MDS-UPDRS (65 items). The MDS-UPDRS has four parts; I: Non-motor Experiences of Daily Living; II: Motor Experiences of Daily Living; III: Motor Examination; IV: Motor Complications. A cross sectional study examining the UPDRS versus the MDS-UPDRS found that the MDS-UPDRS had high internal consistency (Cronbach's alpha = 0.79-0.93) and equally high correlation with the UPDRS (rho = 0.96) [96].

The PDQ-39 is a measure of quality of life in people with PD, a systematic review by Marinus et al, 2002 compared and contrasted disease related quality of life measures for Parkinson's disease [97]. The systematic review found twenty studies examining four scales of quality of

life in people with PD. The four scales were the PDQ-39, the Parkinson's disease quality of life questionnaire (PDQL), the Parkinson's impact scale (PIMS) and the Parkinson LebensQualität (PLQ). Internal consistency was found to be high (Cronbach's alpha > 0.8) in all four measures, test re-test reliability was high for the PDQ-39 (r=0.68–0.94) and overall the study suggested that the PDQ-39 was the most extensively tested and likely most appropriate measure of health related quality of life in people with PD.

Participants attended for a post-intervention appointment in the same hospice out-patient setting as the intervention took place in, where primary and secondary outcome measures were then reassessed. The p1-RM was repeated by the blinded assessor. Participants were also invited to take part in semi-structured interviews facilitated by an external researcher trained in qualitative interviewing; the methodology of these semi-structured interviews will be explained in Section 3.3.3.

3.2.12.3 Six month follow up

A follow-up assessment took place at six months using the same battery of quantitative outcome measures as described above. Assessors were only blinded in 55% of assessments at this follow-up, owing to unforeseen staffing issues for blinded assessment. The main assessor was unavailable for periods of the six-month follow up and as such the author had to take over the assessing of participants for the six-month follow up assessment.

3.2.13 Ethical considerations

Ethical approval for both the qualitative and quantitative sections of this study was granted by the Research Ethics Committee at St. Francis Hospice, Dublin on the 16th of April 2014.

There was a single modifier, however this was reviewed and decided that an unmodified ethical approval would be granted by the Research Ethics Committee on the 25th June 2014 (Appendix XIII). An amendment was made by the author via letter on the 27th of August 2014 to conduct a six month follow-up of participants and this was approved on the 15th September 2014 (Appendix XIV).

In line with the Research Ethics Committee of St Francis Hospice guidelines informed consent was obtained for all participants included in the PEP-PD study. Potential participants were provided with an information sheet by the referring clinician outlining the program. The participants were then contacted by telephone by the author. The patients were given the opportunity to ask questions at this point and, if still interested in taking part in the program, they were invited to an initial assessment. At the initial assessment participants were given the chance to discuss any final questions and then asked to sign a consent form before taking part in the outcome measures. There was at least 7 days between initial referral and a consent form being signed, to allow the patient to make an informed and unpressured decision.

Routine care was not affected for any of the participants involved in the PEP-PD programme and referring clinicians were sent a letter outlining the results of the outcome measure assessment of each participant on completion of PEP-PD. Participants were free to withdraw at any time from the PEP-PD programme.

Data protection was in accordance with the guidelines of the Research Ethics Committee of St Francis Hospice. Paper and electronic records as well as transcribed and recorded semi-

structured interviews were collected during this study. All paper records were stored as medical files in St Francis Hospice, Dublin and followed the standard medical records storage requirements. All data was given a unique coded number, the coding number was retained in the medical records file of participants. These were stored securely in a locked fling cabinet in the physiotherapy office St Francis Hospice Blanchardstown. All data was anonymised and stored on the encrypted "O" Drive of St Francis Hospice in a specific folder accessible only to clinicians involved in PEP-PD. In accordance with the ethical guidelines of the Research Ethics Committee of St Francis Hospice, records will be kept for 5 years to ensure any information requests from patients in future is accessible for a reasonable timeframe.

3.2.14 Statistical analysis

Data was transferred to Microsoft Excel for screening and cleaning. An independent quality check of 20% of entries verified the accuracy of the data entry. Distribution of continuous data was assessed using the Shapiro-Wilk W test for normality, due to the small sample sizes of the included studies; a significant result for normality to be violated was seen as $p < 0.05$. Descriptive statistics were used to represent the data including means and standard deviations. When Shapiro-Wilk W test for normality was $p > 0.05$ the paired t-test was used to assess parametric results and when normality was violated $p < 0.05$ the Wilcoxon signed-rank test was used for all non-parametric results pre and post intervention. The paired-samples t-test is used to compare the mean differences between paired observations and determine if there is a statistically significant difference from zero. Wilcoxon signed-rank test is used to compare median difference between paired or matched observations.

A one-way repeated measures analysis of variance (ANOVA) was applied to examine the change in outcomes over the three time points. Bonferroni methods were used to adjust for multiple comparisons. All statistical tests were completed using STATA version 13 (StatCorp, Texas, USA) and SPSS Statistics version 21 (IBM, NY, USA). Significance was set at $p < 0.05$.

3.3 Qualitative Methods

3.3.1 Introduction

This section outlines the methodology of the qualitative semi-structured interviews post PEP-PD intervention. To further enhance the robust quantitative methods described above, qualitative methods were used to gain a deeper insight into the experience of the participants in taking part in the PEP-PD trial. The COREQ standardised reporting were adhered to, to ensure the uniform conduct and reporting of the qualitative research. The COREQ criteria consists of a 32 item checklist outlined by Tong et al, 2007, after a comprehensive review of the literature to examine existing checklists of qualitative reporting [98]. After reviewing the available literature three studies were found to have examined the impact of physical exercise for people with PD using qualitative methods [99-101].

Crizzle et al, 2012 invited participants with PD (n = 4) who undertook a hydrotherapy programme aimed at improving the functional abilities of people with PD and their caregivers (n = 4) to attend a focus group looking to uncover the motivators and barriers to exercise adherence in people with PD. Two of the participants with PD were stage 2 H&Y

and two were stage 3 H&Y. The focus group may have limited the ability for the participants with PD to discuss openly their motivators and barriers as the group included both people with PD and their caregivers. The authors discovered three themes that motivated people with PD to remain exercising on analysis of the transcripts; reassurance from the instructor; group structure and group support; and improved psychological well-being from perceived physical benefits.

Eriksson et al, 2013 examined eleven people with PD after participation in one of two exercise programmes based at a physiotherapy department in a Swedish hospital. The exercise programmes were multi-modal and consisted of either aerobic training or a circuit of strength training, joint mobility and gait training. Two of the participants were at stage 4 H&Y and the remaining nine participants ranged from stage 1 to 3 H&Y. In-depth individual semi-structured interviews were conducted by the author to explore and capture participants' experiences of exercising when living with PD. The study identified one core category and six other categories that helped to maintain exercise adherence for participants. The core category was 'Keep moving to retain the healthy self' and the six other categories were; 'Having explicit life goals'; 'Having confidence in one's own ability'; 'Taking rational position'; 'Exercising to slow progression'; 'Exercising to achieve well-being'; and 'Using exercise as coping strategy'.

Finally, O'Brien et al, 2008 was the only qualitative study found to examine progressive resistance training only in people with PD as a stand-alone community based exercise

intervention. Thirteen individuals with Parkinson's disease were included in the study of which only three participants were stage 3 or 4 Hoehn and Yahr. The main themes identified were; motivators for participation in the strength programme were broader than physical outcomes; the outcomes of the programme were broader than just physical outcomes; indicators of success for participants varied; and the participants' experience of a disease-specific exercise programme was positive.

Overall the three studies provided a template for the development of the PEP-PD semi-structured interviews. Crizzle et al, 2012 highlighted the importance of separating caregivers and people with PD as a potential limitation for interviewing. Crizzle et al, 2012 also highlighted the need to examine the impact of the instructor and group support on people with PD. The author found the idea of participants retaining 'the healthy self', in the study by Eriksson et al, 2013, to be pertinent to a group of advanced stage people with PD integrating with a palliative care setting. Finally the O'Brien et al, 2008 study showed the importance of combining qualitative methods and quantitative methods to develop the full understanding of the impact of progressive resistance exercise on the non-physical outcomes of patients. The main points in analysing the challenges and barriers of the participants in the PEP-PD study, following review of the above studies, were the following: the participants' personal experience of PEP-PD, their experience of a hospice setting and palliative team, the physical and non-physical effects as experienced by the participants and the key areas for improvement for this study.

The advanced PD cohort of participants and unique environment of a hospice outpatient clinic setting are the unique characteristics of the PEP-PD qualitative semi-structured interviews. The aim of the qualitative semi-structured interviews was to examine the lived-in experience of people with advanced PD who took part in a progressive strength training protocol in a hospice out-patient clinical setting.

3.3.2 Theoretical framework

A grounded theory methodology and phenomenological framework were used in the data analysis of the qualitative component of this study. A phenomenological framework and grounded theory methodology have previously been used successfully in the analysis of rehabilitation for people with Parkinson's disease [65]. Phenomenological theory subscribes to the view that the researcher should put away their own beliefs and conceptions and look at an issue through the view point of the person experiencing them. This theory suggests that rather than a single correct answer or set of answers each individuals experience is inherently different, unique and therefore subjective. Phenomenological studies aim to identify, understand, describe and ultimately maintain the unique experiences of participants and in so doing develop new understandings [102]. The interviews allowed for this exploration of the 'lived-in' experiences of the PEP-PD participants.

Grounded theory methodology provides a structure for the analysis of data through grounding the resulting theory in the data collected [103, 104]. Similar to phenomenological theory, grounded theory assumes that data should not be influenced by previous theories

and should be grounded in the data collected. The aim of the PEP-PD author was to set aside any pre-conceptions of the assessors and any knowledge they have of the barriers and facilitators to exercise for people with PD. This includes not only negative but also positive experiences, pre-conceptions or knowledge they might have.

3.3.3 Qualitative study

An independent experienced qualitative researcher blinded to participant results undertook a semi-structured interview with participants. The assessor is a physiotherapist and to that end, there was a requirement to identify preconceived perceptions on the role of exercise and rehabilitation in PD so that the potential for any interviewer bias was considered a priori [105]. The semi structured interview questions were based on previous literature, as outlined above, focusing on the experience of exercise for individuals with PD and their caregivers [99-101]. In the current study, question one examined the benefits and negatives of the PEP-PD programme and was based on questions 2 and 3 from the Crizzle et al, 2012 study. Question two of the current study focused on the experience of being in a hospice and the palliative stage of the disease was based on the theme of 'Exercising to slow progression', from the Eriksson et al, 2013 study, particularly relating to the connotations that a hospice setting would have a negative impact on motivation for PEP-PD participants. Question four was based on the theme of 'outcomes of the programme were broader than just physical outcomes' as identified in the O'Brien et al, 2008 study, to further explore the impact of the PEP-PD programme in the broader context of the disease. The remaining questions were based on the clinical experience of the author and his supervisor.

The questions consisted of five main topic areas and questions with clarification questions to aid the interviewer and participants if prompting was necessary. The topic areas and questions are outlined below in Table 3.2.

Table 3.2 - PEP-PD qualitative semi-structured interview questions

Topic and questions	**Clarification points**
	1. Experience of PEP-PD
Q. What are your thoughts about taking part in this exercise programme?	Were there any benefits to taking part for you? Were there any negatives or barriers to taking part for you? Would you recommend the programme to another patient?
	2. Experience of being in a hospice setting
Q. What are your thoughts about attending a programme in a hospice setting?	Do you feel that the terms 'advanced Parkinson's' and 'palliative Parkinson's' are the same? Do you have any concerns or reservations about attending a programme in a hospice setting?
	3. Changes to the programme
Q. Is there anything that you change about the exercise programme?	What were your thoughts on the assessment at the beginning and at the end? Was the assessment too long/too short? Did you think the information you were given could be improved or changed in any way? Do you think the class was too slow or too fast? Were the exercises relevant to you? Did you experience any difficulty/challenges in completing all of the exercises?
	4. Effect of PEP-PD
Q. Do you think taking part in this programme has changed your attitude to exercise in any way?	Will you continue to exercise after this programme? What would you need to continue exercising? Explore the barriers and challenges.

Additional questions: Why did you come to the class initially? What did your next of kin or carer or family think of you attending the group?

3.3.4 Interview scheduling

The interviewer conducted the interviews over three separate days as the study was conducted over several months. Through examination of the questions and participant responses the interviewer was able to revise or amend the questions as the interviews progressed to explore further any relevant topic areas. Topic 2 – 'Experience of being in a hospice setting' main question 'Did you have any concerns or reservations about attending a program in a hospice setting?' was amended to explore the negative connotations further and the term 'Palliative' was omitted due to the potentially confusing connotations once the topic was explored in early interviews. Topic 3 – 'Changes to the programme' was amended to further explore any negative experiences of the programme as early interviews had minimal negative experiences to explore.

3.3.5 Data Analysis

All interviews were audio recorded, transcribed verbatim by professional typists and reviewed by the researcher. A code was assigned to all participants to ensure anonymity and any identifying information (locations, names or patient identifiers) was removed from the transcriptions before analysis began. The transcripts were initially reviewed by the researcher and line by line analysis was used to examine recurring themes which were grouped into subcategories. These sub-categories were documented and then formed the basis for the main categories from this study. An initial coding system was developed from the recurrent phrases and themes and both reviewers (the author and supervisor) met to agree on the suitability of the coding system and discuss any amendments. A final coding

system was agreed upon and the reviewers examined the coding system for suitability by assessing inter and intra-rater reliability.

