FEASIBILITY STUDY TO EVALUATE CYCLOIDAL VIBRATION THERAPY FOR THE SYMPTOMATIC TREATMENT OF INTERMITTENT CLAUDICATION DUE TO PERIPHERAL ARTERIAL DISEASE

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Firstly, I would like to say thank you to my academic supervisors, Professor Karen Ousey, Dr John Stephenson and Dr Warren Gillibrand. Their help, support, encouragement and valued insightful guidance has been amazing throughout the whole of the PhD process. I could not have wished for a better support team, thank you for your faith in me, for the continual motivation and for the laughs and friendship along the way.

I would also like this opportunity to say thank you to all the participants involved in this study, who so generously and enthusiastically gave up their time to be included in this research, without their generosity this work would not have been possible.

As well, I wish to acknowledge Vibrant Medical for their support with the funding of this research, their commitment to investing in research knowledge is admirable.

Additionally, I would like to thank my friends and family for their continual encouragement and support throughout this process. In particular, my two amazing sons, Jacob and Oliver; I apologise for 'mum being stuck behind the computer' every evening and weekend. You have sacrificed a lot and I have wholeheartedly appreciated your love, patience and kindness – I love you both loads. And finally, I owe particular gratitude to my husband, Steve, who has walked every step of this PhD journey with me. Thank you for your acceptance of the PhD process; for appreciation of the time commitment required; for the motivation, for dealing with my anger and tears; for the numerous hours spent proofreading; for filling the vacant roles of cleaner, cook and bottle washer and most importantly for never losing faith in me, even when I had lost it myself. I really could not have finished this without you in my life – thank you.

ABSTRACT

Introduction

Peripheral arterial disease (PAD) is a strong prognostic indicator of poor long-term survival (Norgren et al., 2007). A symptom of PAD is intermittent claudication which affects 5% of the adult population aged over 55 years (Fowkes et al., 2013). Intermittent claudication (IC) occurs during ambulation when the peripheral circulation is inadequate to meet the metabolic requirement of the active leg muscle, resulting in severe pain (Gardner et al., 2008). Consequently, patients suffering from IC find that the ambulatory dysfunction limits daily physical activity and negatively affects health-related quality of life. Current recommended first-line treatment for IC is for the patient to undertake a supervised exercise programme (NICE, 2012), supervised exercise is designed to improve symptoms by improving rate of formation of new blood vessels and establishing collateral flow. However, there are limitations with supervised exercise. These limitations include: difficulties with accessing exercise programmes (Stewart et al., 2008, Shalhoub et al., 2009, Harwood et al., 2016), poor completion rates/high dropout rates (Kruidenier et al., 2009, Treat-Jacobson et al., 2009, Nicolai et al., 2010), high number of patients unsuitable to participate due to concomitant disease (Suzuki and Iso, 2015, Kruidenier et al., 2009), and lack of patient motivation/willingness to undertake exercise therapy (Muller-Buhl et al., 2012, Stewart et al., 2008). Due to these limitations there is a need to investigate alternative treatments to help improve patients' symptoms of intermittent claudication. One potential option is cycloidal vibration therapy (CVT).

CVT has been shown to increase blood flow (Maloney-Hinds et al., 2009, Button et al., 2007): it is hypothesised that improvement in blood flow would positively impact on patients' symptoms of IC. This prospective feasibility study explored whether there is an association between CVT and patients' symptoms of experiencing IC, measuring changes in pain free walking time and maximum walking time. Focusing on evaluating the research protocol and assessing the feasibility of undertaking a large study in this area and providing detailed information about the variability of the primary outcome measures to facilitate the design of future randomised controlled trial.

Methods

A feasibility study was designed and undertaken. National Health Service (NHS) research and ethical approval was obtained. Patients reporting intermittent claudication were identified from vascular out-patients clinics within Mid Yorkshire NHS Trust. They were screened to ensure they met the inclusion/exclusion criteria for this study, and if suitable were approached to be included within the

study. The patients were than consented and recruited into the study based on sample of convenience.

CVT if provided through a portable machine called Vibropulse (Vibrant Medical) which is designed to be used by the patient at home. The device is a rectangular soft pillow style pad, approximately the size of the lower leg, which is connected to a transformer powered via mains electricity. The machine is fully portable and comes within its own carrying case. The CVT was self-applied at home for 30 minutes twice a day over a 12-week period. Participants were reviewed at weeks 4, 8 and 12, then again at weeks 24 and 36 to assess whether any changes were sustained. Primary outcomes were: change from baseline of both pain free walking time and maximum walking time. Secondary outcome measures were: ankle brachial pressure index (ABPI), limb systolic pressure, mental health component summary score and physical component summary score of the SF-36 quality of life questionnaire, treatment compliance and patients' ease of use of product assessed via a simple questionnaire.

Results

Thirty-four participants with IC were recruited, of which 30 (88%) were male and four (12%) were female. Mean age of all participants was 68 years (IQR 60-75 years). After 12 weeks, 29 participants improved their pain free walking time, with an average improvement of 215% from baseline, (range of -8% to 1005%). Comparison of differences in time to event (event being pain onset) showed a statistically significant difference, between comparison time points at baseline and week 12 ($\chi^2_{(1)}$=25.6; p<0.001).

Furthermore, at week 12, 23 participants recorded improvement in their maximum walking time, with an average improvement of 161%. Comparison of differences in time to event (event being termination of walking due to pain) showed that there was a statistically significant difference between comparison time points at baseline and week 12 ($\chi^2_{(1)}$=15.36; p<0.001).

Analysis of the results showed that improvements in participants' pain free walking time and maximum walking time were most pronounced within the first eight weeks of CVT treatment. Additionally, the long-term follow-up results showed that the improvements seen in pain free walking time and maximum walking time within the treatment phase were sustained once the CVT therapy had been discontinued.

Assessment of changes in participants' lower limb perfusion showed evidence of a statistically significant difference between ABPI at baseline and at the end of week 12 (t_{29}=-2.008, p=0.046). Furthermore, statistically significant changes were seen in the treated leg when comparing systolic leg

pressure at baseline and week 12 (t_{31}=-2.273, p=0.03). However, in the untreated leg there was no evidence of a statistically significant difference (t_{31}=-0.597, p=0.555).

The results showed a positive improvement in participants' quality of life, with their overall physical functioning scores improvement from 35.34 (SD 8.93) at baseline increasing at the end of active therapy to 44.52 (SD 9.11). During the follow-up period there was a decline in scores; however, at week 36 the physical functioning scores were 39.55 (SD 12.37), which is an increase from the starting baseline.

Conclusion

Following 12 weeks of CVT there was statistically significant improvement in pain free walking time and maximum walking time in participants experiencing IC, with improvements being most pronounced within the first eight weeks of treatment. On average, participants' pain free walking time increased by 215% from baseline, this level of improvement is comparable to improvements seen from other treatment options such as supervised exercise (Stewart et al., 2002). This improved walking ability resulted in improved quality of life, measured by physical functioning scores. Additionally, participants' lower limb perfusion had increased, both ABPI and systolic leg pressure showed statistical evidence of improvements, and these changes in lower limb perfusion were not seen in the untreated limb.

This is the first study investigating the feasibility of using CVT as a treatment for IC and has provided novel information relating to duration/positioning of treatment, sample size, number of potential eligible participants and potential association between CVT and improved symptoms. Additionally, it has established that CVT treatment is highly acceptable, as indicated by no participant drop out in the treatment phase, and may potentially offer an alternative treatment option for patients experiencing IC. Furthermore, this study has assessed the variability of the primary outcome measure which provides vital information needed to calculate sample sizes for any future studies. In conclusion, this study has established the feasibility of using CVT to improve patients' symptoms of IC and provides essential information which will contribute to the design of any future investigations.

ACADEMIC BIOGRAPHY

I grew up within a divorced family, but both my parents were equally influential in my upbringing despite being raised in a single-parent environment family. My parents had decent jobs, where they had climbed through the career pathway rather than pursuing formal education. Neither of my parents went to university, my dad is a retired pit deputy and my mum was a manager within the estate department at a local hospital. Money was tight at times but I never felt we were poor by any stretch of the imagination. I lived in a nice housing estate with some middle-class families, but Castleford, where I was brought up, was not a place where the word university was ever spoken. None of my friends went any further than high school. The option of going to university was never spoken about in my home even though I excelled at my GSCEs. I think part of this may have been financial reasons but a major part will have been that I knew I wanted to be a nurse and at that time to become a nurse you needed to get a place in a nursing school not a university.

In fact, I can clearly remember speaking to the Principal at college saying that I was leaving and dropping my four A-Levels and going to become a nurse. He was truly disgusted with this, stating that I was too clever to become a nurse! I was a stubborn young lady (still am stubborn) and told him that I had made my decision and left. His parting words were 'you will regret not doing your A-Levels for the rest of your life!'

I entered nursing college at the age of 17½, the minimum age you were allowed to start. Within the first week I knew this was going to be a career for the rest of my life. I loved nursing, the patients, the team, the everyday learning – it truly felt like it was a huge privilege to call myself a nurse.

I have now been nursing for 25 years, and within this time I have never stopped learning, completing my diploma, degree and then my Master's degree in 2010. During this time, I have progressed through the nursing ranks from Staff Nurse, to Senior Staff Nurse, Deputy Sister and Ward Sister and for the last ten years I have worked as an Advanced Vascular Practitioner. I would never have dreamed that when I first started nursing I would be given the autonomy I have today, being able to diagnose, prescribe, investigate and list patients for interventions. A lot of my clinical skills and the level at which I practise is down to having a fantastic mentor and ambassador for progression of nursing roles and I do not believe I could have achieved all I have without the support from Mr Craig Irvine, Vascular Consultant.

In today's NHS, advanced nurses are working at the level of consultants and part of this clinical role is to independently run out-patients' clinics for patients with suspected intermittent claudication. This

is where my passion for PAD started. This group of patients really is the 'Cinderella' of cardiovascular disease. Everyone knows about heart attacks and strokes, but how many people have even heard of PAD?

As part of my career path I started giving guest lectures at the University of Huddersfield and there I met one of the most inspirational people in my whole career, Professor Ousey. Karen was a nurse from Manchester who had made it all the way to the role of Professor within the University. If you met her in the street to talk to, you would not believe she is a professor! - In the nicest way! Karen believed in me from the outset and pushed me to start clinical research work. As soon as I had completed and published my first paper a fire within me ignited and since then I have not stopped.

Since meeting Karen, I have now published over 50 journal articles and been involved in clinical research that has made a difference to nationwide clinical practice. Even throughout the final years of my PhD I have led on two other research projects running alongside my PhD. The ability to be able to influence practice through research is amazing. In this way, you have the chance to improve many patients' lives, not just the ones you come into personal contact with.

Clinical frustrations brought me to start my PhD (that and a little gentle push from Professor Ousey). For patients with claudication the current first line treatment recommendation is to undergo a supervised exercise programme (NICE, 2012). However, there is no such provision within the organisation for which I work, in fact there are no supervised exercise programmes in the whole of the wider regional spoke centre the 'Leeds Vascular Institute'. So, the National Institute for Health and Care Excellence (NICE) group recommended a treatment which I cannot provide to my patients, leaving the only options of a simple 'go home and walk' advice or to potentially look at the possibility of undergoing revascularisation to improve symptoms. Neither of these options seems great, as the former will probably not work and the latter option involves a degree of risk of complications arising from any procedure. This led me to start reading about what other options were out there – was there any emerging evidence of other new/alternative treatment options? After reading the literature I realised there was nothing new in the pipeline.

I have used Cycloid Vibration Therapy (CVT) for patients with ulceration for many years, and have found this to be of clinical benefit. One day when reading around CVT, I noticed the claims about improved blood flow. This eventually led to a piece of research and the subject of this thesis.

The journey to completing the PhD has been hard but so rewarding. Having a lecturer practitioner role within the University and a clinical job as Vascular Nurse Specialist, I have, in effect, two full time jobs. The National Health Service (NHS) has supported me with the funding for the PhD but I have only ever

been able to gain one hour study leave per week to complete the whole of this research. This obviously has created its own challenge along the way, especially as I am also a mother and a wife. But luckily, I have a very supportive family.

I started this PhD journey as a nurse, and at my half way viva one of the assessors said “you are more than a nurse now, you are a scientist”. This is another of those moments I will never, in my lifetime, forget. When I heard the word ‘scientist’, I could not help myself but to laugh a little: ‘no not me, I am not clever enough!’ However, at the end of this journey I really do believe I am now a scientist (as well as a passionate nurse). I love the new knowledge and skills I have gained through working towards the PhD qualification and the way that I now question practice, the evidence base and the gaps in the literature. I know that I will use the skills that I have acquired forevermore, helping to grow the knowledge base which will have the ability to impact the lives of many patients now and in the future.