Inter-rater and intra-rater reliability was established based on the described methods from Miles and Huberman, 1994 [106]. Measuring intra and inter-rater reliability is similar to the reliability and validity analysis of quantitative research and ensures transparency of quality and trusted research methods [107].

Miles and Huberman 1994 suggest that several authors review unencoded text using the same coding system. In this study two authors reviewed the coding system by analysing an unencoded interview independently. The authors responses were reviewed and compared for analysis of reliability. Inter-rater reliability is suggested to be near 70% by Miles and Huberman, 1994. In PEP-PD inter-rater reliability was 87% for the unencoded interview.

Intra-rater reliability was assessed for this study for the main author by using the coded interview and allowing an appropriate time to elapse, in this case several days after coding. The second coding was then compared with the original coding used for inter-rater reliability. Miles and Huberman, 1994 anticipate a higher level of reliability of near 80%, in this study the intra-rater reliability was 90% for the newly coded interview.

Following the analysis of inter and intra-rater reliability the two authors met to discuss the above disagreements and resolve the differences identified. One new code and an amended theme nomenclature was agreed to ensure an accurate representation of the data collected.

3.3.6 Triangulation of qualitative and quantitative data

The use of mixed methods or plural methodology, the inclusion of more than one viewpoint that of objective impact and also subjective experience, is increasingly recognised as a crucial part of research methodologies [108]. The term triangulation is used to describe this pluralistic approach and the inherent benefits to the analysis of a research phenomenon. Through analysis and examination of a research phenomenon using two different approaches the anticipation is that the two sets of evidence will converge on a single outcome [108]. The probability of an inaccurate result from the research in question is thusly diminished through triangulation.

In the PEP-PD study the participants were firstly assessed using a battery of quantitative outcome measures spanning the international classification of function domains and secondly assessed using qualitative semi-structured interviews. The basis of triangulation in the methodology employed in this study further enhances the depth and breadth of the results outlined in the preceding Chapter 4 and Chapter 5 and the resulting conclusions drawn.

Chapter 4 Quantitative Results

4.1 Introduction

In Chapter 3, both the quantitative and qualitative methodologies were described and justified in full. This chapter outlines the results from the quantitative component of the PEP-PD study. The results are broken down into discrete sections that serve to describe the participants' demographic data, outcomes on the primary outcome measure and secondary outcome measures. A discussion of the results in the context of the current literature follows the results section and describes the clinical implications of PEP-PD. Finally, the strengths and limitations of the PEP-PD study are considered.

4.2 Results

4.2.1 Demographic data

In total, nineteen referrals were received via mainly postal referral from two main neurological clinics and one community based physiotherapist within the catchment areas over a six month period. The referrals were received over three separate recruitment phases for each group of between four to five participants.

Four participants answered no to one or more sections of the Physical Activity and Readiness Questionnaire (PAR-Q) at the initial phone call stage. The most common positive responses were for the following questions 'Do you lose your balance because of dizziness or do you ever lose consciousness?' (n = 1) and 'Do you have a bone or joint problem (for example, back, knee, or hip) that could be made worse by a change in your physical

activity?' (n = 3). The participants' preferred healthcare professional was contacted by the author and the four participants were included following discussion with their general practitioner or neurologist. The reasons for participant concern in relation to issues with balance and dizziness were due to the participants' known hypotension as a result of the PD medications they had been prescribed. This was not considered as an absolute contraindication to exercise by the participants' health professional as safety issues regarding falls risk were assessed prior to and during the intervention. The three participants reporting a bone or joint problem that could be exacerbated by exercise were considered appropriate to engage in exercise owing to the minimal impact of the bone or joint problem on their engagement in the class.

Sixteen participants consented to participate in the study and were screened by the primary author by initial phone call. Two participants were subsequently deemed ineligible as they were medically unwell prior to assessment. Fourteen participants took part in the full PEP-PD programme and only one participant was unable to attend all sessions due to unrelated back pain.

The programme ran over nine months and included three groups of between 4 and 5 participants. Thirteen participants completed the pre and post outcome measure assessments; one was unable to complete the post p1-RM on medical advice following minor surgery. Nine participants completed the six month follow up assessment. The flow of participants through the study is displayed in Figure 4.1.

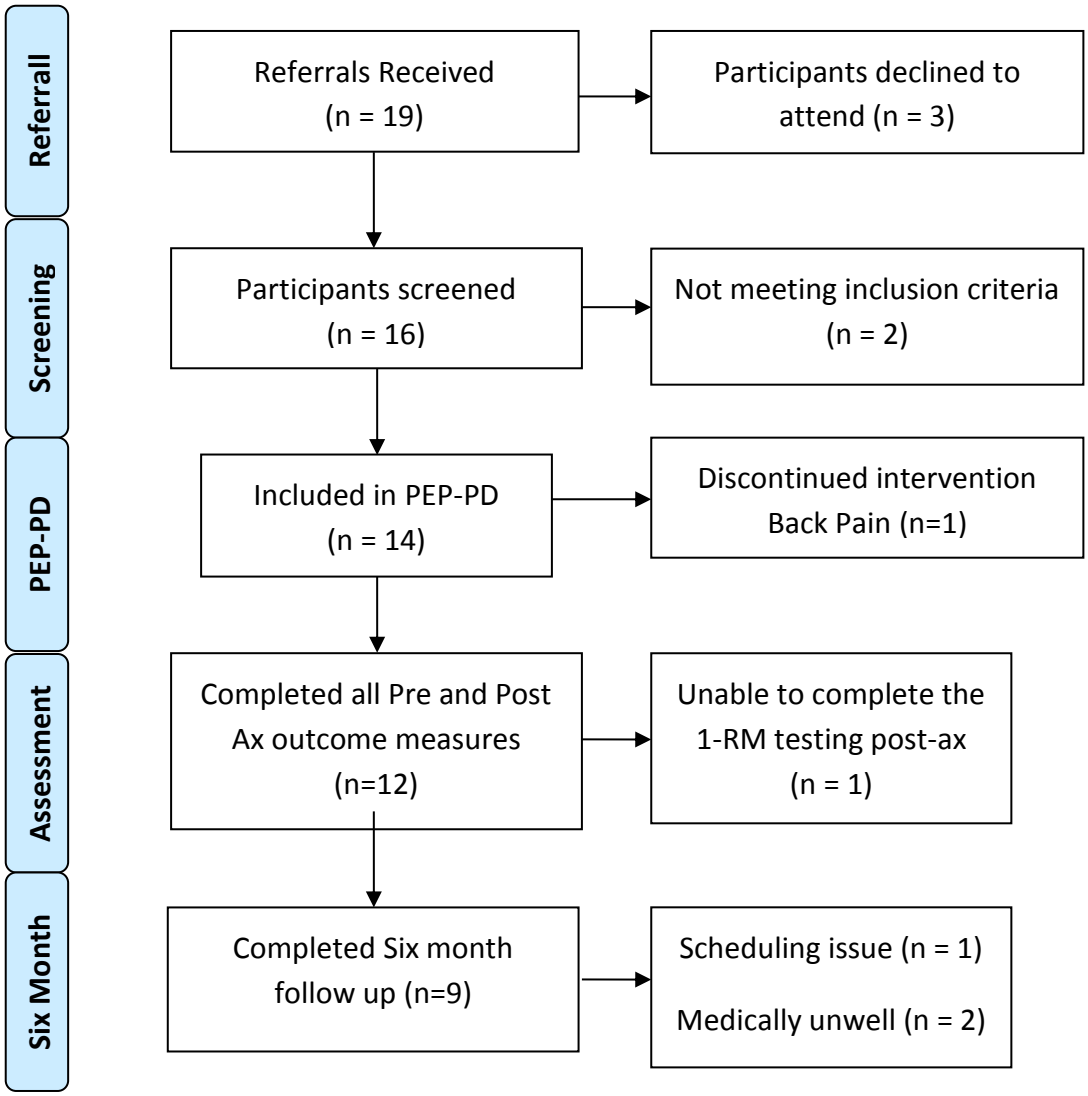

Figure 4.1 - Flow diagram of participants included in PEP-PD

Participants were aged between 57 and 85 years with a mean age of 69.8 years (SD = 7.2 years). Time since diagnosis varied from three months to over 44 years, with a mean of 14.1 years (SD = 16.3 years). All participants were diagnosed by their consultant neurologist with idiopathic PD and seven were classified at stage 3 H&Y and seven were classified at stage 4 H&Y by the blinded assessor at the pre-assessment point.

Three separate group interventions were completed over a nine month period from December 2013 to August 2014. Ankle weights were increased in 13 of the participants at either the third or fourth week of the exercise programme. This was based on the clinical opinion of the treating therapist who used the outlined subjective and objective assessment points, as outlined in section 3.2.7 in Chapter 3. Weight range remained within 40-70% of the p1-RM, and was increased by 0.5-1 kilogram for all participants.

All participants completed the home exercise programme twice weekly, as reported on attendance at the supervised class or by a weekly phone call. One participant completed the exercises daily for one of the six weeks with some increased leg discomfort and stiffness. The participant was advised to revert to a twice weekly home programme and no adverse events were reported after this. A further participant that was not included due to back pain was advised to discontinue the weighted exercises and was excluded from the final assessment.

The retention rates for the pre and post assessment were very positive with all but one participant taking part in both assessment time points. The six month follow up retention

rate was noticeably worse than previous assessments with three participants failing to attend as seen in Figure 4.1. Attempts were made, where appropriate, to follow up these participants for the purposes of the study. However, the author was unable to contact these individuals to make a follow up appointment.

4.2.2 Activity limitation – primary outcome measure

There was no significant difference in walking capacity from baseline, as measured by the SMWT, at the post intervention assessment [mean change 26.9 meters, 95% CI -8.6 - 62.4), p=0.12] or over the three time points, including the six month follow up [$F(2,16) = 1.442$, $p = 0.266$].

4.2.3 Impairment

A significant improvement was observed in all measures of strength of the lower limb, including hip flexion, hip extension, hip abduction, knee flexion and knee extension at both post intervention ($p<0.05$) and six month follow up ($p<0.05$). There was no significant difference in the measure of disease severity MDS-UPDRS total at either the post intervention [mean change -4.15, 95% CI -13.20 to 4.90, $p = 0.34$] or over the six month time period [$F(2,16) = 0.528$, $p = 0.6$].

4.2.4 Participation restriction

Non-significant changes were also reported for the PDQ-39 total score at both the post intervention [mean change -1.03, 95% CI -6.98 to 4.92, $p = 0.70$] or over time [$F(2,10) = 0.05$, $p = 0.952$].

The results of the outcome measures across the time-points are displayed in Table 4.1.

Table 4.1 – PEP-PD summary of the qualitative outcome measure results and data analysis