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LIST OF ABBREVIATIONS

ABPI	Ankle Brachial Pressure Index
BP	Blood Pressure
CLI	Critical Limb Ischaemia
CRF	Clinical Research File
CTA	Computer Tomography Angiogram
CVA	Cerebral Vascular Accident
CVD	Coronary Vascular Disease
CVT	Cycloidal Vibration Therapy
HbA1c	Haemoglobin A1c
IC	Intermittent Claudication
IHD	Ischaemic Heart Disease
IQR	Intra Quartile Range
GPS	Global Positioning System
MCS	Mental Health Component Summary
MI	Myocardial Infarction
MRA	Magnetic Resource Angiogram
MWT	Maximum Walking Time
NIHR	National Institute for Health Research
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NO	Nitric Oxide
PAD	Peripheral Arterial Disease
PCS	Physical Component Summary

PFWT Pain Free Walking Time

PTA Percutaneous Transluminal (balloon) Angioplasty

SIGN Scottish Intercollegiate Guidelines Network

SREP School Research Ethics Panel

TIA Transient Ischaemic Attack

TASC Trans-Atlantic Inter-Society Consensus

WIQ Walking Impairment Questionnaire

UK United Kingdom

ABSTRACT PRESENTATIONS

Atkin L (2016) Feasibility study to evaluate non-invasive cycloidal vibration therapy for the symptomatic treatment of intermittent claudication. Vascular Society Scientific Conference, Manchester 30th November 2016.

Atkin L (2016) Feasibility study to evaluate non-invasive cycloidal vibration therapy for the symptomatic treatment of intermittent claudication. Society of Vascular Nurses Annual Conference, Manchester, 1st December 2016.

Atkin L (2016) Feasibility study to evaluate non-invasive cycloidal vibration therapy for the symptomatic treatment of intermittent claudication. Post Graduate Research Conference, University of Huddersfield, 18th November 2016.

Three Minute Thesis – Runner up - 'Time for pain?' University of Huddersfield, June 2016.

1 INTRODUCTION

Peripheral arterial disease (PAD) is caused by the development of atherosclerosis in the lower limb arteries and is associated with increased morbidity and mortality. PAD is underdiagnosed, undertreated and poorly understood by the medical profession (Olin and Sealove, 2010, Vedula et al., 2011). A common symptom of PAD is intermittent claudication (IC), which is a severe cramp-like pain in the muscles of the lower legs experienced when walking. This is caused by the reduction in blood supply, leading to lack of oxygenation of the muscle cells. These symptoms severely limit exercise performance and walking ability/distance, and as such negatively affect patients' quality of life (Norgren et al., 2007). PAD affects approximately 20% of the population over the age of 55 in the western world, with an estimated prevalence of over 27 million people in North America and Europe (Hankey et al., 2006).

The National Institute for Health and Care Excellence [NICE], (NICE, 2012) and the Scottish Intercollegiate Guidelines Network [SIGN], (SIGN, 2006), have published guidelines for the management of PAD. The guidance states that all patients with IC should be offered a supervised exercise programme as a first line of intervention and that further treatment options, such as angioplasty or medication, should only be offered when a supervised exercise programme has failed to lead to satisfactory improvements in symptoms. Supervised exercise has been shown to improve peripheral circulation that can provide symptomatic relief and improve walking distance before pain is experienced (Fokkenrood et al., 2013). However, currently, supervised exercise programmes are not widely available in the National Health Service (NHS) across the United Kingdom (UK), (Shalhoub et al., 2009). This is reported to be due to the running costs, lack of resource, and poor patient compliance with exercise programmes (Nicolai et al., 2010, Shalhoub et al., 2009).

Due to the limitations of the treatment options currently available, this provides an opportunity to explore alternative therapies to improve patients' symptoms of IC. A potential alternative to current treatments is that of cycloid vibration therapy (CVT). CVT is a low frequency and amplitude form of oscillatory non-invasive energy. The transmission of these vibrations into the tissues generates a range of mechanical forces and stresses on vascular endothelial cells that have been shown to induce the release of nitric oxide (NO) (Ichioka et al., 2011). Vascular-produced nitric oxide is an important vasodilator which regulates vascular smooth muscle tone and maintains healthy blood flow. Additionally, the presence of NO is the mediator for angiogenesis (the formation of new blood supply) (Cooke and Losordo, 2002). CVT has been shown to increase NO levels, leading to increased blood flow (Maloney-Hinds et al., 2009, Ichioka et al., 2011).

This research focuses on whether the stimulation of these mechanisms through CVT in the lower limb at the point of, and surrounding area of, arterial disease could improve blood flow; therefore, increasing arterial perfusion and thus increasing patients' walking distance. If CVT improves patient symptoms, this would support the use of CVT as an alternative treatment for patients with IC, especially those who are not able to undertake a supervised exercise programme and/or those not wishing to be exposed to the risks or side effects that angioplasty or medication bring.

This chapter introduces the concepts of PAD and IC, discussing the epidemiology of the disease, associated risk factors and detection/classification of disease. It will then provide insight to the impact of PAD on patients' quality of life, including morbidity and mortality rates. Current treatment options will be described and limitations of these discussed. Finally, the mechanisms of CVT will be explored and the potential of this treatment in the management of PAD leading to rationalisation of research will be discussed.

1.1 Peripheral arterial disease

PAD is the term used to describe partial or complete obstruction of one or more of the arteries which perfuse the lower limbs causing a reduction in arterial blood supply. Other terms used to describe this condition are peripheral vascular disease, peripheral arterial occlusive disease and lower extremities arterial disease. The most frequent cause of PAD is atherosclerosis; however, other causes are possible such as vasculitis, popliteal entrapment and cystic adventitial disease (Andras and Ferket, 2014). Fatty deposits on the walls of the arteries (atherosclerosis) leads to the narrowing of the artery (stenosis) or obstruction (occlusion), resulting in a reduction of blood flow. Often the primary symptom of PAD is IC. However, symptoms range in severity from asymptomatic (where the patient does not report any symptoms, but there is evidence of PAD on assessment), to IC with continuous pain at rest (known as rest pain), which can eventually result in critical limb ischaemia (reduced tissue oxygenation) or tissue loss (due to the formation of gangrene). It is important to remember that atherosclerosis is a systemic disease, and therefore patients with PAD have a similar relative risk of death from myocardial infarction, stroke, and other vascular causes as those patients with symptomatic coronary or cerebrovascular disease.

1.2 Claudication

Claudication, from the Latin 'claudios' meaning 'to limp', refers to the occurrence of muscle cramping or tightness when an exercising muscle requires more oxygen and nutrients than the circulatory system is capable of delivering. Intermittent claudication is a symptom of PAD, and does not occur in

individuals with a healthy arterial blood supply. Intermittent claudication is, in itself, a relatively benign condition that need not result in major disability if patients are happy to accept the limitations imposed on their lifestyle. However, this reduction in patients' walking distance can have a significant impact on a patient's quality of life (Dumville et al., 2004, SIGN, 2006). IC is often described as a severe cramp or tightness in either the calf, thigh or buttock muscle which is present after a short period of exercise; these symptoms settle after a period of rest, but return with muscle exercise. More severe pain or discomfort is suffered when walking, which involves greater muscle effort; for example, walking up an incline. Due to the nature of intermittent claudication occurring when muscle oxygen demand increases, it never occurs when a patient is at rest, either sitting or lying down. Characteristically, the symptoms of intermittent claudication are readily repeatable (the distance at which pain occurs is constant), and patients will, at a given distance, pre-empt the pain. The cramp pain will be experienced distal to the disease in the arterial tree; therefore, patients who experience calf claudication often have disease in the superficial femoral artery (deep artery within the thigh), those with thigh claudication have disease in the profunda artery (a branch of the superficial femoral artery), and individuals experiencing buttock claudication disease often have disease within the aorto/iliac system (arteries within the abdomen/pelvis).

1.3 Epidemiology of peripheral arterial disease

It is estimated that over 200 million people have PAD worldwide (Fowkes et al., 2013). Prevalence of both symptomatic and asymptomatic disease is estimated at 13% in the over-50 years age group (Hirsch et al., 2001). Symptomatic PAD affects about 5% of the Western population between the age of 55 and 74 years (Khan et al., 2007). PAD is relatively uncommon among younger people, but prevalence rises sharply with age. Several population-based studies have found the prevalence of PAD to be between 3% to 10% in those aged over 55 years, with prevalence increasing to between 5% and 20% in people aged over 70 years (Criqui et al., 1985, Fowkes et al., 1991, Hiatt et al., 1995, Selvin and Erlinger, 2004, Shammas, 2007, Fowkes et al., 2013). Prevalence of IC is higher in the male population compared to females; for every woman affected by IC there are 2-3 times more men suffering. This ratio remains constant even with increasing age (Fowkes et al., 2013).

1.4 Risk factors

Risk factors for the development of PAD are similar to those of coronary vascular disease (CVD); these include: cigarette smoking, hypertension, high cholesterol, previous cardiovascular disease and diabetes (Norgren et al., 2007). Global data suggests that smoking and diabetes are the strongest predictive factor for development of PAD (Fowkes et al., 2013). A variety of other potential risk factors

for the development of PAD have been examined. These include: obesity, alcohol consumption, race and ethnicity, abnormal homocysteine levels, increased C-Reactive protein levels, chronic kidney disease and genetic factors. In the United States, the National Health and Nutrition Examination Survey (1999-2000) analysed 2174 participants over the age of 40 and identified a 4.3% prevalence of PAD based on an Ankle Brachial Pressure Index (ABPI) of less than 0.90 in either lower limb. Using age and gender-adjusted logistic regression analyses, the survey reported odds ratios for risk factors significantly associated with PAD, including: current smoking (4.46), black race (2.83), diabetes (2.71), poor kidney function (2.00), hypertension (1.75) and hypercholesterolaemia (1.68) (Selvin and Erlinger, 2004). Risk factor management/reduction is a fundamental aspect of PAD clinical management.

1.4.1 Smoking

Smoking (active or passive) is an established vascular risk factor (Leone, 2011, Oberg et al., 2011, Mazzone et al., 2010) and is the single most etiological component for the development and progression of PAD (Hobbs and Bradbury, 2003). The risk of PAD is four times higher in smokers than non-smokers, with smokers experiencing the onset of symptoms almost a decade earlier than non-smokers (Olin and Sealove, 2010). The severity of PAD has a proven relationship with the amount of tobacco consumption (Willigendael et al., 2004). Furthermore, smokers have a greater chance of developing critical limb ischaemia, and once critical limb ischaemia is established, smokers have an increased rate of major limb amputation, decreased arterial bypass graft patency rate and generally poorer survival rates when compared to non-smokers (Olin and Sealove, 2010). However, patients who are able to successfully stop smoking reduce their chance of developing critical limb ischaemia and have an overall improved survival rate (Ratchford and Evans, 2016).

1.4.2 Hypertension

Hypertension is a major risk factor for PAD development, (Piller et al., 2014). On presentation, between 35% and 55% of patients with PAD also have hypertension (Hirsch et al., 2001, Singer and Kite, 2008, Clement and Debuyzere, 2007). Additionally, hypertension is known to contribute to the progression of atherosclerosis (Lane and Lip, 2013). Patients who suffer from either hypertension or PAD have a high risk of MI (myocardial infarction) and stroke, and when hypertension and PAD are both present, the risk of MI or stroke is greatly increased (Clement and Debuyzere, 2007, Singer and Kite, 2008, Fowkes et al., 2013).

1.4.3 High blood cholesterol levels

Total cholesterol is an independent risk factor for the development of PAD (Meijer et al., 2000, Murabito et al., 2002, Murabito et al., 1997). In addition, the ratio of total cholesterol to high density lipoprotein cholesterol has also been documented as a predictor of occurrence of PAD (Ridker et al., 2001). A fasting cholesterol level above 7 mmol/L is associated with a doubling of the incidence of IC (Norgren et al., 2007).

1.4.4 Diabetes

Diabetes mellitus is strongly associated with an elevated risk of PAD (Criqui and Aboyans, 2015). Overall, IC is twice as common in diabetic patients compared to non-diabetic patients. Haemoglobin A1c (HbA1c) is a marker of glycaemic control: for every 1% increase in HbA1c there is a corresponding 26% increased risk of PAD (Selvin et al., 2004). The duration of diabetes, level of glycaemic control and the use of insulin increases the risk of PAD (Kallio et al., 2003). The outcomes for patients with diabetes and PAD are substantially worse than non-diabetic patients. Diabetic patients with PAD are five times more likely to have a major limb amputation than other patients with PAD; additionally, patients with diabetes have a three times increased risk of mortality and die at a younger age than non-diabetic patients (Jude et al., 2001).