Outcome measure	Baseline		Post		Mean difference**	P value	6 Month		Mean difference	P value
Predicted 1-Rep Max (Kg)										
	N	Mean (SD)	N	Mean (SD)			N	Mean (SD)		
Knee Extension Right	14	10.52 (SD 3.69)	12	14.19 (SD 5.85)	4.09 (1.92 - 6.26)	<0.00	8	14.84 (SD 2.93)	5.55 (1.99 – 9.11)	<0.00
Knee Extension Left	14	9.5 (SD 3.49)	12	13.87 (SD 5.35)	4.81 (3.14 - 6.47)	<0.00	8	13.60 (SD 3.61)	5.51 (2.36 – 8.66)	<0.00
Hip Flexion Right	14	9.62 (SD 3.50)	12	15.95 (SD 7.23)	6.51 (3.74 - 9.28)	<0.00	8	17.54 (SD 3)	9.60 (6.27 – 12.93)	<0.00
Hip Flexion Left	14	8.94 (SD 3.3)	12	15.47 (SD 6.29)	6.79 (3.56 - 10.03)	<0.00	8	17.38 (SD 3.17)	10.42 (5.73 – 15.1)	<0.00
Hip Extension Right*	14	8.56 (SD 3.51)*	12	15.15 (SD 6.93)		<0.00	8	18.75 (SD 5.22)	11.88 (6.04 – 17.71)	<0.00
Hip Extension Left	14	7.82 (SD 3.88)	12	15.15 (SD 7.11)	7.74 (4.64 - 10.85)	<0.00	8	16.9 (SD 4.89)	11.61 (5.83 – 17.38)	<0.00
Hip Abduction Right	14	10.47 (SD 4.37)	12	16.58 (SD 7.29)	6.90 (4.17 - 9.63)	<0.00	8	19 (SD 4.3)	11.03 (5.71 – 16.35)	<0.00
Hip Abduction Left*	14	9.40 (SD 4.06)*	12	16.63 (SD 8.15)		<0.00	8	17.4 (SD 3.94)	10.66 (5.72 – 15.6)	<0.00
Knee Flexion Right	14	7.96 (SD 3.20)	12	15 (SD 5.75)	7.34 (5.51 - 9.18)	<0.00	8	16.51 (SD 2.47)	9.54 (5.44 – 13.64)	<0.00
Knee Flexion Left	14	7.60 (SD 2.95)	12	14.46 (SD 6.24)	7.14 (4.20 - 10.08)	<0.00	8	14.76 (SD 4)	8.71 (3.53 – 13.89)	<0.00
Six minute walk test (m)	14	305.71 (SD 138.41)	12	327.30 (SD 134.04)	26.92 (-8.62 - 62.47)	<0.12	9	335.44 (SD 82.92)	19.33 (-72 - 110)	1.00
MDS-UPDRS										
Part 1	14	15.57 (SD 5.87)	14	16.46 (SD 6.39)	0.38 (-2.55 - 3.32)	<0.78	9	18.44 (SD 6.25)	1.56 (-5.75 – 8.86)	1.00
Part 2	14	20.93 (SD 6.86)	14	20.08 (SD 8.27)	-1.23 (-5.18 - 2.72)	<0.51	9	21.22 (SD 5.91)	0.44 (-6.86 – 7.75)	1.00
Part 3	14	49.07 (SD 12.11)	14	48.46 (SD 8.59)	-1.69 (-6.15 - 2.76)	<0.42	9	46.78 (SD 11.04)	-2.22 (-13 – 9.55)	1.00
Part 4	14	3.86 (SD 2.93)	14	2.69 (SD 2.1)	-1.46 (-3.11 - 0.19)	<0.08	9	6.9 (SD 5.88)	2.22 (-2.18 – 6.63)	<0.5
Total	14	89.57 (SD 23.64)	14	87.69 (SD 20.18)	-4.15 (-13.20 - 4.90)	<0.34	9	93.67 (SD 20.96)	2.11 (-23.12 – 27.35)	1.00
PDQ-39										
Mobility	13	54.03 (SD 33.1)	13	53.54 (SD 31.49)	-2.71 (-8.97 - 3.55)	<0.36	7	55.71 (SD 17.9)	-0.74 (-24.35 – 22.92)	1.00
Activities of Daily Living*	12	46.18 (SD 22.23)*	12	47.57 (SD 18.42)		<0.69	7	50 (SD 20.83)	9.57 (-11.32 – 30.45)	<0.55
Emotional well being	13	38.46 (SD 23.02)	13	39.90 (SD 18.53)	-.24 (12.87 -13.35)	<0.97	6	41.67 (SD 17.87)	7.64 (-18.81 – 34.09)	1.00
Stigma	13	28.4 (SD 27.2)	13	25.51 (SD 21.73)	-5.22 (-12.76 - 2.32)	<0.15	7	24.11 (SD 22.66)	-8.04 (-26.91 – 10.82)	<0.63
Social support	12	11.78 (SD 16.85)	12	15.97 (SD 15.68)	2.29 (-4.37 - 8.95)	<0.46	7	14.28 (SD 13.36)	1.23 (-19.81 – 22.28)	1.00
Cognitions*	13	42.3 (SD 18.62)	13	42.19 (SD 15.35)*		<0.78	8	34.89 (SD 16.84)	-0.24 (-21.13 – 20.65)	1.00
Communication	12	33.34 (SD 27.98)	12	40.26 (SD 31.75)	4.53 (-7.04 - 16.10)	<0.40	8	36.46 (SD 18.87)	1.04 (-21.23 – 23.31)	1.00
Bodily discomfort	12	49.28 (SD 29.79)	12	60.40 (SD 15.54)	6.08 (-4.53 - 16.70)	<0.23	8	54.17 (SD 24.8)	11.46 (-0.55 – 23.46)	<0.06
Total	12	37.75 (SD 14.7)	12	39.53 (SD 12.92)	-1.03 (-6.98 - 4.92)	<0.70	6	37.48 (SD 4.74)	0.68 (-13.15 – 14.52)	1.00

MDS-UPDRS – Movement Disorder Society Unified Parkinson's Disease Rating Scale, PDQ-39 – Parkinson's Disease Questionnaire 39, *non-parametric results, **(95% Confidence interval)

4.3 Discussion

4.3.1 Statement of principal findings

The results suggest a six week progressive resistance training programme significantly improves lower limb strength in people with advanced PD, stage 3 and 4 Hoehn and Yahr (H&Y), and this improvement is maintained after six months follow up. However, these gains in muscle strength do not translate into functional mobility improvements as measured by the Six Minute Walk Test (SMWT). Furthermore, there was no significant change in the severity of condition as measured by the MDS-UPDRS or in participation restrictions as measured by the PDQ-39, indicating that the nine participants who attended all assessments had neither regressed nor improved over the six month period. This study has confirmed the feasibility of this progressive resistance training programme as evident from the high compliance rates with the programme, low levels of attrition (15% post intervention) and lack of adverse events reported by participants.

4.3.2 Results in the context of the current literature

4.3.2.1 Referrals

It was agreed by the author and clinical physiotherapists at the hospice site that the number of referrals (n = 19) was a manageable level for ongoing service provision, particularly given the consistency of the referral throughout the study.

4.3.2.2 Pre-exercise screening

The PAR-Q provisionally excluded PEP-PD screened participants (n = 4, 25% of participants screened) from this programme. An exclusion rate of 25% is below expected numbers as previously seen in a comparative study by Cardinal et al, 1996 [91]. The study by Cardinal et al, 1996 examined non-institutionalised adults (n = 193) of a comparable age to this cohort (mean age= 64.82 years, SD ± 2.85) and found that 66.32% of participants were excluded on screening with the revised PAR-Q. This may be explained due to the broad inclusion criteria of the Cardinal et al, 1996 cohort. The lack of adverse events throughout the programme is a supporting indicator of participants' ability to engage in this programme and the author felt the number of participants excluded provisionally was appropriate and also helpful in clarifying their general practioners/neurologists support of engagement in the programme.

4.3.2.3 Demographics

The mean age of participants in the current study (69.8 years) was higher than in other studies but still comparable for study results. A cohort of PD participants engaging in progressive resistance training within a non-randomised controlled trial by Morberg et al, 2014 had a mean age as low as 61.33 years [109]; the Lima et al, 2013 review of progressive resistance training had a combined mean age of 66.25 years while the strength review from Chapter 2 showed a mean age of 67.03 years for the included studies [10]. All of these resulting average ages from the above study and systematic reviews are comparable to the PEP-PD study however it is likely due to the PEP-PD study specifically target people with PD at a later stage of their disease that a marginally higher mean age was reported.

The mean time since diagnosis (14.1 years) of the participants included in PEP-PD is a clearer indicator of the difference in disease severity. The Lima et al, 2013 study did not report the disease duration for the studies included however the systematic review in Chapter 2 had a mean disease duration of 8.9 years for the combined studies included, see section 2.3.2. The review in Chapter 2 also had a much lower mean disease duration of 5.6 years, see section 1.3.2. The low time since diagnosis seen in both the resistance training and aerobic intervention reviews of the literature serves to highlight the clear lack of research examining exercise in the later stages of PD.

Finally the inclusion of Hoehn and Yahr stage 4 participants has been identified throughout this thesis as a clear limitation of the current literature examining exercise in people with PD. The even split PEP-PD participants in disease severity between stage 3 (n = 7) and stage 4 (n = 7) was unintentional but helpful in supporting this pilot study as a more comprehensive view of the PEP-PD programme between the two disease severity stages of interest.

4.3.2.4 FITT

Frequency, intervention, time and type for this exercise intervention have been found to be safe and feasible for this cohort of people with PD. This can be seen in the low attrition for post-intervention assessments (15%). It should be noted that this intervention was of short duration and it was seen in Chapter 1 that studies of shorter duration often had reduced attrition rates, see section 1.3.4. In the review of aerobic exercise literature in Chapter 1, 13

studies were included and of those studies the attrition rates were high in three studies (≥20%), of these studies the intervention duration was from 12-68 weeks; the remaining aerobic review studies, with attrition below 20%, had a noticeably reduced duration from between 6-16 weeks. In the Chapter 2 review of the progressive strength training literature it was unclear if duration effected attrition however the lowest attrition rate was found in the study by Hass et al, 2012 (10 week duration, 0% attrition) [71].

4.3.2.5 Primary outcome measure

An improvement in walking ability was found post intervention (mean change 26.9 metres), and at six months follow up (mean change 19.33 metres); however these improvements did not reach statistical or clinical significance. These findings are at odds with the findings from two previous systematic reviews that focus on strength training in people with PD. The reviews reported an improvement in both muscle strength and walking capacity following strength training programmes [10, 110]. The Lima et al, 2013 systematic review has been described previously as a justification for the methodology of this study. The Brienesse and Emerson, 2013 systematic review retrieved 27 papers of which 22 were excluded and the resulting 5 included for review by the authors. The systematic review by Brienesse and Emerson, 2013 did not complete a meta-analysis but did report improvements in SMWT in two of the studies included with one study reporting a significant improvement in SWMT ($p<0.01$) [32].

There are many factors that may have contributed to the non-significant improvement seen in this study. Firstly, the study is underpowered with thirteen participants at pre and post intervention assessments and nine at six month follow up. The lack of a power calculation is due to the fact that this was primarily a feasibility study and the author was not aiming to recruit a large enough cohort to meet a power sample calculation.

Secondly the population of interest are people with more advanced PD whereas most research in strength training for people with PD focused mainly on the mild to moderate stage of PD. It may be that the more advanced stages of PD will require a multi-modal exercise programme to improve measures of walking capacity. It has been found previously that the SMWT is also not just a measure of cardiovascular fitness but also a measure of overall mobility in the PD population [95]. It should also be noted that the SMWT might not have been sensitive enough as it has a high minimally detectable change of 82 metres as seen by Steffen and Seney, 2008 [38]. The Steffen and Seney, 2008 comparative study examined 37 community dwelling people with PD with a mean age of 71 years and Hoehn and Yahr stage 1 to 4. A battery of outcome measures were assessed in the study including the SMWT (mean = 316 metres, SD - 142 metres, 95% CI 269 to 364). The large standard deviation and confidence interval was due to large variances across disease severities, as reported by Steffen and Seney, 2008.

Thirdly, it may be that the study fell short on the intensity or duration of intervention required to elicit a significant improvement in SMWT. It is likely that the duration of the

study was one of the main contributing factors due to the outcomes of the systematic review in Chapter 2. The progressive resistance training review included studies with duration of between 10-24 weeks and the Lima et al, 2013 review included studies of between 8-24 weeks. However, in context of the constraints of the current study, a six week training programme was deemed an appropriate duration of intervention for the purposes of this study. Finally, the lack of a control group in the study limits the possibility of comparison to a similar group.

4.3.2.6 Secondary outcome measures

The improvement in muscle strength in the PEP-PD results is in keeping with current research results. It has been previously shown that people with PD present with reduced muscle strength in their lower extremity musculature [111]. A cross-sectional controlled study by Durmus et al, 2010 examined patients with PD (n = 25, mean age = 62.2 years, H&Y stage 2 to 3) and healthy controls (n = 24, mean age = 61.5 years) using isokinetic dynamometer. The Durmus et al, 2010 study found that muscle strength was lower in people with PD ($p < 0.05$) when compared with healthy controls. To date, several primary research studies have found an improvement in the muscle strength of people with PD, at H&Y stage 1 to 3, after strength training of various frequencies and intensities [32, 59]. The results from systematic review with meta-analysis of progressive resistance training in Chapter 2 examined the totality of evidence available; the review suggested a frequency and duration of twice weekly over 10 weeks for mild to moderate people with PD. The improvement in muscle strength found after a reduced duration of training (6 weeks) seen in this study supports the decision by the author to reduce the study duration. It should be

noted that these results were seen in a cohort of advanced stage people with PD, H&Y stages 3 to 4. The improvement in muscle strength however did not result in a significant improvement in walking capacity in the PEP-PD cohort.

Furthermore, it was noted that these improvements in strength were maintained six months after the post-intervention assessment. In the Chapter 2 systematic review, none of the studies included a follow up assessment time point. The lack of a follow up assessment limits the ability of any exercise intervention to examine the retention of any benefits post-intervention. The maintained muscle power improvement suggests that even the short PEP-PD intervention using progressive resistance training in this population could have a prolonged impact on measures of muscle strength.

The results of disease severity (MDS-UPDRS) are also at odds with the current literature. The two reviews of progressive strength training did not examine disease severity however the study by Li et al, 2012 was the only study to include people with PD at an advanced stage. The Li et al, 2012 study examined a progressive resistance training programme as part of the six month randomised controlled trial. The Li et al, 2012 study examined three separate groups of participants; a tai chi group (n = 65), resistance group (n = 65) and stretching group (n = 65). It found that there was a significant improvement in UPDRS III ($p < 0.01$) in the progressive resistance training group following training. The duration of the Li et al, 2012 study was significantly longer (six months) when compared with the PEP-PD trial (six weeks). The reduced duration of the PEP-PD trial may have limited the ability to improve disease symptoms in the cohort examined. Despite the lack of improvement in MDS-UPDRS scales in this study, it can be noted that no significant increase in disease severity occurred,

indicating a patient cohort with relatively stable disease severity during the assessment period.

The results of the PDQ-39 were also non-significant, however this was difficult to assess in the context of the current literature as none of the studies that formed the systematic review in Chapter 2 examined quality of life in people with PD following a progressive training programme. It has been shown previously in the quantitative methodology outlined in Chapter 3, section 3.2.12.2, that Marinus et al, 2002 recommended the PDQ-39 as the measure of health related quality of life most likely appropriate for studies to use. Owing to the complex nature of PD, the author undertook semi-structured interviews to explore the lived experience of participating in the intervention and the results will be reported in the next chapter. These interviews were completed to gain a deeper insight into the broader issues that impact on quality of life assessment for people with PD engaging in progressive resistance training. A systematic review by Brienesse and Emerson, 2013 included three randomised controlled trials and two non-randomised controlled trials with a total of 288 participants [110]. Despite the large number of participants and the included studies there were no outcome measures of quality of life reported. The lack of quality of life measures in studies of progressive resistance training was also seen in the Chapter 2 systematic review and previous Lima et al, 2013 systematic review. The PEP-PD methodology is based on the theory of triangulation as outlined in Chapter 3, section 3.3.6, which prescribes a combination of qualitative and quantitative assessment and analysis in order to examine both the subjective and objective outcomes of a given intervention to explore its impact on participants.