1.4.5 Previous history of cardiovascular disease

Given the similarity of risk factors for PAD and CVD, it is not surprising that patients with PAD are more likely to have concomitant coronary or cerebrovascular disease and *vice versa*. The prevalence of a history of myocardial infarction (MI) was found to be 2.5 times higher in a subject with PAD than in those without. Furthermore, the prevalence of previous cerebral vascular accident (CVA) or transient-ischaemic attack (TIA) was 3.1 and 2.3 times higher respectively, in patients with PAD compared to those with no PAD (Newman et al., 1993, Bhatt et al., 2006). Conversely, the prevalence of PAD was 2.1 times higher in patients with a previous MI event compared with patients who had not had an MI. Similar increased rates of PAD were seen in patients with a history of TIA or CVA (Bhatt et al., 2006, Newman et al., 1993). With PAD being a manifestation of atherosclerosis, as is the case for CVD and cerebral disease, it is not surprising that there is an overlap of these three diseases: in general, 65% of patients with PAD have clinical evidence of other vascular disease (Bhatt et al., 2006).

1.5 Defining PAD

IC is caused by atherosclerosis in the arteries leading to the lower limbs. Atherosclerosis is the thickening in the wall of an artery caused by fibro-fatty plaques. Although the plaques are focal,

patients often have multiple lesions, either in the same arterial tree or in different arteries. Atherosclerosis significantly reduces the blood supply to areas served by affected vessels. Symptoms of IC arise because the oxygen demands of a specific muscle become greater than the diseased artery can supply (Dieter et al., 2002). Claudication is classified in line with severity (Norgren et al., 2007).

1.6 Classification of PAD

Traditionally both Fontaine and Rutherford classifications systems have been used to classify patients' symptoms and functional limitations (Norgren et al., 2007). Consistent and reproducible grading of patients is important, as this leads to objective criteria against which patients can be treated. The first published classification system emerged from the European Society of Cardiovascular Surgery and was published in 1954 (Fontaine et al., 1954). The Fontaine's classification scale consists of: asymptomatic (stage I), intermittent claudication at greater than 100 metres (stage II a), intermittent claudication at less than 100 metres (stage II b), rest pain (stage III), and ulceration or gangrene (stage IV) (Fontaine, 1954 cited in De Backer et al*.,* 2009).

The Fontaine classification was adapted by Rutherford in 1986 (Rutherford et al., 1986) with further revision in 1997 (Rutherford et al., 1997). The Rutherford classification (Figure 1-1) uses six degrees of severity (rather than the five stages in the Fontaine classification scale) and includes additional non-invasive diagnostic information, aimed to aid stratification of patients.

Figure 1-1 Rutherford classification for chronic limb ischaemia

Category	Clinical Description	Objective Criteria
0	*Asymptomatic – no haemodynamically significant occlusive disease*	*Normal treadmill or reactive hyperaemia test*
1	*Mild Claudication*	*Completes treadmill exercise; Ankle Pressure after exercise > 50 mmHg but at least 20 mmHg lower than resting value*
2	*Moderate Claudication*	*Between categories 1 and 3*
3	*Severe Claudication*	*Cannot complete standard treadmill exercise and ankle pressure after exercise <50 mmHg*
4	*Ischaemic rest pain*	*Resting ankle pressure <60 mmHg; flat or barely pulsatile ankle or metatarsal pulse volume recording; Toe pressure < 40 mmHg*
5	*Minor tissue loss – non-healing ulcer, focal gangrene with diffuse pedal ischaemia*	*Resting ankle pressure <40 mmHg; flat or barely pulsatile ankle or metatarsal pulse volume recording; Toe pressure < 30 mmHg*
6	*Major tissue loss – extending above trans-metatarsal level, functional foot no longer salvageable*	*Same as category 5*

Fontaine and Rutherford classification systems are based on clinical symptomatology and non-invasive diagnostics. Other newer classification systems such as Bollinger Angiographic Classification (Bollinger et al., 1981) and the Trans-Atlantic Inter-Society Consensus Document II (TASC II) (Norgren et al., 2007) have been developed, but these are based on the location and severity of atherosclerotic lesions which requires the use of invasive imaging to stratify patients. Therefore the Rutherford or Fontaine Scales remain commonly used, especially on initial assessment of a patient (Gardner and Afaq, 2008).

1.7 Detection of PAD

PAD can be detected via a clinical examination of the patient and through careful history-taking. However, the reliability of these methods is limited (Norgren et al., 2007). Palpation of the pulse status of the lower limb is useful to identify and locate the level of abnormality, but can lead to an overestimation of the presence of disease; whereas reliance of the presence of symptoms can lead to an under-diagnosis. Due to the limitation of limb and symptom assessment a more objective measure of detection is required. The Ankle Brachial Pressure Index (ABPI) provides a valid and reliable marker

of PAD (Leng et al., 1996). It offers a semi-quantitative and objective measure of the severity of symptomatic PAD, and additionally allows for the identification of asymptomatic PAD (Norman et al., 2004). In the general population, the specificity of ABPI has been reported as 97%, with sensitivity between 80% and 100% (Lijmer et al., 1996, Ouriel et al., 1982, Yao et al., 1969, Dachun et al., 2010). Sensitivity is reduced in the presence of mild disease or arterial calcification (Aboyans et al., 2008, Stein et al., 2006). ABPI has shown high intra and inter-rater reliability (Aboyans et al., 2003), making it a dependable and widely used method of PAD detection. Additionally, ABPI is a predictor of cardiovascular events with a strong correlation between ABPI level and cardiovascular mortality (Fowkes et al., 1991, Norgren et al., 2007).

1.7.1 ABPI

ABPI is a 'bedside' non-invasive test which is used to facilitate the diagnosis of PAD, and can also be used to assess the severity of the disease (NICE, 2012). The ABPI test uses a sphygmomanometer (manual blood pressure machine) and a Doppler machine. The practitioner locates an audible signal with the Doppler probe in the artery, and the sphygmomanometer cuff is inflated until the artery is occluded and the sound disappears. The cuff is then slowly released and the pressure at which the sound reappears is recorded (Figure 1-2). This process is repeated in both arms and legs. The ABPI ratio is calculated by dividing the highest ankle pressure (obtained in the posterior tibial, dorsalis pedis or the peroneal artery) by the highest systolic pressure in the arm. Current guidelines endorse the use of ABPI for the diagnosis of PAD (NICE, 2012). Ratios of 0.9 to 1.3 are considered normal for an adult population, ratios less than 0.9 are suggestive of arterial stenosis, and ratios less than 0.5 are associated with severe arterial disease and critical limb ischaemia (NICE, 2012, Bhasin and Scott, 2007, Crawford et al., 2016). Elevated readings greater than 1.3 indicate the presence of medial sclerosis, and as such invalidates the ABPI as a dialogistic tool. This is due to the arterial wall becoming stiffer and resistant to compression from the sphygmomanometer cuff. This stiffness and resistance to compression potentially gives a falsely elevated pressure value (Suominen et al., 2008).

Figure 1-2 ABPI assessment

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1.7.2 Diagnostic imaging

Whilst ABPI measurements are useful at identifying patients with PAD, they do not provide any anatomical information, whereas diagnostic imaging does. This information is vital when assessing patient suitability for endovascular or surgical intervention. Additionally, imaging is used to confirm the presence of PAD when ABPI results are borderline or inconclusive. Imaging options include: Duplex ultrasound, which allows identification of location of disease and also quantifies degree of stenosis via comparison of waveforms and peak systolic velocities (Figure 1-3) and CTA (Computer Tomography Angiogram - Figure 1-4) or MRA (Magnetic Resource Angiogram – Figure 1-5), both of which permit the imaging of the whole of the arterial tree from the level of the renal system down to the foot arch. This level of information is very useful especially if surgical revascularisation is being assessed. However, there are limitations in the use of CTA or MRA scans, as both require the injection of a contrast agent (which has to be used with caution in patients with renal failure). Additionally, the quality of the images can be affected by the presence of arterial calcification or other artifacts. Angiography provides the most detailed assessment of the condition of the artery and severity of disease. However, this is an invasive test, requiring the puncturing of the femoral artery, and therefore is not recommended for diagnostic purposes only.

Figure 1-3 Example of Arterial Duplex Scan

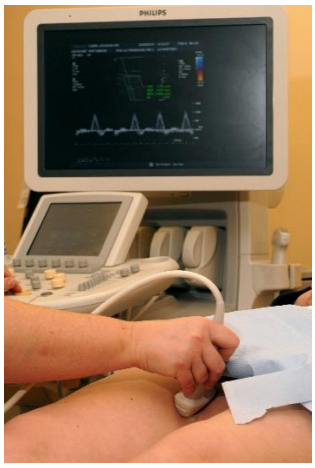

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Figure 1-4 Example of CTA imaging

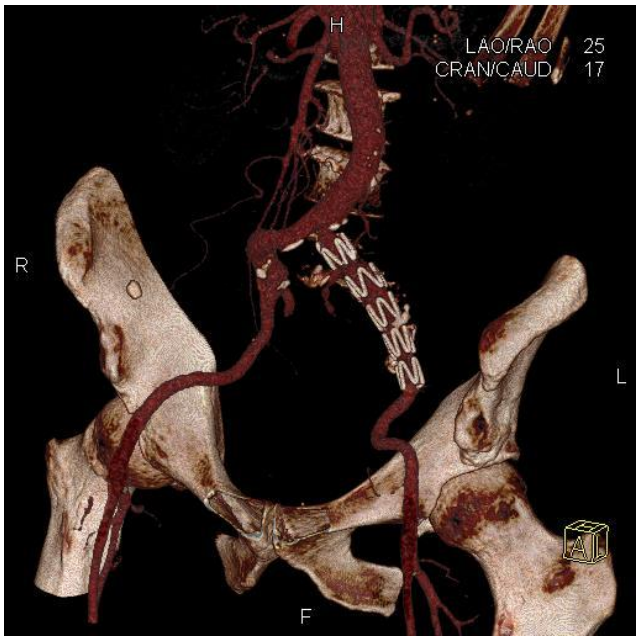

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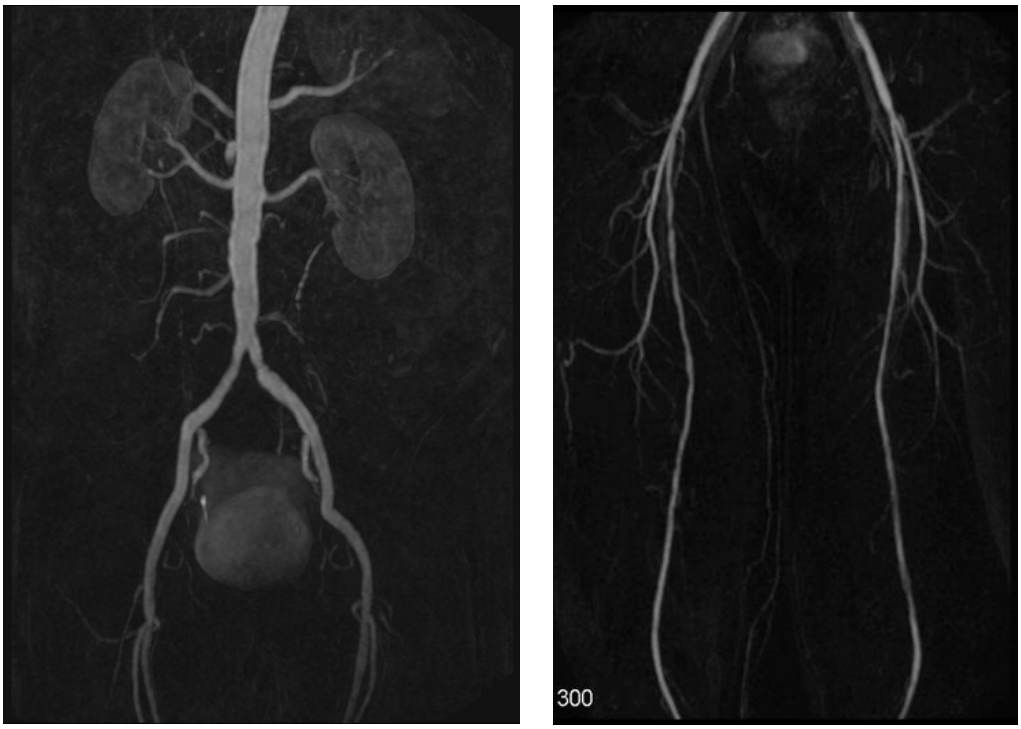
Figure 1-5 Example of MRA imaging



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1.8 Impact of PAD and IC

1.8.1 Physical function/quality of life

PAD impacts patients' quality of life (Nehler et al., 2003, Garg et al., 2009, Dumville et al., 2004), and has been found to affect both physical and mental functioning (McDermott et al., 2000b). Patients with PAD have a significantly lower physical activity level compared to patients without PAD (McDermott et al., 2000b). Walking endurance is reduced in patients with PAD and the more severe the PAD (as indicated by a lower ABPI value), the greater the impairment of walking endurance (McDermott, 2013). This limitation in walking ability leads to deconditioning of the individual that results in a chain of events; further functional decline, eventual physical disability, and loss of independence, all leading to impaired quality of life (Stewart et al., 2002). This impaired functioning is a known predictor of loss of mobility and nursing home placement (Dolan et al., 2002). This is of real concern, especially when taking into account the prevalence of PAD increases with age, and that almost 20% of adults over 70 years have PAD (Hiatt, 2001).

1.8.2 Progression of disease – impact to life and limb

Little is known about the early natural progression of PAD in the asymptomatic to early symptomatic group (Criqui and Aboyans, 2015), but for those presenting with IC over a five-year period, approximately 70-80% will remain with stable claudication, 10-20% will go on to have worsening symptoms and 5-10% will go on to develop critical limb ischaemia (CLI) (Leng et al., 1996, Hirsch et al., 2006). Stabilisation of claudication symptoms occur due to collateral development, metabolic adaptation of ischaemic muscle or gait alteration favouring the non-ischaemic group (Aquino et al., 2001). However, even if the patient's walking distance appears to be stabilised there is, on average, a slight decline in walking distance of 8.4 metres per year (Aquino et al., 2001).

The major impact of PAD is not to the limb itself but to the life of the patient, approximately 10-15% of individuals with PAD die of cardiovascular causes within five years, and a further 20% will have a non-fatal cardiovascular event (Park et al., 2007, Hooi et al., 2004). There is high mortality in those who develop CLI, with approximately 25% dying within a year and about one third requiring a major lower limb amputation within a year (Park et al., 2007). In general, patients with claudication have an annualised 12% risk of death (Muluk et al., 2001).

Cardiovascular diseases (CVD) are the leading cause of death worldwide. An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke (World Health Organization, 2016). The life expectancy of claudicants is short due to the high risk of cardiovascular events: it is reported that this group of patients have a predicted mortality rate of up to 48% within 10 years (Criqui et al., 1992, Mueller et al., 2016).

1.9 Management of IC

The aims of management of IC is to reduce the risk of secondary cardiovascular events and to improve lower limb symptoms and associated quality of life.

1.9.1 Cardiovascular risk reduction

Due to the strong association between PAD and cardiovascular mortality, the initial treatment of intermittent claudication concentrates on prevention of secondary cardiovascular disease. Patients require 'best medical therapy', which is a term used to describe a range of approaches, including the prescribing of antiplatelet agent and statin therapy, and modification of any risk factors including: smoking cessation, diet, weight management and exercise, prevention, diagnosis and management of diabetes and hypertension.

1.9.2 Antiplatelet therapy

All patients with PAD need to be prescribed antiplatelet therapy, (NICE, 2012, SIGN, 2006). Antiplatelet therapy will not provide improvement in patients' symptoms of IC, but will help reduce the risk of secondary disease formulation/cardiovascular events (Norgren et al., 2007). Antiplatelet therapy has been shown to reduce the rate of adverse vascular events by around 20-25% (Norgren et al., 2007). Antiplatelet agents include aspirin, Clopidogrel and Dipyridamole. Current recommendation is that patients with PAD should be prescribed Clopidogrel as the preferred antiplatelet agent. If Clopidogrel is not tolerated or contraindicated then low dose aspirin be prescribed; if both Clopidogrel and aspirin are contraindicated or not tolerated, then modified release dipyridamole may be used (NICE, 2015).

1.9.3 Lipid therapy

Lipid modification with statin therapy is recommended for all patients with PAD, regardless of blood serum cholesterol level (NICE, 2012, SIGN, 2006). This is due to the reduction of cardiovascular events and death in patients with PAD using statin therapy. A large placebo-controlled, randomised controlled trial, the Heart Protection Study, reported that statin therapy in patients with PAD (including those without prior coronary disease) resulted in 25% reduction in secondary major vascular events (Heart Protection Study Collaborative Group, 2002). There is also some evidence that Atorvastatin may improve patients' walking distance with IC (Mohler et al., 2003). Current guidelines state that Atorvastatin is the recommended first-line statin agent within the UK (NICE, 2016a). Further to the known benefits of secondary disease prevention, treating hyperlipidemia (increased concentration of fats or lipids with the blood) with statin therapy also reduces the progression of PAD (Norgren et al., 2007).

1.10 Treatment of intermittent claudication

The first step in managing patients' symptoms of intermittent claudication is to decide whether it needs management at all, other than 'best medical therapy'. Many patients present for treatment in fear that their claudication is a harbinger of imminent gangrene and subsequent amputation, and often simple reassurance about the natural history of claudication is all that is required (Earnshaw, 2007). However, there is a substantial proportion of patients for whom the restriction on walking distance severely impacts on their quality of life, and as such are seeking treatment to improve their walking distance. Current treatment options include exercise programmes, medication or endovascular intervention or surgical bypass: the latter is usually reserved for incapacitating disease, CLI or tissue loss.

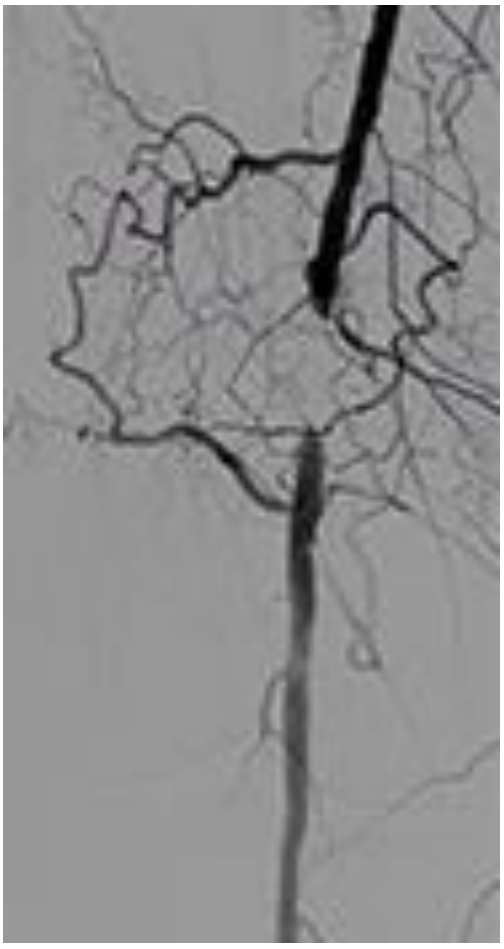
1.10.1 Exercise therapy

Supervised exercise programmes are recommended by the NICE as first-line management for IC (NICE, 2012). It is stated that exercise programmes should include two hours of supervised exercise a week for a period of three months (NICE, 2012, Norgren et al., 2007). Additionally, supervised exercise is also endorsed as an initial treatment by the American College of Cardiology Foundation/American Heart Association (ACC/AHA) and the Trans-Atlantic Inter-Society Consensus (TASC II) (Norgren et al., 2007, Hirsch et al., 2006). During supervised exercise, which would normally be held within hospital physiotherapy gymnasiums, patients are encouraged to exercise to the point of maximal pain. This exercise involves either track or treadmill walking for a period of 30 to 60 minutes, two or three times a week, for a period of three months (Lauret et al., 2014). Several randomised prospective studies have demonstrated that supervised exercise is an effective method of treating patients with IC (Gardner and Poehlman, 1995, Stewart et al., 2002, Lauret et al., 2014). Furthermore, Lane et al. (2014) completed a large systematic review for the Cochrane group which included 30 controlled trials and involved over 1800 patients. They compared supervised exercise programmes with standard care and concluded that supervised exercise programmes are of significant benefit compared with placebo or usual care in improving walking time and distance in people with leg pain from IC. It is clear even with all the evidence supporting supervised exercise, that there does not seem to be a clear dose-response relationship between exercise volume or intensity, and symptom relief (Norgren et al., 2007, Parmenter et al., 2011). Meta-analysis of outcome data from trials investigating supervised exercise in patients with IC found that, after completion of the supervised exercise programme, patients improved their pain-free walking by an average of 120%, and maximum walking distance by an average of 180% (Stewart et al., 2008).

Exercise is proposed to improve symptoms of IC by increasing the rate of angiogenesis (formation of new blood vessels). This elevation in angiogenesis leads to the formation of a collateral blood supply, bypassing the area of arterial stenosis or occlusion, and consequently improving the blood supply to the limb. An example of collateral formation is shown within Figure 1-6 (Lane et al., 2014, Stewart et al., 2008). However, other studies have highlighted potential other underlying mechanisms, through which exercise may mediate an improvement in patient symptoms. These include improved nitric oxide dependent vasodilation, improved muscle mitochondrial metabolism, increased exercise pain tolerance, a reduction in systematic inflammatory activation and adaptations within the walking gait (Hamburg and Balady, 2011, Norgren et al., 2007, Stewart et al., 2008, Zwierska et al., 2005). The true nature of whether improvements are due to angiogenesis have been questioned in many previous studies, all of which reported improvement in patients' walking distance but did not find significant

improvements in blood flow or pressure (Larsen and Lassen, 1966, Slørdahl et al., 2005, Kakkos et al., 2005, Hiatt et al., 1990, Gardner et al., 2005, Collins et al., 2005, Gardner et al., 2001, Mika et al., 2005, Zwierska et al., 2005). The mechanisms of improvements were further questioned by recent studies which reported that isolated upper limb training led to increased walking performance in patients with intermittent claudication. These improvements were believed to be due to enhanced cardiac function (Walker et al., 2000, Bronas et al., 2011). Consequently, the true underlying mechanisms by which exercise generates improvement in function remains unclear, and is more than likely multifactorial rather than due to a single element (Parmenter et al., 2011).

Figure 1-6 Occlusion with the Superficial femoral artery and the formation of collateral vessels around the diseased area



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The use of unsupervised exercise regimes has been investigated and can be useful. Unsupervised exercise involves simple advice to patients to increase level of exercise aiming to walk "through the pain" for 30-60 minutes three times a week. However, supervised exercise has been shown to provide

significantly greater benefits in improvement of symptoms compared to unsupervised exercise (Fokkenrood et al., 2013, Stewart et al., 2008) and, as such, supervised exercise is recommended as first-line management for IC (NICE, 2012).

Despite a wealth of evidence dating back over the last 30 years supporting the use of supervised exercise programmes, plus national guidance stating that they should be used as first-line intervention, the provision of supervision exercise programmes remains poor (Stewart et al., 2008). Access remains highly variable across the UK. In 2009 it was reported that only 24% of vascular departments had access to supervised exercise for their patients (Shalhoub et al., 2009). Even after the recommendation from NICE in 2012 stating that first-line management of IC should be supervised, exercise access remains limited: there are currently only 41% of vascular units that have access to supervised exercise programmes (Harwood et al., 2016). Furthermore, it has been highlighted that the provision of supervised exercise is mostly within hub arterial centres (normally larger teaching hospital/trauma centres) and not locally within vascular spoke hospitals, making convenient access for patients difficult (Harwood et al., 2016).

Even if patients can access supervised exercise, uptake is variable. A significant number of patients decline to participate, claiming difficulties in transportation, distance to travel, impact on working life and general unwillingness to participate (Stewart et al., 2008). It has been reported that overall compliance to supervised exercise is often poor, and only a small proportion of patients have the motivation and commitment to complete the 12-week programme (Muller-Buhl et al., 2012). High dropout rates from supervised exercise programmes are a problem, with 12-week treatment completion rates being reported at 47% (Kruidenier et al., 2009), 66% (Treat-Jacobson et al., 2009) and 70% (Nicolai et al., 2010).

In addition, certain patients with IC are not capable of completing the exercise protocol because of concomitant disease or comorbidities, such as ischaemic heart disease (IHD), pulmonary/cardiac disease, severity of claudication pain, diabetic foot complications or arthritis (Suzuki and Iso, 2015). Trial data reports up to 22% of patients were unable to take part in exercises programmes due to comorbidities (Kruidenier et al., 2009).

There are, however, other important benefits of exercise that are not only related to improvement in walking distance. Exercise therapy has been found to have other physiological impacts, including reduction in heart rate during exercise, and enhanced peak exercise oxygen consumption (Hiatt et al., 1990, Hiatt et al., 1994, Walker et al., 2000, Stewart et al., 2008). These effects are thought to be a

result of improved cardiac function and improved cardiac efficiency during exercise. This, in turn, could aid overall risk reduction of secondary disease formation.