4.3.3 Clinical implications

A structured evidence search by Keus et al, 2009 looking at physical therapy in people with PD identified 38 randomised controlled and controlled clinical trials, 11 systematic reviews, two best-evidence summaries and two guidelines for physical therapy in PD [112]. The paper by Keus et al, 2009 identifies three main limitations of clinical practice; the small number of unique PD patients treated annually by physiotherapists (n = 4), the poor communication between care providers in the management of the person with PD specifically neurologist's referring to physiotherapists and the fact that most physiotherapists lack experience and knowledge of PD patients. The recent publication of a 'European Physiotherapy Guideline for Parkinson's disease' and subsequent dissemination through an annual Parkinson's disease summer school hosted by members of Parkinsonnet, a network of over 2,700 medical and allied health professionals based at Radboud University Nijmegen Medical Centre in the Netherlands, is a driving force in the attempt to address the Keus et al, 2009 findings. The lack of PD specific knowledge and expertise is one of the main limitations of evidence translating to practice and was highlighted by the author as an important factor in the development of the PEP-PD programme to ensure it could be implemented with minimal difficult in a clinical setting [112].

The primary aim of this study was to examine the feasibility of a pragmatic, clinically applicable strength training programme in people with advanced PD. In terms of clinical practice, the resources needed to implement a similar programme include adequate space, seating, appropriate ankle weights, facilitation of home based programmes and to provide minimal staff training.

The need for adequate space is owing to the management of a group class of 4 to 5 participants. Seating would be required to allow for rests between sets throughout the progressive resistance training programme and also to allow patients with medication induced postural hypotension, as seen in the PEP-PD study, to sit down if they became symptomatic during training.

The ankle weights used in this study were also portable for participants and allowed for home based exercises to take place, which reduces the burden on services to provide more frequent supervised training sessions. A UK national cost-impact report 'Parkinson's disease: diagnosis and management in primary and secondary care' outlines the cost of physiotherapy for PD in the UK as over 37 million pounds sterling [113]. The National Institute for Health and Clinical Excellence sets out only eight multi-disciplinary sessions per year for new PD patients. Taking into account the pre and post assessment appointments this report would only account for six treatment sessions per annum for group interventions. The management of funding for people with PD is a constant demand on therapists. The engagement of participants in a home exercise programme optimises the carry-over from the supervised sessions and allows for cost-effective treatments.

The PEP-PD programme aims to facilitate thrice weekly training, in a pragmatic and cost effective manner as this frequency of training is often prescribed in PD exercise interventions and translation into clinical practice is often unfeasible due to a lack of personnel and resources [20, 32, 50, 114]. Finally the need for minimal training of staff is to address the identified lack of PD specific expertise for physiotherapists as seen in the paper by Keus et al, 2009. The authors also found that a group environment allowed for greater

social support for participants of PEP-PD as seen in the coming chapter on the qualitative results.

4.3.4 Limitations of the study

The findings of the study need to be interpreted in the context of the study limitations. The small sample size was a limitation as this study is primarily a feasibility study and a sample size calculation was not undertaken. Sample size calculations involve several areas such as; the accepted level of significance (usually $p < 0.05$ or a <5% chance of an erroneous result), the power of the study (usually set at 10-20% of times a 'false-positive' result may occur), expected effect size as calculated from previous studies, underlying event rate which is also calculated from previous studies and finally the standard deviation in the population or the variability of the results in a given population [115]. The lack of a sample size calculation here excludes the areas of analysis mentioned above and limits the significance and generalisability of the PEP-PD results.

The lack of a comparison group is also a limitation. The evaluation of healthcare interventions where reporting, design and management meet set standards has been identified as the reference standard of research methodology in the CONSORT 2010 statement [35].

Unfortunately due to the limited ability for blinding of outcome assessors at the six month assessment, the internal validity of this study is reduced. The detection bias associated with non-blinded assessors is part of the Cochrane risk of bias tool which has been outlined in

Chapter 1, Table 1.2. To this end, a number of areas for future research are identified in the next section.

4.3.5 Areas for further research

Study Design – a pragmatic exploratory randomised controlled trial that conforms to the CONSORT statement 2010 in terms of conduct and reporting is needed to improve the external validity of the findings as the gold standard of healthcare intervention evaluation.

Population – Consideration should be given to co-morbidities in advanced PD such as depression and apathy as these may impact perceived changes in quality of life. An experimental mouse model study by Tuon et al, 2014 examined the impact of two types of exercise (strength training and treadmill training) on depressive like behaviour and levels of brain-derived neurotrophic factor. The study found that exercise, regardless of modality but potentially related to intensity, improved the neurochemical status of the mice used [116]. A qualitative study by O'Brien et al, 2015, which consisted of semi-structured interviews (n = 8) after a six month exercise intervention for falls prevention in people with PD, found that apathy was a factor that influenced involvement in exercise for people with PD [117]. Quality of life should also be examined not only through outcome measures but also qualitative methods; this could include pre-intervention focus groups and post-intervention semi-structured interviews and is due to the lack of examination of the impact of exercise on quality of life in current literature, as outlined in section 4.3.2.6. Acute medical or surgical interventions should also be taken into account as strenuous exercise may

exacerbate these health issues; one participant was excluded due to a minor surgery in the PEP-PD study.

Intervention –The FITT principles of the PEP-PD programme were feasible in a hospice out-patient setting. The frequency of thrice weekly, intensity of 40-70% of predicted one repetition maximum and type of exercise as progressive resistance training were effective in improving measure of muscle strength. The author would recommend increasing the duration of the overall PEP-PD programme as a potential amendment to achieve clinically meaningful improvements in walking capacity in this population. Hass et al, 2012 found that a duration of 10 weeks could produce improvements in measures of gait in people with PD [71]. Expansion of the intervention to include functional and core-strengthening exercises may also be beneficial. The inclusion of exercises for improving ankle musculature is recommended in particular by Liao et al, 2014 [118]. The study by Liao et al, 2015 examined the factors influencing obstacle crossing in people with PD (n = 42) stage one to three H&Y. This single assessment comparative study highlighted ankle dorsiflexion as the main determinate in crossing stride velocity; the inclusion of further functional and core exercises should also be implemented for further studies. A recent randomised controlled trial, published in April 2015 after the Chapter 2 strength review was completed, by Morris et al, 2015 examined the impact of three interventions on falls in people with PD [119]. The interventions were progressive resistance strength training using weighted vests or therabands (n = 70), movement strategy training (n = 69) and life skills training (n = 71). The protocol of progressive resistance training was outlined in a previous published protocol and consisted of mainly lower limb exercises (toe raises, heel raises, step-ups, lateral pelvic hold)

however the programme also included functional tasks (sit to stand) and core exercises (abdominals, trunk extension and rotation). The randomised controlled trial found a significant improvement, 84.9% less falls, when progressive resistance training was compared with controls ($p < 0.01$). The Morris et al, 2015 study included participants of stage 1 to 4 H&Y. It should be noted that the Morris et al, 2015 study also found a significant reduction, 61.5% less falls, when movement strategy training was compared with control participants ($p < 0.01$). The author does not recommend using movement strategy training in conjunction with progressive resistance training however in this patient cohort as this improvement should be taken cautiously when looking at stage 4 H&Y people with PD. A randomised comparative study by Stephan et al, 2011 examined sequence learning in people with PD (n = 39) when compared with age-matched healthy controls (n = 39) [120]. The study found that people with PD can acquire motor sequences however the ability to learn is reduced in the more advanced stages of the disease and this study only examined stage 1 to 3 H&Y. The ability for people with PD at stage 4 H&Y to learn new movement strategies is still under investigation.

Outcomes – Several additional outcome measures should be included in any trial examining progressive resistance training in people with PD identified by the author. It should be noted that the outcome measures suggested here form a high burden of assessment expected of an advanced PD cohort; the need to comprehensively examine the phenomenon involved in progressive resistance training is an important factor in the management of advanced stage PD patients and this should be outlined clearly to participants prior to engaging in a research trial.

Firstly, a prospective measure of falls was lacking in the current study. The randomised controlled trial by Morris et al, 2015, outlined above, had a comprehensive approach to examining falls rate in a PD population. Morris et al, 2015 educated participants in the definition of falls and the appropriate method for recording a fall on the initial assessment. Falls calendars were provided with a definition of falling printed on the calendar as a reminder. A falls hotline was administered by Morris et al, 2015 and participants called the hotline following a fall. All falls were followed up during structured interviews, hotline phone calls and using falls calendars throughout the duration of the study [119]. This was feasible for the Morris et al, 2015 study and a similar methodology should be used in further randomised controlled trials for people with PD where possible.

Secondly, a measure of gait speed was not included in the PEP-PD study despite the clear improvements ($p < 0.01$) as seen in the Chapter 2 systematic review on measures of gait velocity. The author decided that the six minute walk test was a more robust measure of walking capacity [95] and was more therefore more appropriate to examine the reported 'problems with mobility' as identified by late stage people with PD as one of four most reported symptoms of PD in a recent cross sectional study by Saleem et al, 2013 [1].

Finally, a measure of perceived exercise self-efficacy such as the Physical Activity Scale for the Elderly (PASE) should be considered in future research studies. A cross-sectional study by Ellis et al, 2011 included 260 participants with PD and using the PASE, activity monitors and responses to the Stages of Readiness to Exercise Questionnaire designated 164 (63%) of

participants as ‘exercisers’ and the remaining participants as ‘non-exercisers’ [121]. The study found that participants with reported high self-efficacy were more than twice as likely to be regular exercisers as those with low self-efficacy. The PASE is an appropriate measure for inclusion in subsequent studies to examine perceived self-efficacy in people with PD.

4.4 Conclusion

Overall the findings from this study indicate the potential benefits of engaging in regular progressive exercise for people with advanced PD. Further research should consider optimising the generalisability of these findings through the implementation of a pragmatic randomised controlled trial. The next chapter will outline the qualitative results from this study.

Chapter 5 Qualitative Results

5.1 Introduction

This chapter will present and discuss the findings from the qualitative semi-structured interviews, the rationale and methodology of which is described in Chapter 3. The reporting of these results is in line with the COREQ standardised reporting, to ensure the uniform conduct and reporting of the research [98]. These findings represent the qualitative component of the mixed methods study undertaken and serve to add to the depth and breadth of the results of this Masters by research thesis.

5.1.1 Participant characteristics

Thirteen participants took part in the pre and post assessments of the PEP-PD study. Nine individuals took part in the semi-structured interviews and their individual demographic details are outlined in the Table 5.1 below.

Table 5.1 – PEP-PD characteristics of participants involved in semi-structured interview

Participant ID	Age (yrs)	Gender	H&Y	TSD (months)
1	64	M	3	48
4	68	M	4	468
5	67	F	3	11
6	71	M	3	7
8	69	M	4	234
9	70	M	4	516
10	85	M	4	528
13	66	M	3	72
14	84	M	4	3

H&Y = Hoehn and Yahr staging, TSD = time since diagnosis

The remaining participants (n=4) from the PEP-PD study were unable to complete the semi-structured interviews due to scheduling issues as participants were unable to attend for both the qualitative and quantitative assessments. Interviews were conducted in an assessment office at the hospice out-patient setting and relied on voluntary drivers and staff to support interviewing. The mean time since diagnosis was 17.47 years (SD = 19.34 years) and mean age 71.56 years (SD = 7.63 years) for the cohort.

After data analysis by the two authors, four main themes emerged from the coded interviews. These themes included the *nature and content of programme*, the *role of the*

therapist, *support from peers and family* and the *nature of the condition*. Each of the key themes has been explored further below with supporting quotes from the analysis.

5.1.2 Nature and content of programme

All participants of the PEP-PD intervention each expressed the benefits of the programme. None of the participants were critical of the programme contents, however some expressed opinions on further items for inclusion and issues with the location in relation to where they lived. All of the participants reported benefits from taking part in the programme and these benefits were at once both similar and individual based on their own experiences. The PEP-PD study was focused on the improvement of leg strength and the potential functional gains this may elicit from people with PD. All of the participants noted that their walking and/or leg strength had improved after the intervention.

'…[the exercise] made me stronger and my legs improved immensely…'- Participant 14

'Strength, yes, walking I'd say improved…' - Participant 9

'Walking yeah. Walking is a big improvement.' - Participant 6

The design of the exercise intervention focused on leg strength and individually tailored weight selection clearly resulted in participants experiencing a similar improvement in leg strength and that this translated into an improvement in walking function. This is at odds with the results of the quantitative results from Chapter 4 where results demonstrated a non-significant improvement in the measure of walking capacity. The overall perceived

improvements in mobility and function were evident on examination of the individual improvements in participants function and impact on their life. Participant 6 experienced an improvement in their golfing ability and this translated to an improvement in their individual quality of life.

'I was more happier in myself like, you know.'

'…like, first of all I play a lot of golf and I was only playing three and four holes but now I'm up to twelve.' – Participant 6

The increase in walking capacity allowed for an increased involvement in golfing and an improvement in quality of life and this was attributed, by the participant, to taking part in PEP-PD.

Participant 5 experienced an improvement in walking attributed to the resistance training. This improvement in walking was perceived as a way to maintain independence and ability to care for a family member. This improvement and functional benefit was then seen as a critical point to continue and prioritise exercise.

'It was the weights with your legs, which I thought was good now. I feel I'm walking better'

'…but I mean I have a 'family member' to look after so that takes up my time too. But I get my exercise in between, I have to because, you know I have to think about me too. I'm no good to [them] if I'm laid up.'

‘Because I actually thought I was really getting worse. I could feel myself getting worse, I wasn’t walking properly and I was nervous falling, I was nervous to go out on my own. And now I’m not.’

– Participant 5

While participants were positive of the outcomes of the programme, some (n = 5) noted the level of difficulty when exercising and the resulting leg stiffness and muscle soreness associated with weight training. However this did not impact these participants functionally during the programme and the stiffness or pain ceased as they became used to the programme.

‘Yeah. Next day I’d be sore’ – Participant 1

‘Some nights at the end of it I feel my leg starting to stiffen up a bit but I think in a way it’s helped me along a lot’ – Participant 13

‘No, at the beginning I was in pain but I mean after that it just went out of my head, just didn’t even think about it then.’ – Participant 5

‘Well the first two week I wasn’t too happy but then as the third week came I improved all the time’ – Participant 6

Participant 4 noted that their initial weight level had to be changed as they were not managing to complete the programme with this initial weight. The therapist reduced their

weight from seven kilos to five kilos in the initial class. This had an impact not only on the initial exercise session but also on their experience throughout the PEP-PD trial.

'I tried to start at seven kilos…I worked my way down… Yeah, I just couldn't manage'

'I have to go back to what I said earlier I had low weights at the beginning and then work up, psychologically that was difficult' – Participant 4

The physical demands of the assessment points of this programme were also noted, particularly in the later staging of the disease.

'It was tough the toughest test I've ever had to do with Parkinson's in one day without a break' - Participant 4 (H&Y stage 4)

Location was viewed as both a facilitator and a barrier to exercise participation for several participants. It should be noted that volunteer drivers supported the transport of participants to and from the hospice setting as outline in Chapter 3, section 3.2.2. The availability of this service positively influenced participants' involvement and attendance for the programme.

'I was. It was a little bit far for me but it was alright… I'm glad you brought me over here' – Participant 9

'Bring it closer to [home]' – Participant 1

This was not a concern for all participants but is worthy of note as a potential barrier for participants who have functional impairments and require transport support.

'No problem travelling' – Participant 13

In keeping with the myriad of symptoms in PD affecting both upper and lower limb, the lack of upper limb exercise in the programme was a common issue for participants. It is worth noting that the participants that found upper limb exercises relevant were those who experienced specific upper limb functional impairments.

'I would not just do the lower body I would bring the arm into it and the neck because the neck is stiff, try to get the arms in and try to get the upper body moving' – Participant 4

'Well, I think it…my upper body could do with it really, you know. Because my head seems to be hanging down, you know' – Participant 6

Participants who did not explore upper limb symptoms affecting their function did not recommend any changes during their interview.

'Nothing I could see in it that I would want to change anyway' – Participant 13

Finally, the delivery of an exercise intervention through group sessions was perceived as beneficial by all but one participant and this is further explored in the theme of *support from peers and family.*

5.1.3 Role of the therapist

This theme was reported by all participants as a significant component to their motivation and involvement in exercise. Within this theme, opinions and experiences of people with PD were explored in relation primarily to the therapist involved in administering the exercise intervention but also the motivators and influencers to initiating an exercise intervention. It should be noted that although adherence and improvements from an intervention are often attributed to the administering health professional; initial attendance is attributed to several factors which are often individual and experiential in nature. Participants highlighted that the referring health professionals, specifically medical staff and physiotherapists, were a key driver in promoting engagement in an exercise intervention. In response to why they attended the PEP-PD programme the following responses were collected. Participant 1 and 4 both noted that the referring clinician served as a motivator for involvement.

'The [physiotherapist] in Beaumont...[asked me to]' – Participant 1

'I was asked [by referring medic]' – Participant 4

There were other motivators to engagement such as social enjoyment.

'Why did I come to the class?...[To] socialise' – Participant 10

Improvements from and involvement in exercise were the primary motivators for other participants.

‘Well when I was asked at first, I just thought for about five minutes and I said if it has to do me any good I’d be delighted to take part in it.’ – Participant 13

‘Because I actually thought I was really getting worse’ – Participant 5

‘To get exercise and that you know.’ – Participant 6

Exposure to previous research was also noted by two participants as a facilitator to participation. Participant 9 and Participant 4 had previous experience of a research project and this positively influenced their involvement in another research project.

‘Completed it for [referring medic] and it worked out well’ – Participant 9

‘I don’t want to refuse anything since day one I was in [a university] in a research [study]…anything that will help I’ll do.’ – Participant 4

Separate to the myriad of influencers and motivators for engagement are the subjective experiences, and individual thoughts on the role of the therapist administering the intervention. This was noted almost unanimously by the participants as a positive component of the PEP-PD study.

‘He [the physiotherapist delivering the intervention] was good, he was a very good talker’ - Participant 4

‘Couldn’t do any better. The chap that done it was very good he was’ – Participant 6

The benefit of a positive relationship with the intervention therapist was evident in the motivation and empowerment of the participants throughout the study.

‘Yeah, I think it’s when someone is there telling you. I love to have someone like that to keep telling me you’ve to do this and you’ve to do that because I find you do more when someone is...’ - Participant 5

‘Yeah the biggest benefit is the motivation the fact you had a physiotherapist’ – Participant 4

A sense of trust in the professional capabilities of the treating therapist also emerged from the data analysis process.

‘I wouldn’t have changed anything, I think, [the therapist] I think was the chaps name. He took us along nice and handy. If I wanted to stop he would stop with you and if he thought you were able to keep going he would keep going a little bit extra with you.’ - Participant 13

‘[The therapist] said to us “if you can’t manage just take your time…don’t force yourself. And it was a very quiet concern’ – Participant 4

‘And you know I mentioned that to [the therapist] and he instantly understands’ – Participant 4

A reduced understanding or knowledge of PD was seen by Participant 4 as an immediate barrier to developing a patient-therapist relationship.

'…with respect to your professions, they don't know, a lot of people don't know about Parkinson's and motor neuron and MS. There's finer detail with them that people don't know, difficulty walking and speech, and they don't know what it feels like' – Participant 4

Throughout the interviews there was a clear appreciation for the wider hospice staff and the support given, however this did not seem to impact the patient involvement in the programme but rather their experience of the hospice setting.

'I'd just say that I'm thankful for the whole staff went through a lot of work to get us all through' – Participant 6

'Nicer people in the hospice' - Participant 1

5.1.4 Support from peers and family

The support through peer support, family engagement and motivation to exercise was a clear theme throughout all of the interviews recorded. The separate importance of peer support was coupled with family support in this section as this programme was based not only in group supervised sections but also home based exercises. Motivation for participants varied depending on which location they were exercising in but it was clear that support from an external motivator was a factor in adherence, enjoyment and engagement. Positive interactions in the group were widely reported.

‘Yeah I liked the group, you know I really did’ - Participant 5

‘Yeah, a class would work, yeah.’ - Participant 6

Peer engagement was also facilitated throughout the programme as participants were provided with light refreshments at the end of each exercise session. During these informal gatherings, participants were invited to share their thoughts and experiences with each other and ask questions of the therapist. One of the most frequently reported comments from participants in the interviews was the opportunity to engage with and interact with peers during the programme. This understanding of the condition was a uniting experience for individuals and helped to develop positive interactions within the group.

‘Well, meeting other lads that have the same thing as myself, some worse, some maybe better, you know. It was nice meeting somebody else.’ - Participant 13

‘such a lot of things can happen in Parkinson’s going round the courts so many problems and to speak up and say how many problems I have like [the therapist] would have us sit around the table and have a cup of coffee together each programme and each talked about what we liked to talk about. Makes sense.’ – Participant 4

The exercise programme was individually beneficial as seen in the theme of the *nature and content of programme* but the motivation often came from an external source and the group was a motivating factor for several participants.

‘Usually I would say ah I won’t do it today. And because I was coming and there is a group there, it motivations me to do it, it was a good start.’ – Participant 4

‘You might say to yourself if you are on your own I’ll slow up a little bit but when you have somebody with you, you are inclined to go that extra little step’ – Participant 13

The group was not the only motivating influence and family support was seen by Participant 5, 6, 9 and 13 as a source of validation of the success of the programme.

‘They asked me how I liked it and was I doing well and they thought I was walking a bit better.’ - Participant 5

‘Well [my wife] did she told me, she told me she felt I’d come on’ - Participant 9

‘[My family] were delighted that I was doing it…well just to see me up, getting up and not being slouched in a chair… I get up and get out and as my wife said you met somebody the same as yourself.’ – Participant 13

‘…my wife, she’s behind me, she’s pushing me, she’s the one who said my head was dropping you know’ – Participant 6

Validation of the programme is also coupled with support when exercising and encouragement to exercise.

‘All depends on herself, how she’d be feeling, she might say tonight, ah we won’t go out tonight leave it until tomorrow night’ – Participant 1

5.1.5 Nature of the condition

Parkinson’s disease is a condition that impacts each person affected in an individual manner. Through examination and analysis of the data collected the variety and variability of experiences was collated under the theme of the *nature of the condition*. The quotations illustrated below highlight the impact of the disease on participants of PEP-PD. Most participants explored the nature and impact of the disease on their daily life. Participant 4 specifically spoke about the impact of the incurable aspects of the condition and that the current treatments were no curative but rather a reduction of the impact of the disease. This sense of eventual decline is a common theme throughout all interviews but is most clearly alluded to by participant 4.

‘…[medical treatment] is not a cure and it’s important that you think of that. It’s a relief of symptoms and the horrible side effects of the tablets…it’s not a cure.’ – Participant 4

‘…advanced Parkinson’s means there is no other medication they can give to me. That’s the hardest thing I find to take’ – Participant 4

The clinical manifestations of Parkinson’s disease over time, initially through the loss of physical ability and eventually the loss of participant’s lifestyle prior to diagnosis, also featured in the semi-structured interviews. Participant 4, 5, 6 and 14 each discussed their experienced loss of physical ability.

‘I wouldn’t be able to do a routine of exercise now for a number of years’ - Participant 4

‘Because I actually thought I was really getting worse. I could feel myself getting worse, I wasn’t walking properly and I was nervous falling, I was nervous to go out on my own. And now I’m not’ - Participant 5

‘Well I wasn’t walking very well, I was starting to walk bad like, you know, starting to walk feet together like, you know…’ - Participant 6

‘…I was always fit and I always kept up to date with exercise and walking and that…but I didn’t realise it that I had become so unfit’ - Patient 14

This loss of physical ability had a direct impact on participant’s sense of self and their independence in life. The loss of social interactions such as work and recreation for participants was detrimental for participant’s quality of life. Participant’s 10 and 14 were both unable to engage in their preferred recreation due to their physical limitations.

’I used to do a lot of dancing…now that’s all stopped’ - Participant 10

‘I was doing nothing. I was lying about’ - Participant 9

‘Up to three years ago I was able to play two games of golf a week’ - Patient 14

Notably Participant 4 struggled with the loss of work and had to retire, despite significant improvements in their physical function after medical intervention this did not impact their ability to engage again in work.

'I went to work and worked from a wheelchair and when I retired which was the funny thing I came out of the wheelchair after an operation and came back walking, and then [my line manager] said [I have] to retire and I said, why? Well it's an incurable illness and you have to retire in another couple of weeks' – Participant 4

In response to a specific question on PD terminology there were conflicting opinions from participants. Participants were asked 'do you feel that the terms 'advanced Parkinson's' and 'palliative Parkinson's' are the same?'. Four participants did not feel they understood the terms sufficiently to decide on whether they were interchangeable or not. Three participants felt the terms were different with two participants associating their PD with 'advanced Parkinson's' and only one associating with the term 'palliative Parkinson's'. One participant felt the terms were interchangeable and finally one participant felt that the fact that the term 'hospice' had been used that there was some medical information they did not know.

'Are they trying to tell me something?' – Participant 10

The participant felt the information for the programme was appropriate; the participants' misunderstanding came simply from the mention of a hospice. The idea of the hospice as a

negative place of care was not in relation to the level of care provided but rather the perception of ill health.

'No, no. I support the hospice in Artane, I think they are a wonderful group' - Participant 4

Other participants who had previous experience of a hospice environment did not experience similar anxiety.

'No. I'm used to going to the hospice…my relative died there so I was used to going over there to visit them' - Participant 5

'A hospice? No, no, because you can be bothered with these things if you let it into your head but you know, people associate hospice with the end of the rail' - Patient 14

5.2 Discussion

5.2.1 Principal findings

The aim of the qualitative semi-structured interviews was to examine the lived-in experience of people with advanced PD who took part in a progressive strength training protocol in a hospice out-patient clinical setting. PEP-PD was delivered over six weeks in a hospice setting with pre and post quantitative assessments occurring before interviews took place at post assessment. The interviews explored the subjective experience of the training programme from the point of view of the people with PD. The four themes that emerged were the *nature and content of programme*, the *role of the therapist*, *support from peers*

and family and the *nature of the condition* reported above. These themes are consistent with results from previous research looking at people with PD and exercise [99-101].

All individuals involved in the PEP-PD programme reported both physical and psychological improvements as a result of taking part in the intervention. The interviewees described several beneficial aspects of the programme. Specifically the role of group/peer support, support of family/carers, presence of an engaging and knowledgeable therapist and clearly explained and recognisable physical improvements were seen as some of the elements needed for a successful exercise intervention.