1.10.2 Medication Treatment

There are only four medications in the UK licensed for the treatment of intermittent claudication: Pentoxifylline, Cilostazol, Inositol Nicotinate and Naftidrofuryl. However, only one of these (Naftidrofuryl) is approved by NICE in the treatment of claudication (NICE, 2012).

Pentoxifylline inhibits erythrocyte phosphodiesterase, resulting in improved erythrocyte flexibility and a reduction in blood viscosity (Zhang et al., 2004). The value of Pentoxifylline for the treatment of IC has been questioned because of its variable efficacy in clinical practice (Standness et al., 2002). Furthermore, a systematic review of the available evidence revealed insufficient high-quality data to support the benefits of Pentoxifylline for intermittent claudication (Salhiyyah et al., 2015). Because of the lack of evidence, Pentoxifylline is not recommended by NICE in the treatment of IC (NICE, 2011, NICE, 2012).

Cilostazol is a relatively new drug for the treatment of IC and was introduced in the United Kingdom in 2002. It acts through the inhibition of phosphodiesterase type III, inhibiting platelet aggregation and promoting vasodilation (Sallustio et al., 2010). Cilostazol is contraindicated in patients with cardiac failure, renal impartment or hepatic impairment, so its use is limited, as these diseases are commonplace because of the nature of atherosclerosis diseases. Initially, Cilostazol was recommended for the treatment of IC due to the improvements in pain-free and maximum walking distance (Bedenis et al., 2014). However, a meta-analysis by Stevens et al. (2012) compared medication treatment options for IC and showed that the increase from baseline walking distance was only 25% compared with 60% with the use of Naftidrofuryl. Additionally, Cilostazol had a higher rate of reported side effects, leading to a change in NICE guidance. This additional data resulted in Cilostazol no longer being recommended for the treatment of IC (NICE, 2012).

Inositol nicotinate is a compound made from niacin (vitamin B3) and inositol (vitamin B8) and as such is classed as a ‘natural medicine’. Once broken down in the body it results in a steady increase in the level of free nicotrinic acid in the blood and plasma, increasing endothelium-dependent vasodilation. Inositol Nicotinate is not recommended by NICE (2012) for the treatment of IC as there is limited effectiveness evidence (Meng et al., 2012). Additionally, it is the most expensive of the available treatment at £56.14 per month, and provides benefits below the threshold of quality-adjusted life years (QALY) cost-effectiveness analysis (NICE, 2011, Squires et al., 2012).

The final licensed medication for the treatment of IC is Naftidrofuryl Oxalate, which is a vasoactive drug that has been marketed since 1968. The drug induces vasodilatation by two mechanisms: firstly by increasing the levels of adenosine triphosphate production; and secondly by selectively blocking vascular and platelet 5-hydroxytryptamine 2 (5-HT2) receptors (McNamara et al., 1998). In a systematic review of the evidence, Stevens et al. (2012) found that Naftidrofuryl had the greatest effect, compared to other medication, on maximum walking distance, with an average improvement of 60% (range of 20% to 114%). The meta-analysis directly compared the effects of Cilostazol, Naftidrofuryl and Pentoxifylline simultaneously and concluded that on the basis of published evidence, Naftidrofuryl is the most effective drug for the treatment of IC (Stevens et al., 2012). Additionally, Naftidrofuryl was shown to be associated with the lowest cost (£4.90 per month), and resulting in the largest increase in QALY (Squires et al., 2012). The combination of the most effective agent and lowest cost led to NICE (2012) recommending Naftidrofuryl oxalate as an option for the treatment of intermittent claudication, but stating that it should only be used for patients for whom vasodilator therapy is considered appropriate after taking into account other treatment options.

The difficulty with medication to improve symptoms of intermittent claudication is that all the medications rely on vasodilatation as their mode of action; therefore, side effects of headaches, nausea and diarrhoea are common. The medication needs to be taken regularly to have effect, not just on the days when experiencing claudication pain, and in some patients the side effects can be so severe that the patient cannot tolerate the medication. Furthermore, as previously described, the most effective medication is Naftidrofuryl but this only improves maximum walking distance by, on average, 60% (Stevens et al., 2012). For many patients, the degree of impairment in walking distance is of a level that even a 60% increase would not result in meaningful improvement in their functional status or quality of life. For these reasons, medication (Naftidrofuryl) is only recommended for the management of IC if supervised exercise has not led to satisfactory improvements and the patient prefers not to be referred for consideration of endovascular intervention (NICE, 2012).

1.10.3 Endovascular treatment options

Endovascular treatment incorporates percutaneous transluminal (balloon) angioplasty (PTA), which may or may not include the use of bare metal stents, drug-eluting balloons or drug-eluting stents. PTA is a technique which involves the dilation and recanalisation of a stenosed or occluded artery. If successful, this leads to an increase in the internal diameter (caliber) of the arterial lumen and results in increased arterial flow and an immediate relief to symptoms. The success of the angioplasty depends on the site of the lesion, the length of the lesion and the severity of disease. However,

angioplasty is not without risks. Risks include the formation of haematoma at point of arterial entry (puncture site), thrombosis (clotting), rupture of artery and embolisation (movement of clot). If the embolisation is severe or irreversible there is a risk of limb loss (amputation). Furthermore, restenosis can be an issue, with recurrence of disease being present in 55% of patients one year following intervention (Schmieder et al., 2008). Angioplasty can provide instant clinical benefits, but the associated risk of the procedure and the low patency rates at one year leads to angioplasty not being the preferred treatment option for many patients. National guidance states that angioplasty should only be recommended for patients when risk modification has been achieved, and supervised exercise has not led to a satisfactory improvement in symptoms (NICE, 2012).

1.11 Cycloidal vibration therapy

Cycloidal vibration therapy (CVT) is a form of oscillatory non-invasive vibration energy which has a small amplitude and low frequency waveform. In the 1940s, a Canadian coal miner noticed how his colleagues would lean against a vibrating coal grading machine to relieve their aching backs. In 1949 he patented a therapeutic cycloid vibration device that recreated the vibration movement on a smaller scale (Trent Medicines Information Centre, 2014). Vibration is known to increase the bodies production of nitric oxide, (Maloney-Hinds et al., 2009). Vascular-produced nitric oxide (NO) is an important vasodilator which regulates vascular smooth muscle tone and maintains healthy blood flow. The transmission of CVT into the tissues generates a range of mechanical forces and stresses on the vascular endothelial cells which has been shown to induce the release of NO, resulting in a direct vasodilatory response (Ichioka et al., 2011) and an increased blood flow (Maloney-Hinds et al., 2009, Button et al., 2007).

Vibropulse (Vibrant Medical) is a portable machine which delivers CVT. Vibropulse is promoted as a therapy for cellulitis, venous leg ulcers and lower limb oedema (Johnson et al., 2007, Cherry and Ryan, 2005, Wilson et al., 2002). The device is a rectangular soft pillow style pad, approximately the size of the lower leg, which is connected to a transformer powered via mains electricity (Figure 1-7).

Figure 1-7 Vibropulse machine

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1.12 Rationale for study

Potentially, the stimulation of the mechanisms of nitric oxide production, leading to local vasodilation at the point of, and in the surrounding area of, arterial narrowing or occlusion could improve blood flow; therefore, increasing arterial perfusion and thus improving patients' symptoms of IC. There have been limited case studies (Jurkovic cited in Ellin, 2016, Askari cited in Niagara Healthcare, 2011) demonstrating these improvements, and the majority of these case studies have been performed on patients with critical limb ischaemia. There is currently no evidence to state whether CVT will aid improvements in patients' symptoms of IC. If CVT is effective in improving patient symptoms, this would support the use of CVT as an alternative treatment for patients with IC, especially those who are not able to access or undertake a supervised exercise programme and/or those not wishing to be exposed to the risks/side effects that medication or endovascular intervention brings.

1.13 Summary

This chapter has introduced the concepts of peripheral arterial disease and intermittent claudication, discussed the epidemiology of the disease, the risk factors for development of PAD, and explored how PAD is detected and classified. The impact of PAD/IC on patients' quality of life and overall mortality

rates have also been highlighted. Current treatment options, including the recommendation that the first-line treatment should be supervised exercise programmes, the difficulties in accessing these programmes and their limitations have been presented. The background and possible mechanisms of CVT have been introduced and the potential of CVT improving blood flow has been discussed. The question of whether CVT would be beneficial for patients with PAD has been proposed. If CVT improves patient symptoms, this would support the use of CVT as an alternative treatment for patients with IC, especially those who are not able to undertake a supervised exercise programme and/or those not wishing to be exposed to the risks or side effects that angioplasty or medication brings.

The current literature underpinning the mechanism and impact of CVT will be explored and critically analysed in the next chapter.

2 LITERATURE REVIEW

This chapter details the search strategy used to identify current literature underpinning the mechanism of cycloidal vibration therapy and the role of vibration therapy in the treatment of peripheral arterial disease. This will lead to the justification of this investigation into the use of cycloidal vibration therapy for the symptomatic treatment of intermittent claudication, due to peripheral arterial disease.

2.1 Search strategy

The following search strategy was undertaken to generate a comprehensive list of both published and unpublished evidence. Every attempt was made to ensure that the process of identifying studies was as complete and unbiased as possible, so as to heighten the validity of the literature review findings. The search strategy was designed to include all papers relating to vibration therapy for the treatment of peripheral arterial disease.

The following electronic databases were searched: Allied and Complementary Medicine Database [AMED] (1985 - Jan 2017); Centre of Reviews and Dissemination Database; Cumulative Index Nursing and Allied Heath Literature [CINAHL] (1982 - Jan 2017); Evidence based medicine reviews, including the American College of Physicians Journal Club, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects, Health Technology Assessments and National Health Service Economic Evaluation; Embase (1980 – Jan 2017); National Research Register; and Ovid Medline (1950 – Jan 2017). All databases were searched from their date of creation through to January 2017; the results were not restricted to recent years to ensure that all published studies, no matter how old, were included. Articles written in languages other than English were included in the search and, in these cases, the English abstracts were used in the assessment. The search strategy resulted in the inclusion of a range of study types, including randomised controlled trials, qualitative data and mixed methodology papers.

The most recent publications of specific vascular journals were searched separately by hand to identify recent publications that potentially had not yet been included in the electronic databases or cited in other publications. These key journals included: Journal of Vascular Surgery; Journal of Vascular Medicine; Journal of Vascular Research; Angiology; Perspectives in Vascular Surgery and Endovascular Therapy; The British Journal of Diabetes & Vascular Diseases; Journal of Vascular Nursing; European Journal of Vascular and Endovascular Surgery.

Furthermore, reference lists from primary and review articles retrieved from database searches were hand searched to ensure no relevant articles were missed. In addition to searching for published data, hand searching was performed of all abstracts included in 'The Vascular Society of Great Britain and Ireland Annual Meeting' (2000 to the present date), attempting to identify any abstracts that have been presented but never been published.

A comprehensive search term list was constructed and applied to the electronic databases (see below). The research question was broken down into its key components: Population (patients with claudication) and Intervention (vibration therapy). For each component of the literature review a group of search terms were compiled. The words used within each group were in line with the search strategy suggested by the Cochrane Peripheral Vascular Disease Group (2009).

For each electronic database, the search strategy was re-entered and mapped to its specific subject heading (indicated with mp. in search terms) with was undertaken to ensure that the search was as comprehensive as possible. Truncations were also used on terms such as "claudication" (indicated with $ in search terms, for example "claud$) to ensure that all word terms were included, such as claudicating, claudication and claudicant. The results were then combined with the word 'or' to ensure that all possibilities were included in final numbers.