The majority of participants were happy with the programme exercises and continuing them at home. The inclusion of unsupervised exercise sessions at home was not seen as a negative aspect or lack of treatment. Home based exercises actually helped family and carers to become involved and engage in supporting the interviewees. The use of home based exercise coupled with supervised exercise sessions should be seen as a pragmatic solution to achieving the high frequency of intervention often prescribed by research in a cost saving health service.

5.2.2 Results in the context of current literature

The themes identified are consistent with previous literature exploring the experiences of people with PD and exercise [99-101]. The theme of the *nature and content of programme* is also in-keeping with that observed in the study by O'Brien et al, 2008 which highlighted the positive experience participants had of a disease specific progressive resistance exercise programme. The Crizzle et al, 2012 theme of *constant reassurance from trainer* was seen as central for adherence to an exercise programme. Adherence was excellent for the current PEP-PD study with 12 of 14 participants completing pre and post assessments equal to 85% adherence. The high levels of adherence are not surprising when looking at the similarities in the *role of the therapist* theme in this study to that observed in the study by Crizzle et al, 2012 theme of *constant reassurance from trainer*. Crizzle et al, 2012 also explored the role of group exercise and social interaction as a key theme for exercise adherence. The theme of *support from peers and family* could be seen emerging in Crizzle et al, 2012 however in Crizzle et al, 2012 the caregiver was interviewed separately and the main focus of the interviews was adherence to exercise. Finally the theme of the *nature of the condition* can be seen throughout each of the three previous studies examining exercise in people with PD through qualitative methods.

PEP-PD did not establish a significant improvement in walking for the participants; however the majority of participants experienced a perceived improvement in walking, increased confidence in mobilising independently, improved balance and improved leg strength, as evidenced in the output from the qualitative interviews. The design of the exercise intervention focused on leg strength and individually tailored weight selection clearly

resulted in participants experiencing a similar improvement in leg strength and this translated, in their opinion, into an improvement in walking function. There is a lack of triangulation between the qualitative findings and the results of the quantitative results from Chapter 4, which did not find a significant improvement in the measure of walking capacity.

5.2.3 Adverse events and side effects

No adverse events were reported for the PEP-PD trial by participants. The side-effects of the intervention noted by five of the participants as either 'pain' or 'stiffness' ceased as they became used to the programme. Any side-effects of the programme were monitored closely by the author and it is possible this close monitoring may have also alleviated and allayed the concerns of the PEP-PD participants.

It is also important to note the impact of 'going backwards' in the initial resistance training for Participant 4. The theory of self-efficacy outlined by Bandura, 1997 suggests that an increase in perceived self-efficacy has a subsequent effect on the outcomes associated with a persons' perception [122]. This has been examined by Arnold et al, 2011 in a randomised controlled trial of 54 older adults engaging in a falls exercise intervention [123]. The trial identified that participants with low self-efficacy and one or more falls risk could benefit from exercise intervention and self-efficacy enhancing education. The impact of perceived self-efficacy could also impact negatively on outcomes for people with PD as outlined by

Participant 4 and their ongoing and unresolved reduced self-efficacy as a result of the initial weight being inappropriate.

The intervention was not the only impactful experience of the PEP-PD study. Research methodology often demands the inclusion of several outcome measures to assess a range of functional and disability domains. Exercise interventions are strictly reviewed by ethical bodies and conform to recommendations by guidelines [46], however the testing procedure and time frame are often less stringently monitored. The variability of functional level of people with PD of differing stages is evident in the quantitative outcome measure SMWT having such a large minimal detectable change 82 meters [38]. People with PD have varied and complex symptoms and each individual experience these differently both functionally and experientially. The difficulty outlined by Participant 4 in completing the programme should be highlighted when researchers are designing the battery of outcome assessments used in clinical trials.

The exercise location of a hospice out-patient setting did result in confusion and even suspicion in some participants. Upon completion of the programme all participants reported that this was no longer an issue. Further interventions for people with PD in a hospice setting should be explicit on the reasons for admission to an intervention and what participants should expect upon arrival. The hospice setting was also universally seen as a positive and holistic health care setting and was ideal for people with PD to attend exercise sessions.

5.2.4 Triangulation of results with quantitative output

As mentioned in Chapter 3, section 3.3.6, this study was developed to examine the outcomes of both qualitative and quantitative research by using mixed methods or plural methodology. Through analysis and examination of the research phenomenon in this study using two different approaches the author found that both methods were in agreement for the secondary outcome measures of interest. Walking capacity (six minute walk test) did not demonstrate a significant improvement as seen in Chapter 4, section 4.2.2; this was not confirmed by the qualitative semi-structured interviews where participants reported and improvement in walking as outlined above in section 5.1.2.

The improvement in muscle strength (predicted one repetition maximum) was seen in both the qualitative and quantitative results from Chapter 4, section 4.2.3, and this chapter, section 5.1.2. Improvements in disease severity (MDS-UPDRS) are not evident in the quantitative or qualitative results; however as mentioned in Chapter 4, section 4.3.2.6, there was no significant increase in disease severity, indicating a patient cohort with relatively stable disease severity during the assessment period. Improvements in quality of life were not seen in the quantitative results (PDQ-39) Chapter 4, section 4.3.2.6, however the qualitative results show a clear link between improved perceived functioning after PEP-PD and an improvement in quality of life (being happier and caring for a dependant) in this chapter, section 5.1.2.

A review of the results using the principle of triangulation outlines the fact that perceived improvements in leg strength and a lack of perceived improvement in disease severity were confirmed by qualitative interviews. The perceived improvements in walking capacity and quality of life not captured by the quantitative outcome measures is indicative of the need for a comprehensive randomised controlled trial for further evaluate the impact of progressive resistance training in people with advanced PD.

5.2.5 Strengths and limitations of study

This is the first study to look exclusively at advanced stage people with PD taking part in a hospice based exercise programme. This study used qualitative methods to explore the lived-in experience of participants taking part in the PEP-PD.

The hospice location and advanced stage of the condition limit the generalisabilty of this study. The findings from the study can only be applied to individuals with advanced PD within a hospice setting and who meet the inclusion criteria of this study. There is also the additional influence of patient satisfaction being related to the physiotherapist relationship with participants. The questions posed may have elicited more positive findings as a result of this relationship. To reduce the risk of bias all interviews were conducted by an independent researcher. Finally four participants were excluded from analysis due to inability to schedule times for participants (n = 4). The lack of interviewing all participants may have increased the likelihood of selection bias however it was deemed unethical to

attempt to influence participants to attend assessments on separate days for both qualitative and quantitative assessments.

5.3 Conclusion

This chapter outlines the qualitative results from semi-structured interviews of participants in PEP-PD. This model explores patients' 'lived-in' experience of this exercise intervention and specifically looks at the impact of a hospice setting for advanced stage PD. The four main themes outline the potential challenges and benefits of exercise programmes for people with PD. Firstly, exercise within a hospice setting is beneficial not only physically but also psychologically for people with advanced PD. Peer group support and family/carer support is a key component in adhering and engaging with exercise. Home based exercise to supplement weekly exercise sessions did not have any negative connotations for the participants. And finally a subjective benefit on walking ability was seen despite a lack of significant improvements in walking through quantitative analysis. The participants of the PEP-PD programme were treated alongside similar sufferers of PD. There is still a need to explore the experiences of people with PD when integrated with other hospice patient groups such as heart failure, end stage chronic obstructive pulmonary disease (COPD) and terminal cancer. Furthermore the impact of hospice care on families and carers of people with PD and the ability of hospice staff to engage and support this varied patient group needs to be explored further.

A project underway by Dr Siobhan Fox to create the first Irish guidelines for palliative care in PD is another development in the changing landscape of conditions to be cared for in a hospice setting. This thesis project supports the idea that people with PD can engage with and benefit from interventions within a hospice environment.

Conclusion

The aims of this thesis were twofold: (1) to examine the feasibility of an exercise intervention for people with advanced stage Parkinson's disease (PD) in a hospice out-patient setting using a mixed methods research framework, (2) to examine the impact of this programme on impairment, activity limitation and participation restriction in people with advanced stage PD.

In Chapter 1 a systematic review was undertaken to examine the impact of aerobic exercise on aerobic capacity in people with PD. The primary outcome measure of VO_2peak did not show a significant improvement after meta-analysis ($p=0.10$). Secondary outcome measures of impairment (UPDRS motor), activity limitation (SMWT) and participation restriction (Beck depression inventory) showed significant results in favour of the intervention group ($p<0.05$) after sensitivity analysis. Despite these promising results none of the studies examined focused on individuals at stage 4 H&Y. Based on this external evidence, the author decided that an aerobic intervention was not suitable for advanced stage people with PD.

In Chapter 2 an updated systematic review that focused on progressive strength training and its impact on measures of muscle strength and secondary outcomes of physical performance was conducted. This review represented an update of the findings of a previous review [10]. The findings from this updated review, coupled with the results of the original review, demonstrate that there was evidence for progressive resistance training

interventions as a treatment to improve the symptoms of people with PD (H&Y 1 to 4), specifically muscle strength, walking capacity and most recently gait velocity.

Following on from these findings, the author then designed an intervention based on the Chapter 2 results and described the methodology for the quantitative analysis in Chapter 3. In brief the intervention comprised a six week progressive resistance training programme of lower limb exercises once weekly supervised in a hospice out-patient setting and twice weekly unsupervised in the participants home environment. The primary outcome measure was the SMWT. Secondary outcome measures included the predicted one repetition maximum, MDS-UPDRS and PDQ-39. Assessments took place at the pre, post and six month follow up point. Semi-structured interviews were also outlined in this chapter and took place at the post assessment time point.

The results of the quantitative outcome measures were reported in Chapter 4 which found a significant improvement in muscle strength ($p < 0.05$) of the lower limbs and non-significant improvement in the SMWT, MDS-UPDRS and PDQ-39. The qualitative interviews results, in Chapter 5, reported participants experiencing a perceived improvement in walking capacity and identified and outlined four main themes that impact exercise in people with PD; these themes included the *nature and content of programme*, the *role of the therapist*, *support from peers and family* and the *nature of the condition.*

Taken together, there were some areas of triangulation between the output from the qualitative and quantitative findings, particularly regarding improvements in impairments.

Finally, the author has outlined the clinical implications of the findings from the primary research studies, as well as areas for future research. In particular, further research is needed to examine the impact of progressive resistance training for advanced stage people with PD in a hospice setting. Research should include randomised controlled trials looking at longer duration progressive resistance strength training within a hospice setting and also the impact of integrating people with PD into the current cohort of palliative care patients in Ireland.

In conclusion this study has found that a progressive resistance training programme is not only feasible for people with advanced PD (H&Y stage 3 to 4) but can impact positively on the muscle strength in the lower limb of PD patients. The limitations and strengths of this thesis have been outlined in previous chapters.

DISSEMINATION

Following the completion of this study letters were sent to referring clinicians as to the progress of participants in the PEP-PD study. A letter outlining the results of the study has also been sent to participants who requested the results of the study as per ethical approval. The results of this study to date were presented at the Chartered Society of Physiotherapists in Neurology and Gerontology 2014 evening lecture. The results of the

systematic review outlined in Chapter 1 have been presented orally at the 61st Annual and Scientific Meeting of the Irish Gerontological Society and the Irish Society of Chartered Physiotherapists Conference in Croke Park. The results of this feasibility study were also presented at the 15th Irish Association for Palliative Care Annual Education and Research Seminar which took place on the 5th of February 2015 in Dublin, Ireland. An oral presentation submission will be made for the World Parkinson's Congress 2016 in Portland, Oregon, USA. The quantitative results of this study have been submitted and are currently under review at the Irish Society of Chartered Physiotherapists journal 'Physiotherapy Practice and Research'.

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Appendix I - PROSPERO pre-registration draft protocol of Aerobic review

Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

Interventions for improving aerobic exercise capacity in people with Parkinson's disease (PD)

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date

Give the date when the systematic review commenced, or is expected to commence.

28/02/2014

4 Anticipated completion date

Give the date by which the review is expected to be completed.

18/04/2014

5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started **√**

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No

Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

David Hegarty

7 Named contact email

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8 Named contact address

Enter the full postal address for the named contact.

Flat 15, Block 1, Annaville Residence, Dundrum Road, Dublin 14, Republic of Ireland

9 Named contact phone number

Enter the telephone number for the named contact, including international dialing code.

0861016620

10 Organisational affiliation of the review

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Royal College of Surgeons in Ireland (RCSI) and The University of Sydney (UoS)

Website address:

www.rcsi.ie, www.sydney.edu.au

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Mr	David	Hegarty	RCSI
Professor	Colleen	Canning	UoS
Professor	Jennifer	Alison	UoS
Dr	Rose	Galvin	RCSI

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

Funding was received from both the Eastern Branch and clinical interest group Chartered Physiotherapists in Neurology and Gerontology. These groups are both run through the Irish Society of Chartered Physiotherapists, Royal College of Surgeons, St. Stephen's Green, Dublin 2, Ireland. www.iscp.ie

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

1. To assess the effects of interventions designed to improve aerobic exercise capacity in people with PD (PwP)

2. To examine the effects of these interventions on measures of impairment, activity limitation and participation restriction

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following electronic databases will be searched to identify relevant studies published. • AMED • CINAHL • Science Direct • The Cochrane Library • DARE • PEDro • EMBASE • Web of science • and PubMed. The above databases will be searched and adapted for each database according to the example keywords below: 'parkinson's disease' OR 'parkinson's' OR 'pd' AND 'physiotherapy' OR 'physiotherapist' OR 'physical therapy' OR 'rehabilitation' OR 'exercise' Other sources All reference lists of articles identified for inclusion in the review by the reviewer will be searched for additional papers. Grey Literature The following representative bodies will be contacted and asked to provide any relevant papers they feel warrant attention for this review. • Parkinson's Association of Ireland • Dublin Neurological Institute • Chartered Physiotherapists in Neurology and Gerontology • AGILE • World Parkinson's Congress • Association of Physiotherapist in Parkinson's Disease Europe (APPDE)

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Parkinson's disease is a condition that affects the brain, causing a variety of symptoms such as slow movements, tremor or shaking at rest, poor balance and stiffness in the arms or legs. In contrast to conditions such as cancer, the burden of PD lies with its long term disability as opposed to death. It is estimated that there are 1.2 million people living with PD in Europe and

this figure is expected to double by 2030. The American national economic burden of PD exceeded $14.4 billion in 2010. Exercise and physical activity remain the cornerstone in the non-pharmacological management of PD. Accumulating evidence, albeit indirectly, suggests that ongoing and vigorous exercise may have a neuroprotective effect in PD. Exercise as a treatment has the potential to maintain patients' function for longer and hopefully reduce the health care burden for this population.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

We will include trials of participants with a diagnosis of idiopathic Parkinson's disease (as defined by the authors of the studies). Participants of all ages, stages of the disease and either gender will be included for analysis. Drug treatment, initial impairments, duration of PD and duration of treatment will not be exclusion criteria for this trial.

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

A study comparing two or more arms with one arm at least focused on aerobic exercise training. Only trials that include a training component that aims to increase aerobic capacity in PwP will be included. To be included the aerobic capacity training arm must include an explicit measure of intensity and be progressive in nature. A minimal aerobic exercise definition has been included below to aid screening of exercise trials, based on a review of the literature by the authors and also the ACSM guidelines for healthy adults. It is important to note that the ACSM guidelines have been accepted for use in healthy adults and explicitly state that lower aerobic intensities can be beneficial for deconditioned adults. Physical activity has been established in PwP as being lower than in age matched controls therefore a lower level of exercise intensity could improve aerobic capacity in PwP. Additionally the inadequate heart rate increase in response to exercise present in approximately half of PwP has an unknown effect on heart rate assessed intensity levels. The definition below is therefore a guide for this review; studies that conform to the below criteria will be assessed by the reviewers and it will be decided to include these or not by consensus of the reviewers. The definition approved for use in this trial is as follows: Minimal criteria for inclusion: the aerobic exercise training intervention must be: • Intensity must be specified as %VO2 peak, % peak work, % max predicated HR or % HRR • Frequency: at least 2 days a week or = 150 min/wk, for at least 6 weeks • Time: minimum of 20 mins/session • Duration: minimum of 6 weeks • Type: Regular, purposeful exercise that involves major muscle groups and is continuous and rhythmic in nature Where studies do not specify what level of aerobic exercise was achieved the lead reviewer will contact the author for clarification. All modalities of intervention will be included and then analysed collectively before distinguishing between modalities in the analysis section i.e. cycling, treadmill and treadmill with harness.

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

We will include trials comparing two or more arms with one arm at least focused on aerobic exercise training. We will include all control groups (intervention and non-exposed) once they adhere with the below study types.

22 Types of study to be included initially

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

We will include randomised controlled trials and quasi-randomised trials including cross over trials. Should any crossover trial meet the inclusion criteria, we will include the first phase if the order of assignment has been determined randomly or quasi-randomly. We will include randomised controlled trials comparing two or more arms with one arm at least focused on aerobic exercise training, as defined below and one alternative control arm. Articles that are not written in English will be included and translated as necessary.

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)

Give the most important outcomes.

The primary outcome measure is aerobic capacity (VO2 max). VO2 peak will also be included in the analysis of aerobic capacity as many PwP are unable to perform the complete VO2 max protocol.

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

Secondary outcome measures will include, but not be limited to, measures of submaximal exercise efficiency, disease severity (UPDRS), quality of life (PDQ-39), depression and anxiety (HADS), cognition (SCOPA –Cog) and also any outcome measures used by studies that can be included in a meta-analysis.

Give information on timing and effect measures, as appropriate.

26 Data extraction, (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two review authors will independently assess the risk of bias of each included study against key criteria: random sequence generation; allocation concealment; blinding of participants, personnel and outcomes; incomplete outcome data; selective outcome reporting; and other sources of bias (such as whether groups were similar at baseline for important prognostic indicators and if co-interventions were avoided or similar between the intervention and control groups) in accordance with the methods recommended by The Cochrane Collaboration (2010). We will explicitly judge each of these criteria using: low risk of bias, high risk of bias or unclear risk of bias (either lack of information or uncertainty over the potential for bias). We will resolve disagreements by consensus and consult a third review author to resolve disagreements if necessary.

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

Meta-analysis We will use the Cochrane Review Manager software (RevMan 2012) to carry out statistical analyses to determine the treatment effect. For dichotomous variables we will calculate the treatment effect using a fixed-effect/random-effect model and report it as odds ratios (OR) with 95% confidence intervals (CI). For continuous data we will calculate the treatment effect using standardised mean differences (SMD) and 95% CI where different studies used different scales for the assessment of the same outcome, and using mean differences (MD) and 95% CI where studies have all used the same method of measuring outcome.

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. ‘None planned’ is a valid response if no subgroup analyses are planned.

None planned

Review general information

30 Type of review

Select the type of review from the drop down list.

Intervention

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

Ireland

33 Other registration details

List places where the systematic review title or protocol is registered (such as with he Campbell Collaboration, or The Joanna Briggs Institute). The name of the organisation and any unique identification number assigned to the review by that organization should be included.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available

Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36 Keywords

Give words or phrases that best describe the review. (One word per box, create a new box for each term)

Parkinson's Disease

Aerobic Capacity

Meta Analysis

Systematic Review

Exercise

Physiotherapy

37 Details of any existing review of the same topic by the same authors

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status

Review status should be updated when the review is completed and when it is published.

Ongoing

39 Any additional information

Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)

This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.

Give the URL where available.

Appendix II - Example literature search strategy for Chapter 1 Aerobic Review

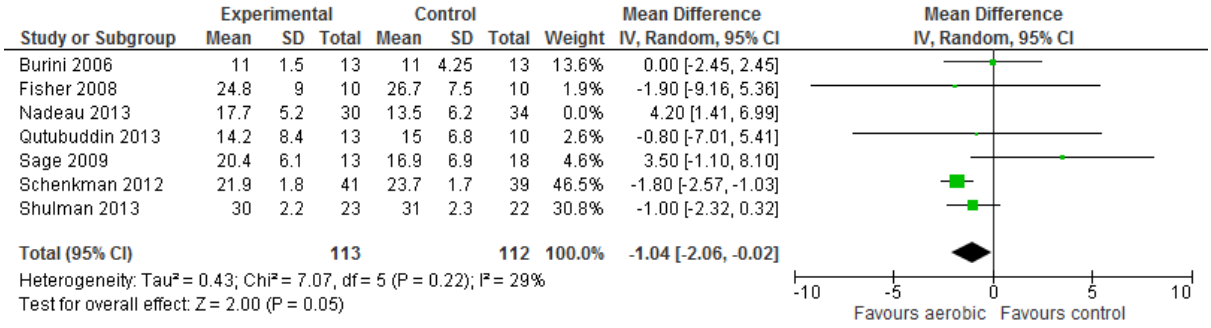
Cumulative Index to Nursing and Allied Health Literature (CINAHL)

1. parkinson*
2. exercise
3. physical activity
4. physical education
5. training
6. kinesio*
7. physical
8. rehabilitation
9. fitness
10. endurance
11. aerobic capacity
12. aerobic
13. strength
14. strength*
15. randomized controlled trials
16. randomised controlled trials
17. randomized controlled trial
18. randomised controlled trial
19. rct
20. controlled clinical trial
21. random allocation
22. double blind method
23. single-blind method
24. single blind method
25. double-blind method
26. clinical trials
27. clinical trial
28. singl*
29. doubl*
30. trebl*
31. tripl*
32. mask*
33. blind*
34. placebos
35. placebo*
36. random*
37. research design
38. comparative study
39. evaluation*
40. evaluation stud*
41. follow-up study

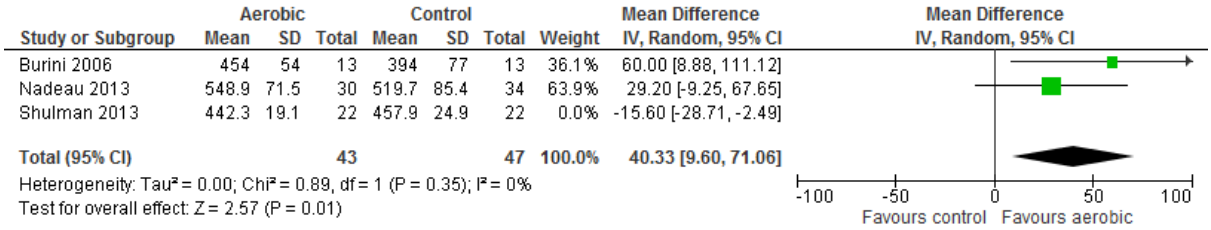
42. prospective study
43. cross-over study
44. control*
45. prospective*
46. volunteer*
47. 2-14 with OR separator
48. 15-46 with OR separator
49. 1 AND 47 AND 48

4025 results

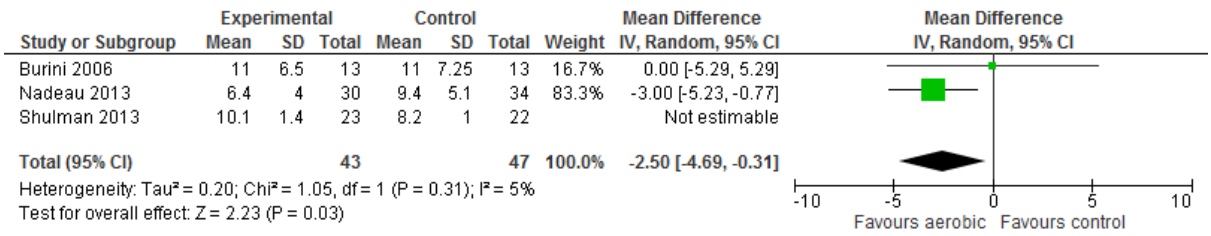
Appendix III - Pooled results of aerobic review for unified Parkinson's disease rating scale motor subscale post intervention after heterogeneity is controlled



Appendix IV - Pooled results of aerobic review for six minute walk test post intervention after heterogeneity is controlled



Appendix V - Pooled results of aerobic review for Beck depression inventory score post intervention after heterogeneity is controlled



Appendix VI - Example literature search strategy for Chapter 2 Strength Review

Databases: Ovid MEDLINE, CINAHL and LILACS

1 explode PARKINSON'S DISEASE/ all subheadings {No Related Terms}

2 (PARKINSON* in TI) or (PARKINSON* in AB) {No Related Terms}

3 1 or 2

4 exercise.mp. or Exercise/

5 exercise therapy.mp. or Exercise Therapy/

6 exercise tolerance.mp. or Exertion/ or Exercise Tolerance/ or Exercise Test/

7 physical therapy.mp.

8 physiotherapy.mp.

9 locomotion.mp. or Locomotion/

10 rehabilitation.mp.

11 sports.mp. or Sports/

12 weight lifting.mp. or Weight Lifting/

13 isometric contraction/ or isotonic contraction.mp.

14 ((training or conditioning) adj3 (intervention$ or protocol$ or program$ or activit$ or regim$)).mp.

15 (exercise adj3 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$)).mp.

16 (muscle strengthening or progressive resist$).mp.

17 ((weight or strength$ or resistance) adj (train$ or lift$ or exercise$)).mp.

18 ((isometric or isotonic or eccentric or concentric) adj (contraction$ or exercise$)).mp.

19 or/4-18

20 randomized controlled trial.pt.

21 randomized controlled trials.mp. or Randomized Controlled Trial/

22 controlled clinical trials {No Related Terms}

23 controlled clinical trial.pt.

24 random allocation.mp. or Random Allocation/

25 single-blind method.mp. or Single-Blind Method/

26 clinical trial.pt.

27 exp clinical trial/

28 (clin$ adj5 trial$).mp.

29 (single adj5 (blind$ or mask$)).mp.

30 placebos.mp. or Placebos/

31 placebo$.mp. or Placebos/

32 random$.mp.

33 research design.mp. or Research Design/

34 multicenter study.pt.

35 intervention studies.mp. or Intervention Studies/

36 cross-over studies.mp. or Cross-Over Studies/

37 control$.tw.

38 alternate treatment.tw.

39 latin square.tw.

40 Comparative Study/

41 exp evaluation studies/

42 follow-up studies.mp. or Follow-Up Studies/

43 prospective studies.mp. or Prospective Studies/

44 prospective.tw.

45 counterbalance$.tw.

46 versus.tw.

47 or/20-46

48 3 and 19 and 47

Database: PEDro
Search strategy: Advanced

Abstract and Title: Parkinson disease

Therapy: Strength training

Subdiscipline: Neurology

Appendix VII - Information leaflet for clinicians referring participants for PEP-PD study

Palliative Exercise Programme for Parkinson's disease (PEP-PD)

STAFF INFORMATION LEAFLET

Aim: To evaluate the feasibility of a progressive resistance exercise program in people with Parkinson's, Hoehn and Yahr stage 3 – 4, in a palliative care setting.