The below search strategy was formulated and applied in Ovid Medline and was adapted for other electronic databases accordingly:

Search Terms

1. Claudica$.mp.
2. Peripheral vascular disease.mp.
3. Peripheral arterial disease.mp.
4. Arterial occlusive diseases.mp.
5. Atherosclerosis.mp
6. 1 or 2 or 3 or 4 or 5.
7. Vibration therapy.mp.
8. Cycloidal vibration
9. Vibropulse

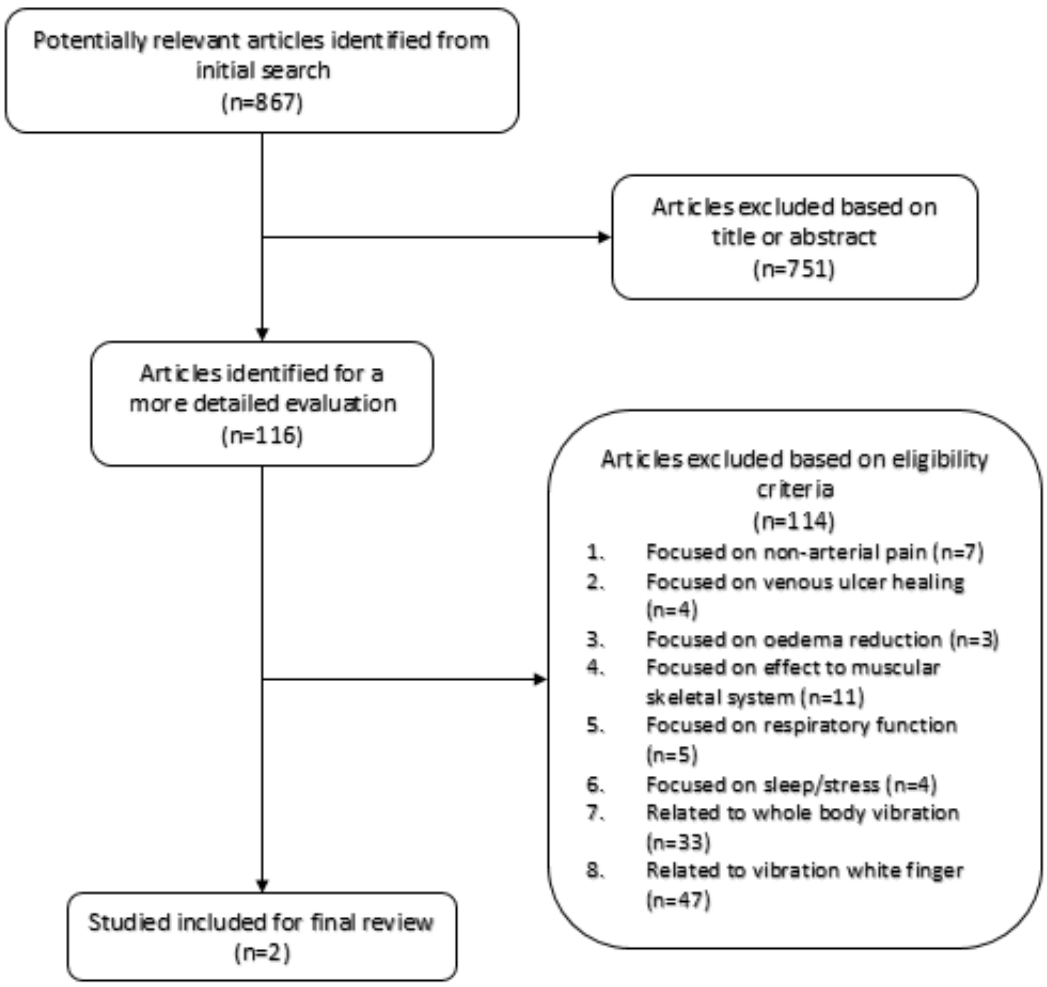
10. 7 or 8 or 9.

11. 6 and 10

The search strategy was designed to be highly sensitive, in order to include all relevant articles relating to vibration therapy for PAD. However, this did reduce the precision of the search, resulting in a large number of retrieved studies that were not related to vibration therapy for the treatment of PAD, the title and abstract was reviewed for each of these and if they did not relate to either arterial disease or vibration they were excluded. 116 articles were identified for more detailed examination of the whole of the paper. At this stage a further 114 articles were discounted as these papers were focused on: vibration white finger; whole body vibration; lower limb oedema reduction; non-arterial pain; venous ulceration; respiratory function; muscular skeletal system; and stress/sleep. The process of limiting the search results is outlined in Figure 2-1.

The inclusiveness of the search strategy was tested by 'snowballing' (Vedula et al., 2011); the reference lists of retrieved articles were checked for any relevant papers that had not been identified through the search strategy. Additionally, retrieved articles were checked for any citations in more recent work, to establish whether there were any recent publications which might not have been identified by searching the electronic databases. All relevant journals within this area were deemed to have been covered by the search strategy used.

Figure 2-1 Flow diagram of literature selection process



2.2 Search results

The extensive literature search resulted in only two papers being identified in relation to CVT being used to treat PAD. No feasibility, pilot or randomised controlled trials considering the use of CVT in PAD were identified. Both of the papers identified were case studies and neither of them was printed within peer reviewed journals, the only publication of these was within a company document promoting the using of cycloid vibration therapy for a number of medical conditions (Niagara Healthcare, 2011), and within a patent application for Vibropulse machine (Ellin, 2016).

The first identified paper focused on the use of CVT in patients with limb ischaemia and tissue loss (Askari cited in Niagara Healthcare, 2011). There is little information about the methodology of the

case study. The title of the work was 'Improvement in blood flow in ischaemic limbs by the use of cycloidal vibration therapy'. The only information provided about this work was a summary statement of findings, which stated that the improvement in rest pain and walking ability was striking. The company (Niagara Healthcare) were contacted in an attempt to gain more information about this piece of work; however, they failed to reply to emails sent.

The second paper identified presented a series of five observational case studies using CVT to aid symptomatic improvement in patients experiencing IC who were attending a vascular clinic in Slovakia (Jurkovic cited in Ellin, 2016). The patients had CVT applied twice a day for 30 minutes. On commencing use of CVT the average pain-free walking distance for the five patients was 126 metres. After four weeks of use, the average pain-free walking distance was 344 metres (range 220 metres to 500 metres); an increase of 273%. At week 5, one patient stopped the use of the CVT as they were satisfied with the results, as their walking distance before pain had improved from 50 metres to 500 metres; an increase of 1000%. By week 12, the average walking distance before pain for the remaining four patients was 500 metres (range 200 metres to 900 metres): an increase of 397%. Therapy and follow-up ended at week 12.

There was limited information regarding the methodology of the case studies, affecting the validity of the findings. There was no information on how walking distance was measured, no statistical analysis of any outcomes was performed, and the information was presented in simple narrative case studies. It was noted that the patient who had a substantial increase of 1000% had stopped smoking during the treatment with CVT; therefore, stopping smoking may have contributed to this substantial improvement. Additionally, these case studies have not currently been published in a peer reviewed journal. Instead, the results of the case studies were found within a patent application by Vibrant Medical to the United States of America patency office (Jurkovic cited in Ellin, 2016). However, the results of these five observational case studies outlined the concept of using CVT in patients with IC and reported clinical improvements in symptoms.

The literature search confirmed that there is little published evidence on the use of CVT in the treatment of PAD. Therefore, this investigation will result in an important contribution to this unknown area.

2.3 History of vibration

Vibration has long been associated negatively with vibration white finger, where vibration results in a decrease in blood supply, causing fingers to feel cold and numb (Ryan, 1981). Taylor and Pelmear

(1975) submitted a number of papers to the Department of Health in England, drawing attention to the hazards of working with any hand-held machinery which produces vibration. This eventually led to legislation to protect workers from the effect of vibration (Control of vibration at work regulations, 2005). Vibration white finger occurs as a result of contact to intense high amplitude vibration. Symptoms increase depending on duration of exposure or continued exposure. This type of vigorous vibration causes damage to the arterial endothelial lining, which affects the blood vessels' ability to regulate via dilation or contraction (Gosta, 1994). This lack of ability to self-regulate results in the symptoms of vibration white finger.

In contrast to the negative reports of vibration white finger, other forms of vibration have been shown to have beneficial effects. There is a wealth of evidence investigating the benefits of whole body vibration and this research has shown that the process improves muscle strength (Roelants et al., 2004), muscle power (Bosco et al., 1998, Delecluse et al., 2003), balance and flexibility (Cheung et al., 2007), and improves muscle tone. Whole body vibration has also been shown to increase local cellular metabolic rate (Friesenbichler et al., 2013). Whole body vibration is delivered by standing on a vibration plate. This delivers low amplitude, low frequency mechanical stimulation. This low frequency and low amplitude vibration is of similar velocity to CVT. However, whole body vibration is delivered throughout the body rather than directed to specific areas, as is the case with CVT. Whole body vibration is known to increase nitric oxide blood concentrations (Sackner et al., 2005), which results in elevated blood flow in the lower limbs of healthy individuals (Lohman et al., 2007). The literature search revealed a wealth of research relating to whole body vibration, but no evidence of prior investigation into whole body vibration in association with PAD or IC. The majority of the search results were related to exercise performance.

2.4 Cycloidal vibration therapy

Cycloidal vibration is characterised by a unique three-dimensional vibration, generated by an electromechanical oscillator. This produces a low amplitude, low frequency vibration motion in three different orthogonal directions. Each of the three different directions of motion is created at different points in the cycle by a complex electronic speed controller. Controlling of the motion within the delivering instrument gives rise to a circular movement, and the term cycloidal vibration. This cycle of change in motion direction spreads the vibration both transversely and radially, allowing for deep penetration in the tissue, which is very different from other forms of mechanical massage (Niagara Healthcare, 2011, Lievens et al., 1981). The company which manufactures CVT machines claim that the cycle of vibration used within CVT results in a comfortable sensation for the user, which they state

is unlike conventional massage units (Niagara Healthcare, 2011). Conventional massage products typically operate in a singular plane, either delivering percussive striking impacts, or orbital oscillations. The standard vibrations produced in conventional massage machines are high amplitude, high acceleration and have a high fundamental frequency which produces aggressive pounding vibrations, which can result in an uncomfortable sensation (Beck, 2006).

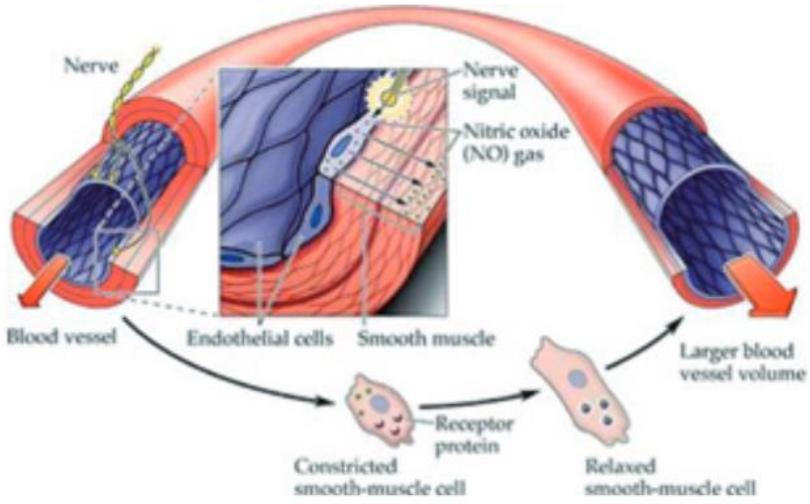
This cycle of vibration used within CVT results in a comfortable sensation for the user, unlike conventional massage units.

2.5 Possible mechanisms for the effect of CVT in improving blood supply

There are two main concepts linked to how CVT can improve blood supply. The first is based on CVT stimulating an increase in nitric oxide production within endothelial cells, leading to vasodilation, which results in increased blood flow (Lievens, 2011). This process would increase blood flow at the time of vibration, but potentially would not result in sustained improvements once the vibration stops. The second concept is related to the increased level of nitric oxide production, causing the formation of new blood supply (angiogenesis) (Cooke and Losordo, 2002). This increased rate of angiogenesis could potentially lead to increased rate of collateralisation, where collateral vessels have the ability to form a natural bypass around the area of arterial disease which could lead to sustained improvements in limb perfusion.

Angiogenesis is the formation of new capillary blood vessels. It is normally initiated by physical stimulus, from the fluid shear stress of the blood on the endothelial cells of the vessel wall. This leads to the endothelial cells producing nitric oxide and vascular growth factors. The nitric oxide acts as a molecular signaler and diffuses through the inner layer of the artery into the smooth muscle layer (Troidl and Schaper, 2012). There it causes relaxation of the smooth muscle tissues leading to vasodilation Figure 2-2. Promotion of angiogenesis has emerged as a potential strategy to improve patients' symptoms of IC (Shimamura et al., 2013).

Figure 2-2 Nitric oxide effect on smooth muscle layer



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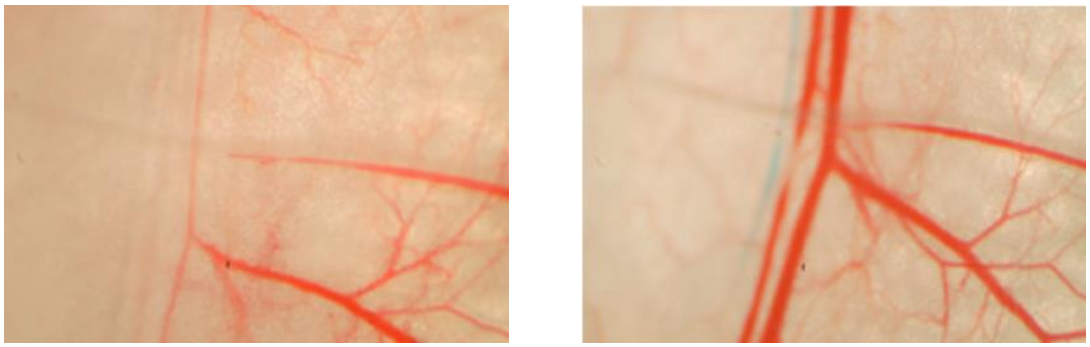
CVT produces a mechanical stimulus which results in similar effects as described above (Lievens et al., 1981, Lievens, 2011). The deep penetration into the tissues from the CVT results in the activation of a number of chemical reactions within vascular cells which line the blood vessels, including the release of nitric oxide (Maloney-Hinds et al., 2009). Nitric oxide has been shown to cause relaxation of the smooth muscle cells of blood vessels, leading to dilation and improved blood flow (Lievens, 2011).