Inclusion Criteria – (see referral form for more details)

- Diagnosed Idiopathic Parkinson's Disease
- 18 years or older
- Residing in the North Dublin City and County Catchment area
- Hoehn and Yahr stage 3-4
- Ability to walk with or without an aid (10m)
- Cognitively able to take part in class i.e. this will be based on clinician opinion
- Not a self-declared exerciser

How to refer patients to PEP-PD?

1. Complete and sign the PEP-PD referral form
2. Provide the patient with a PEP-PD patient leaflet
3. Obtain verbal consent from the patient to be referred to PEP-PD

Recruitment: PEP-PD recruitment will take place from December 2013 – July 2014

Venue: PEP-PD will take place in St Francis Hospice Blanchardstown.

Cost: There is no cost.

Once referred from the clinic:

1. The patient will receive a phone call to discuss the programme further and be offered an initial appointment in St Francis Hospice Blanchardstown
2. They will attend for initial assessment
3. If still eligible – the patient will attend the exercise group for 6 weeks
4. The patient will be re-assessed on completion of the programme and take part in semi-structured interviews
5. There may be a six month follow up assessment depending on resources
6. You will receive a discharge summary outlining the patient's involvement and progress.

Exercise programme for people with advanced Parkinson's Disease

St. Francis Hospice
Blanchardstown

Tel: (01) 829 4000
Email: parkinsons@sfh.ie

This project is joint funded by the

All Ireland Institute of
Hospice and Palliative Care

and

ST. FRANCIS HOSPICE

(Under the Care of the Daughters of Charity
of St. Vincent de Paul)

Located on the grounds of Connolly Hospital in Blanchardstown, Dublin 15.

Accessible by car from the Navan Road

See the below map for the location and please contact St Francis Hospice if you require more help with directions

Introduction
PEP-PD, Palliative Exercise Programme for People With Parkinson's Disease, is a physical exercise programme for people with advanced (often referred to as palliative) Parkinson's disease.

It is recommended that people with Parkinson's Disease take part in regular exercise at least 3 times a week. You have been identified by the Parkinson's clinic in the hospital as being suitable to take part. The PEP-PD programme will take place in St Francis Hospice Blanchardstown.

Aim
Regular exercise has been shown to be very helpful for improving the walking ability of people with Parkinson's disease. This 6 week exercise programme aims to improve your walking ability.

What to expect
You will be contacted by one of the Physiotherapists from St Francis Hospice to discuss the programme.

If you agree to take part in the programme you will be invited for an individual assessment. This will help us to develop an exercise programme that will meet your needs and ability.

The programme will run in a class format for 6 consecutive weeks. Each class will last approximately 90 minutes and will have both an exercise and education component.

You will also be expected to do exercises at home twice a week in addition to the class.

Your walking ability will be reassessed at the end of the programme. You will be asked to attend a short discussion about your experience of the programme. This will help us improve the service for others.

We may offer you an appointment to review your progress in the months following the programme.

Benefits
It is hoped that your walking ability will improve after the 6 week programme. You will also get to meet people with Parkinson's disease who may be experiencing similar difficulties to you.

Will it cost me anything to take part?
No. This is a free exercise group.

Are there any medications provided?
No. It is important to bring in any medications you may need to take during the day.

Where can I get further information?
If you need any more information on the programme please contact David Hegarty, Physiotherapist, St. Francis Hospice either by phone or by email. Contact details on the front page of this leaflet.

Appendix IX - Referral form for clinicians for participants for the PEP-PD study

Palliative Exercise Programme for Parkinson's disease (PEP-PD)

Patient Sticker: **Patient Contact No**:_____

Consultant Name: _____ **Referring Hospital: _____**

Patients are suitable for referral to this programme if they answer <u>'YES' to ALL questions</u>

		YES	NO
1.	Is the patient over 18?		
2.	Does the patient reside in the North Dublin City and County Catchment area?		
3.	Is the patient either stage 3 or 4 Hoehn and Yahr? *Stage 3 – Postural instability/balance issues. Physically independent* *Stage 4 – severe disability, but still able to walk or stand unassisted*		
4.	Can the patient walk with or without an aid for short distances (10m)?		
5.	In your opinion, does the patient have the cognitive ability to take part in an exercise program? *This is for screening purposes and is at the clinician's discretion how to assess.*		
6.	Would the patient say they have **<u>NOT</u>** engaged in regular exercise over the last 6 months? *Exercise: 30 minutes of formal exercise (gym, class, swimming etc) 3 times per week for past 6 months.*		

Leaflet given to patient and verbal information provided on exercise group ☐

Verbal consent obtained to contact patient re: exercise group. ☐

Signed: _____ **Date: _____**

Title: _____ **Bleep No.: _____**

Return Completed forms to: [author contact details]

Appendix X - Written informed consent for participants in the PEP-PD study

Patient Consent Form

Patient Sticker

Study title: Palliative Exercise Programme for Parkinson's disease (PEP-PD)

*I have read and understood the **Information Leaflet** about this project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.*	***Yes ☐***	***No ☐***
I give permission for researchers to look at my medical records to get information. I have been assured that information about me will be kept private and confidential.	***Yes ☐***	***No ☐***
Storage and future use of information: *I give my permission for information collected about me to be stored or electronically processed for the purpose of scientific research and to be used in <u>related studies or other studies in the future</u> but only if the research is approved by a Research Ethics Committee of St Francis Hospice.*	***Yes ☐***	***No ☐***

| |

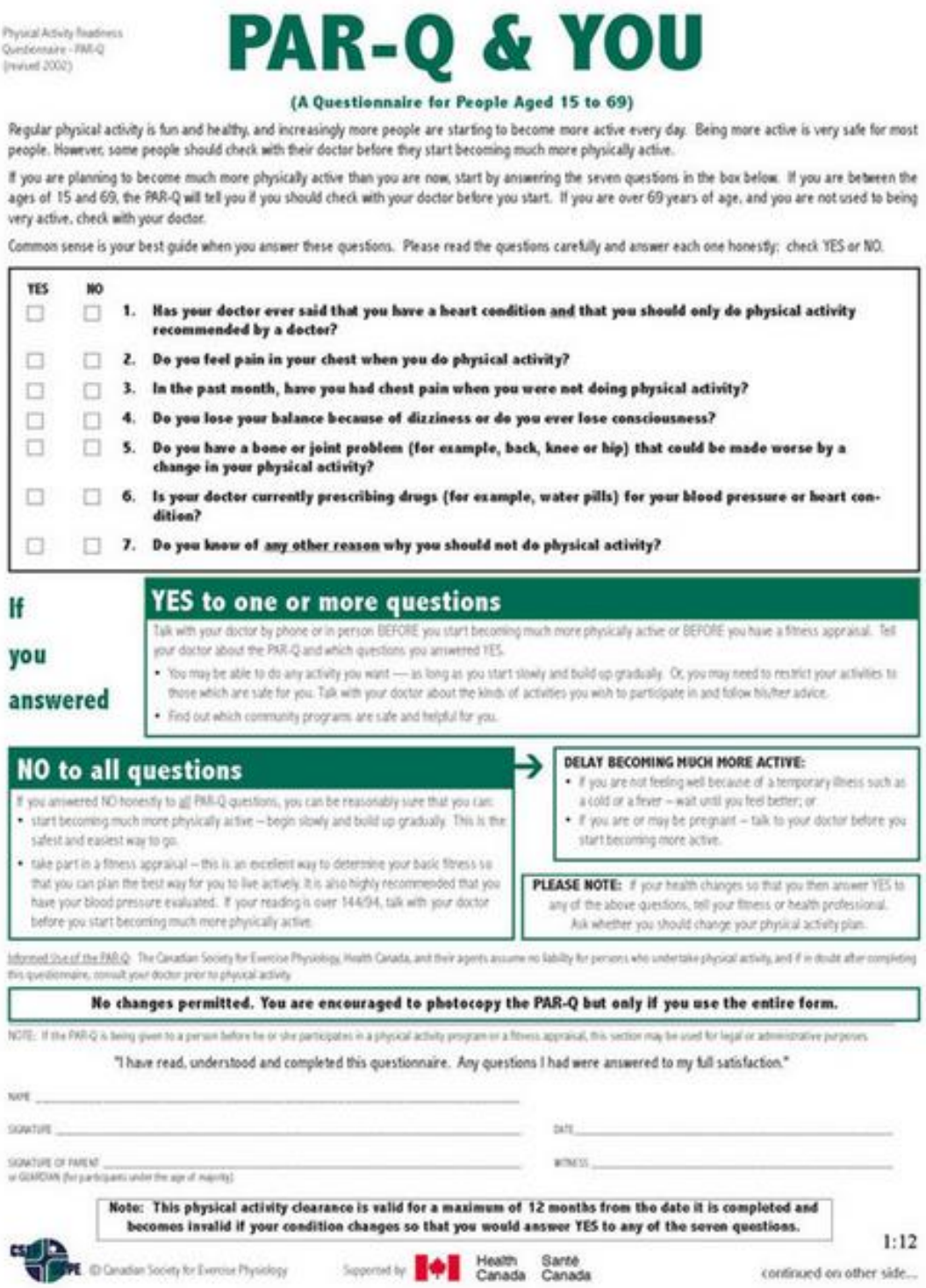
Patient Name (Block Capitals) | Patient Signature | Date

To be completed by the Principal Investigator or nominee.

I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a way that they could understand. I have invited them to ask questions on any aspect of the study that concerned them.

Name (Block Capitals) | Signature | Date

Appendix XI - Physical Activity Readiness Questionnaire used for screening participants in the PEP-PD study



Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
☐	☐	**1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	**2. Do you feel pain in your chest when you do physical activity?**
☐	☐	**3. In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	**4. Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	**5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	**6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	**7. Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- If you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

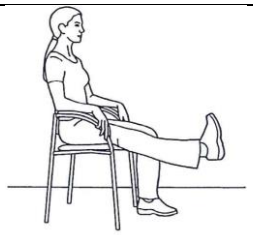
1:12

Supported by Health Canada Santé Canada

continued on other side...

Appendix XII - Blank form used for individualised home exercise programme in the PEP-PD study

Home Exercise Plan – Parkinson's Exercise Class

Exercise	Image	Repetitions	Weight	1st Session (Tick)	2nd Session (Tick)
Knee Extension		**8 repetitions** **3 times**	**Right** **Left**		
Hip Flexion		**8 repetitions** **3 times**	**Right** **Left**		
Hip Extension		**8 repetitions** **3 times**	**Right** **Left**		
Hip Abduction		**8 repetitions** **3 times**	**Right** **Left**		
Knee Flexion		**8 repetitions** **3 times**	**Right** **Left**		

Appendix XIII– Ethical Approval Letter for PEP-PD from the Research Ethics Committee of St Francis Hospice

St. Francis Hospice

(Under the care of the Daughters of Charity of St. Vincent de Paul)

STATION ROAD, RAHENY, DUBLIN 5. TELEPHONE (01) 8327535 FAX: (01) 8327635 E-MAIL: info@sfh.ie WEBSITE: www.stfrancishospice.ie

Mr. David Hegarty,
Physiotherapist,
St. Francis Hospice,
Station Road,
Raheny,
Dublin 5.

25th June 2014

RE: Research Project : "*Physiotherapy led palliative exercise program for parkinson's disease (PEP-PD) patients in an out-patient setting - a feasibility study*"

Dear Mr. Hegarty,

I refer to your research proposal entitled, "*Physiotherapy led palliative exercise program for parkinson's disease (PEP-PD) patients in an out-patient setting - a feasibility study*", which was approved by the Research Ethics Committee at its meeting on 16th April 2014.

At that time you may recall that I wrote to you to request the following modification:

- Page 5, final paragraph: the sentence, "Those who decline the program will be invited to provide a reason for their decision." should be deleted.

Following consideration by the Research Ethics Committee at its recent meeting on 11th June last, it was agreed that there is no requirement to delete this sentence and a reason for declining participation in the programme may be asked.

I would like to take this opportunity to wish you well with your continued research.

Yours sincerely,

Tom McMahon

Tom McMahon,
Chairperson,
Research Ethics Committee.

St. Francis Hospice 25 Years of caring 1989 - 2014 Dignity | Respect | Compassion

Appendix XIV– Ethical Approval Letter for PEP-PD including six month follow-up from the Research Ethics Committee of St Francis Hospice

St. Francis Hospice

(Under the care of the Daughters of Charity of St. Vincent de Paul)

STATION ROAD, RAHENY, DUBLIN 5. TELEPHONE (01) 8327535 FAX: (01) 8327635 E-MAIL: info@sfh.ie WEBSITE: www.stfrancishospice.ie

Mr. David Hegarty,
Physiotherapist,
St. Francis Hospice,
Station Road,
Raheny,
Dublin 5.

15th September 2014

RE: Research Project : "*Physiotherapy led palliative exercise program for parkinson's disease (PEP-PD) patients in an out-patient setting - a feasibility study*"

Dear Mr. Hegarty,

I acknowledge with thanks receipt of your letter dated 27th August 2014 in relation to the above study, which was approved by the Research Ethics Committee at its meeting on 16th April 2014.

I note your request for permission to extend this study to incorporate a six month follow up on patients who have participated in the study and that this follow up would be undertaken by Paula Donovan, Chartered Physiotherapist.

Having considered this request, I consider that it is acceptable to extend the ethical approval for this additional component of the study, provided the additional assessment being undertaken in the follow up mirrors that of the first wave of the study.

I would also draw your attention to the requirement to submit a hard bound copy of your thesis on completion.

I would like to take this opportunity to wish you well with your research.

Yours sincerely,

Tom McMahon

Tom McMahon,
Chairperson,
Research Ethics Committee.