Vascular endothelial growth factors are a critical signal protein in angiogenesis, and it has been shown in healthy adults that non-invasive vibration stimulation also increases vascular endothelial growth factor levels compared to physical exercise alone (Suhr et al., 2007). This increases nitric oxide expression, vasodilation and the resulting flow shear stress at the point of arterial disease, which could increase angiogenesis activity and aid collaterals formation (Ichioka et al., 2011).

Lievens (2011) conducted animal model studies on 20 mice, exploring the influence of cycloidal vibration on skin blood flow. Lievens reported an increase in the diameter of blood vessels leading to improvements in blood flow after 10 minutes of CVT (Figure 2-3). The mechanism for improved blood supply was hypothesised to be due to the mechanical forces from the vibration acting on the endothelium cells and resulting increase in nitric oxide concentration within the blood causing vasodilation (Lievens, 2011). Additionally, Ryan et al. (2000) found similar changes in blood flow in human studies conducted on 16 healthy individuals where the focus of the investigation was

concentrated on changes in lymphatic draining. However, they also found that after 10 minutes of vibration, significant improvements in blood supply were evident compared to baseline measurements (P=0.0033), assessed using laser Doppler assessment. They attributed the changes seen to CVT.

Figure 2-3 Changes in blood flow following 10 mins of CVT (Lievens, 2011).



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Button et al. (2007) investigated multidirectional vibration applied locally and directly to the calf and measured change in mean venous blood flow. The research was of a randomised cross-over design and found that after 30 minutes of localised vibration there was a 14% increase in mean blood flow compared to placebo (P<0.01), with peak blood flow occurring after 22 minutes of vibration.

The increase in the concentration of nitric oxide and vascular endothelial growth factors has been shown to increase the rate of angiogenesis. Lievens and Van den Brande (2004) performed a series of animal models occluding the arterial flow with a ligature, and applying CVT for 20 minutes a day for three months. In the control group, there was no evidence of vessel growth, and in the experimental group there was evidence of 85% growth of functioning collaterals.

2.6 Safety of CVT

There was no evidence within the literature search of any issues related to safety or any reported adverse effects in connection with the use of CVT. However, Vibrant Medical, who supply the Vibropulse machine, state that the product should not be used in any of the following: severe above the knee vascular disease, untreated severe active wound infection, severe tissue necrosis, osteomyelitis, Charcot's foot, active deep vein thrombosis, active pulmonary embolism, active cancer, pregnancy, uncontrolled epilepsy, active bleeding or difficult haemostasis in the wound bed. Additionally, Vibrant Medical advise caution when using CVT in combination with infected wounds receiving antibiotic therapy and patients with unstable lower limb structures e.g. bone fragments,

recent knee joint replacements. There is no evidence to support that CVT should not be used in these situations, and the reasons for these restrictions appear to be linked to the licence for use and potential lack of safety evidence within this group of patients.

2.7 Specific gaps in the literature

The literature has described and supports the links between CVT and increase in nitric oxide production (Lievens, 2011, Maloney-Hinds et al., 2009). Evidence shows that elevated nitric oxide levels lead to vasodilation improving localised blood flow (Lievens, 2011, Ryan et al., 2000, Button et al., 2007). Additionally there is some, albeit limited, evidence confirming that improved blood flow leads to greater rate of angiogenesis (Ichioka et al., 2011, Lievens and Van den Brande, 2004).

There appears to be a physiological concept that CVT could improve rate of collateralisation in patients with PAD. However, there is limited knowledge and evidence surrounding the use of CVT in this group of patients. The literature search revealed only two previous publications (Jurkovic cited in Ellin, 2016, Askari cited in Niagara Healthcare, 2011). Neither of these was published within peer reviewed journals and both are of limited impact due to these articles being based on narrative case studies which lack any methodological detail. Additionally, there was no evidence of statistical analysis. The limited numbers of patients on which the research was based makes generalisation to the wider population difficult. Furthermore, there is uncertainty as to the optimum length of treatment to facilitate improvements; Jurkovic cited in Ellin (2016) reported improvement in walking distance after only four weeks of therapy. However, studies in an animal model suggest that improvements due to the establishment of collaterals may occur over the timescale of months rather than weeks (Lievens and Van den Brande, 2004). Because of the potential benefits of using CVT to provide benefits for patients with PAD, specifically IC, and the lack of clinical evidence in support of this potential benefit, further research is warranted to establish evidence in support of this potential mode of therapy.

2.8 Primary aims and objectives

The primary aim of this research was to determine the feasibility of using cycloidal vibration therapy to improve patients' symptoms of intermittent claudication, assessing the association of cycloidal vibration therapy with patients' pain free walking time and maximum walking time, establishing the length of treatment required and evaluating whether any improvements in patients' symptoms are sustainable. Additionally, the statistical variability of the primary outcomes will be established, information which is vital to estimate sample sizes for any future studies.

2.9 Summary

As previously discussed, there are limitations encountered with current treatment options of IC. Therefore, stimulation of collateral vessel formation, through means other than exercise, would be advantageous. The literature review has established that there is evidence supporting the benefits of CVT in increasing nitric oxide production, improving blood flow and increasing angiogenesis. The research hypothesis has been proposed that if CVT increases angiogenesis in patients with PAD, then this may improve the symptoms of IC. There are substantial knowledge gaps within the literature in this area, warranting further investigation into the feasibility of using CVT to improve patients' symptoms of IC.

3 METHODS

This chapter will outline the study method, describing and evaluating the selected methods and measurements applied in this research.

The purpose of this research was to determine the feasibility of using cycloidal vibration therapy (CVT) to improve patients' symptoms of intermittent claudication. The design of the study allowed the following questions to be answered:

The aims of the study were:

- To explore the association of cycloidal vibration therapy with participants' pain free walking time and maximum walking time
- To establish optimal duration of CVT intervention
- To establish whether any changes in walking distance are sustained after cycloidal vibration therapy is stopped
- To establish statistical variability of the primary outcomes

The objectives leading to the accomplishment of these aims were:

- To observe changes in participants' PFWT (pain free walking time) and MWT (maximum walking time)
- To establish whether any change in participants' lower limb perfusion occurs
- To determine the duration of treatment required to achieve maximum benefits
- To determine the most effective physical location of vibration therapy
- To determine measurement/equipment suitability to assess a degree of change in clinical and functional status
- To determine the final study protocol

The methods which were used will be described as follows: 1) research methodology, 2) research design/focus, 3) approval process, 4) recruitment, 5) research intervention, 6) data collection, and 7) data analysis.

3.1 Research methodology

Quantitative research methods examine the relationships between various factors and are appropriate to be used when testing hypotheses, (Heddle, 2002). This study was based on the approach of quantitative methods to examine the relationship of CVT in patients with intermittent claudication. Quantitative research is depicted as the traditional scientific approach to research underpinned by the philosophical paradigm for human inquiry known as positivism (Walker, 2005). Positivism is based on the idea that science is the only way to the truth, and research driven by the positivist tradition ensures that research is undertaken with a systematic and methodological approach. Positivism, rooted in the 19th century, was explored by philosophers including Comte, Mill, Newton and Locke (Polit and Tatano Beck, 2004, Maltby, 2010).

The positivism paradigm believes that assumptions can be studied, and requires proof or verification to be believed. Adherents to the positivist approach assume that nature is basically ordered and regular and that an objective reality exists independent of human observations (Green and Thorogood, 2013). As such, positivists fundamentally believe an objective reality ensures that they keep their personal beliefs and biases in check during the research to avoid contamination of the phenomena under investigation. Quantitative research gathers empirical evidence as the basis to form knowledge; as such it means that the findings are grounded in reality rather than from researchers' personal beliefs. A distinguishing feature of quantitative research is the collection of numerical data, which can be subjected to statistical analysis in order to support or refute the research claims.

Quantitative research begins with a problem statement which forms a hypothesis and then employs strategies of enquires, such as experimental. Experimental research provides a framework for establishing a relationship between cause and effect, where the researcher uses deductive reasoning to prove or falsify the hypothesis. This includes manipulating an independent variable and observing the effect whilst attempting to hold extraneous variables constant. Experimental research is regarded as the optimum quantitative methodology for obtaining reliable information about a treatment effect, (Polit and Tatano Beck, 2004). However, the power and strength of the research is directly related to methodology adopted. Adopting methodologies where variance is controlled, such as: random allocation, random sampling, the use of a comparison group and blinding, helps to improve the strength of the research. This scientific rigour, especially the use of a control group, enables the researcher to say with confidence that the outcome produced can only be attributed to the intervention, maximising internal validity and increasing generalisability of research.

Nevertheless, there are many methodological limitations which may jeopardise the internal and external validity of experimental research (Polit and Tatano Beck, 2004). These include the methods adopted for sampling and randomisation of participants, recruitment process and measurements undertaken. In relation to CVT and the results of the literature search, there were too many unknowns (such as site of vibration, duration of treatment and size of effect) to ascertain a clear research protocol. Therefore, initial exploratory research was required to establish the feasibility of the concept that CVT improves patients' symptoms of IC. Exploratory research is the preliminary stage in the research process and aims to explore the research topic (Green and Thorogood, 2013). Using exploratory research ensures that new insights and familiarity are assured to increase knowledge of a phenomenon thereby enabling a robust research design for further study. Exploratory research involves less rigorous approaches to describe phenomena and this does limit the extent to which firm conclusions can be drawn (Green and Thorogood, 2013). However, it is a necessary step in gaining greater understanding which will then allow further research to be performed.

3.2 Feasibility study

The literature search carried out as part of this project revealed a lack of robust evidence in relation to the effects of CVT in relation to symptomatic management of IC, as previously discussed in Chapter 2. Feasibility studies are pieces of research assessing the practicality of a proposed plan or method (Eldridge et al., 2016). They aim to answer the vital question 'can this study be done?' Feasibility studies also provide the opportunity to evaluate proposed research methods and research integrity. In addition, they are required to estimate important parameters, such as:

- Variability of the primary outcome measure (information which is needed to estimate sample size for a RCT)
- Willingness of participants to be included and rate of attrition
- Willingness of clinicians to recruit participants
- Number of eligible participants required
- Optimum characteristics for the proposed outcome measure (e.g. frequency of application, length of application, location of application etc.)
- Follow-up rates, response to questionnaire, compliance rates
- Time needed to complete recruitment, collect data and perform analysis.

Because these factors remained to be resolved, a feasibility study was deemed necessary in advance of a full-scale trial. Feasibility studies are an important step in evaluating study design and to aid the contextualisation and conceptualisation of research proposals. It is important to remember also that feasibility studies are very different to pilot studies. A feasibility study is undertaken to answer questions such as 'is this research possible?' and 'what is the best way to design a study?' Pilot studies, on the other hand, mimic the design of the research protocol but are on a smaller scale. The information gained from a feasibility study is vital in order to ensure a robust research protocol can be developed.

3.3 Sample size calculation

Sample size calculations are used to determine the minimum number of participants needed in a clinical trial in order to be able to answer, with confidence, the research question under investigation (Whitehead et al., 2016). However, the objective of a feasibility study is to ascertain whether a study can be performed and highlight important parameters that are needed to design further studies. Therefore, since the purpose of the feasibility study is not to give formal assessment of efficacy, standard sample size formula which are used for calculating research sample size are not applicable for pilot or feasibility trials (Whitehead et al., 2016), as such no sample size calculations were undertaken for this research.

Furthermore, sample size calculations are based on formal power calculations or on other considerations such as the precision of the estimate of interest (Julious, 2005). However, at times, especially in feasibility or pilot studies, there is no prior information upon which to base sample size calculations. Therefore, specific sample size recommendations for feasibility studies are not made, as they depend on the nature of the decision based on the estimate; samples as small as 10–15 per group can sometimes be sufficient (Hertzog, 2008). Furthermore, Julious (2005) recommends that a sample size as little as 12 is appropriate for pilot/feasibility studies. Justification of this number is based on feasibility; gains in the precision about the mean and variance, and regulatory considerations. In terms of this research, sample size calculation was impossible for this feasibility study, due to the issues previously discussed; instead, the sample size was determined by a pragmatic approach, where all patients suitable and willing to take part were recruited into the study and the study closed after a specific time period, that being 14 months.

3.4 Feasibility research design

The study design was a prospective, single-patient group feasibility study to investigate the impact of cycloidal vibration therapy in patients with intermittent claudication and measuring participants' pain-free walking time (PFWT), maximum walking time (MWT), leg perfusion pressure and quality of life.

3.5 Research hypothesis

As this was a feasibility study, research hypotheses are not appropriate (Tickle-Degnen, 2013). For any subsequent research based on the findings of this feasibility study, the suggested null and research hypotheses maybe summarised as follows:

Null Hypothesis – The application of CVT to the lower limbs will have no effect on participants' symptoms of intermittent claudication.

Research Hypothesis – The application of CVT to the lower limbs will change participants' symptoms of intermittent claudication leading to alteration in PFWT and MWT and subsequent quality of life.

For this research the primary and secondary outcomes were:

Primary outcomes:

- Change in pain free walking time between baseline to 12 weeks after CVT therapy
- Change in maximum walking time between baseline to 12 weeks after CVT therapy

Secondary outcomes:

- Changes in ABPI measurements after 12 weeks CVT therapy
- Changes in systolic leg pressure after 12 weeks CVT therapy
- Changes in ABPI measurements at end of study 36 weeks
- Changes in systolic leg pressure at end of study 36 weeks
- Change in pain free walking time between baseline and week 36
- Change in maximum walking time between baseline and week 36
- Change in SF-36 quality of life questionnaire
- Treatment Compliance - as shown by number of treatment applications indicated by the device

- Participants' ease of use of product, assessed by simple questionnaire

Further details and rational for chosen measurements is provided in section 3.16.

3.6 Ethical and research approvals

Ethical approval was sought and obtained from the School of Human and Health Sciences, School Research Ethics Panel (SREP), within the University of Huddersfield. Following this, National Health Service research and ethical approval was granted (REC reference: 14/YH/0080). Subsequently, local site specific approval was granted within Mid Yorkshire NHS Trust and recruitment commenced in July 2014, Ref: IRAS: 146195, (Appendix 1).

3.7 Funding

Vibrant Medical provided funding to complete the research, covering the cost of the Vibropulse machines, required insurance (Appendix 2) and reimbursement for any NHS costs, including patients' expenses for attending follow-up visits. With this being a company-funded research project, the study was accepted and included in the National Institute for Health Research (NIHR) Clinical research Network Portfolio (Appendix 3).

3.8 Research governance and good clinical practice

The investigator (LA) received NIHR training in Good Clinical Practice and all research involving NHS patients was carried out in accordance with guidelines to ensure participant safety and confidentiality.

3.9 Participating centre

One district general hospital participated in the study: Pinderfields Hospital within Mid Yorkshire NHS Trust. Mid Yorkshire NHS Trust is a satellite hospital within the Leeds Vascular Institute network. The research was conducted at a single NHS site due to limitation of resources and lack of research funding. Convenience sampling was undertaken. Convenience sampling is one of the main types of non-probability sampling methods (method whereby samples are selected based on a subjective judgment of the researcher). Subjects were selected because they fulfilled the eligibility criteria and they were the easiest to recruit. There was no consideration whether the subjects would be representative of the entire population. However, the demographic of the population within this clinic is similar to the national population with IC. This has been confirmed by examination of the National Vascular Registry, and there is no reason to believe that patients drawn from this hospital would react differently to the treatment in any systematic way compared to patients from elsewhere.

3.10 Eligibility

Potentially eligible participants were identified by the researcher through vascular clinics within the participating hospital as per the inclusion/exclusion criteria (see Sections 3.11 and 3.12). The researcher staffed these clinics routinely. Consecutive patients meeting the inclusion/exclusion criteria were given a patient information sheet (Appendix 4), and the purpose of the study and the fact that participation was completely voluntary was clearly explained. Patients who agreed to take part were then asked to sign a consent form (Appendix 5). All patients were informed that they could withdraw from the study at any time. Once the patient had consented to be included in the study, a letter was sent to the individual's General Practitioner informing them of the patient's participation in the study (Appendix 6). For the purpose of this study and the writing up of the thesis, participants are referred to as 'patients' prior to recruitment, and, once recruited, are then referred to as 'participants'.

3.11 Inclusion criteria

Inclusion criteria provide a set of predefined characteristics which are used to identify subjects suitable for inclusion into studies. This ensures that prospective subjects have certain characteristics/attributes which are essential for their participation. These criteria often included statements relating to the topic or area of research and can include details to remove the influence of specific confounding variables, for example, in this case the identification of patients with inflow (iliac) disease, where surgery is considered the most appropriate intervention. Inclusion criteria, along with exclusion criteria, ensure that a standard of eligibility is used when selecting members of the target population and optimise external and internal validity of a study (Salkind, 2010). The full inclusion criteria list for this research was:

- Male or female patients aged over 18, experiencing lower limb claudication caused by PAD, as diagnosed and defined as per NICE PAD guidelines (NICE, 2012)
- Patients categorised with PAD according to Fontaine's classification Stage II a or Stage II b
- Patients with palpable femoral pulses and triphasic Doppler signals within femoral artery
- Patients with the ability to provide informed written consent

3.12 Exclusion criteria

Clinical research requires researchers to adhere to strict protocols in order to yield valid information. Exclusion criteria help researchers to eliminate candidates who would not be appropriate to be

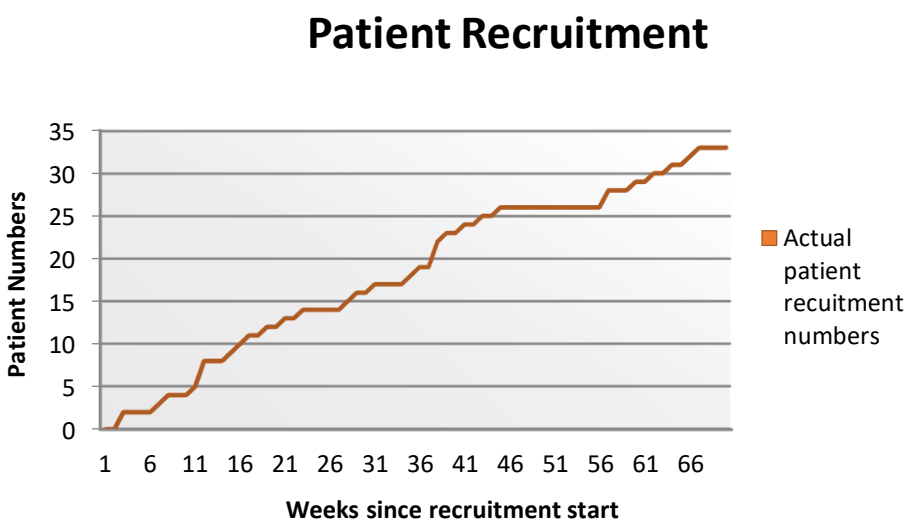
included in certain studies. This helps to protect patient safety, provides assurance of ethical principles and improves scientific rigour. The exclusion criteria for this study included patients who were unable to provide full valid consent, where the CVT was contraindicated and those with severe arterial disease/critical limb ischaemia (indicated by tissue loss or arterial rest pain) who require consideration for surgical intervention. The full list of exclusion criteria was:

- Any patient under 18 years old
- Patients prescribed medication for the treatment of intermittent claudication e.g. Cilostazol or Naftidrofuryl
- Any pregnant female patient
- Patients with a diagnosed deep vein thrombosis within the last six months
- Patients with unstable lower limb bone and joint structures
- Patients with active cancer
- Patients with pulmonary embolism
- Patients with any lower limb soft tissue or bone infection not being treated with antibiotics
- Patients who were terminally ill
- Patients whose mental capacity prevented them from giving informed consent
- Patients with tissue loss on either lower limb
- Patients experiencing arterial rest pain
- Patients with absent femoral pulses
- Patients with monophasic signals in femoral pulses
- Patients unable to read or write English
- Patients unable to apply device whether independently or who required help from another house hold member
- Patients who did not consent to participate in the study

3.13 Recruitment

The 14-month recruitment period commenced in July 2014 and continued until September 2015, with follow-up data collection completed in April 2016. Thirty-four participants were enrolled to the study. Figure 3-1 shows rate of recruitment over study period. On average two participants per month were recruited into the study.

Figure 3-1 Participant Recruitment Graph



3.14 Research intervention

CVT was applied to the lower limb at the point of suspected arterial narrowing or occlusion. As part of the initial clinical assessment, performed within the hospital's claudication clinic, the level of suspected disease was established through either clinical examination or arterial imaging. Thus, the location of CVT application was determined prior to inclusion in the study. Participants were supplied with a Vibropulse machine to be used in their own homes and they were asked to apply CVT for 30 minutes twice a day for a period of 12 weeks. After recording baseline study information including PFWT and MWT, a single dose of 30 minutes CVT was applied within the clinic setting. This allowed for demonstration of the product and to provide the participants with verbal instructions on how to use the machine. This verbal instruction was backed up by providing all participants with a written guide (Appendix 7). Following this initial dose, repeat measurement of PFWT and MWT was

undertaken. A direct telephone contact number was given to the participants and they were encouraged to contact the researcher if they had any concerns or questions relating to the CVT or the research in general. There was no change to prescribed medication and patients were advised to continue with prescribed medication throughout the study period.

The Vibropulse machine is designed to vibrate for 30 minutes in one application. The machine time counter starts at 30 minutes and counts down to zero, and automatically cuts off. The timer is fixed and cannot be changed. Thirty minutes' vibration is recommended by the company Vibrant Medical Ltd. for the treatment of other conditions such as venous ulceration, oedema management and the treatment of cellulitis (Vibrant Medical, 2016). The vibration exposure increases nitric oxide level in the skin after only five minutes of vibration (Maloney-Hinds et al., 2009), with increases in blood flow being evident after 15 minutes of vibration (Ichioka et al., 2011). Previous studies exploring the use of Vibropulse in the treatment of cellulitis, oedema or ulceration have reported positive results using the product twice or three times a day (Wilson et al., 2002, Cherry and Ryan, 2005, Johnson et al., 2007). For this study, it was decided to use the product twice a day. This frequency of use was chosen to try to limit the impact of using CVT on participants' lifestyle. The alternative was to use the machine three times a day, but this frequency of use could interrupt with patients' day-to-day plans and would be difficult for anyone still working and, therefore, could ultimately limit the audience for whom CVT could be useful. The previous literature search (Chapter 2) showed a lack of evidence in relation to the impact of CVT on patients' quality of life; therefore, assessments of patients' quality of life were undertaken during this study to explore this unknown area.

Prior to the commencement of the study, the optimal duration of vibration therapy to provide symptomatic improvements in intermittent claudication was unknown. Therefore, it was decided to apply the therapy for 12 weeks as this is the same length of time patients are asked to attend supervised exercise programmes (NICE, 2012). Throughout the 12 weeks of therapy, outcomes were monitored at week 4 and week 8 to attempt to establish optimum length of treatment required.

The device is portable and is supplied in a purpose-made holdall to allow easy transportation of the machine. Participants were followed up during the active therapy stage, at week 4, week 8, and week 12, and followed by additional reviews during the follow-up period at week 16, week 24 and week 36. Follow-up continued to week 36 to assess whether any changes were sustainable once therapy had stopped, and to monitor changes in medication/smoking status or occurrence of any major clinical events, such as hospital admission, surgical or radiological intervention. All participants were followed up in a hospital outpatient environment.

3.15 Data collection and management

Study-related information was collected in individual Case Report Forms (CRFs) (Appendix 8). All data at entry was checked for accuracy, and cross-referenced with source data documented within participants' medical records. The CRF were stored within locked cabinet in secure room, in accordance to research regulations. The information contained within the CRF was then transferred to a database once the study had closed. The database was password protected and saved on a secure network. All CRFs were completed by the lead investigator, and internal monitoring was undertaken by Mid Yorkshire NHS Research Department.

3.16 Study measures

The choice of study measures was guided by previous research and the recommendations within the Transatlantic Society Consensus guidelines on the management of PAD (Norgren et al., 2007) and the National Institute Clinical Excellence guidelines relating to PAD, (NICE, 2012).

3.16.1 Demographic and disease information

Information regarding participants' general demographic was recorded. This included: age, gender, smoking status, medications, blood pressure, location of pain (thigh or calf), previous arterial investigations (MRA, CT scan or Duplex scanning), location of arterial disease (inflow, superficial femoral artery or crural vessel disease), past history of PAD and previous PAD interventions (surgical, endovascular or conservative).

3.16.2 Pain free walking time (PFWT)/maximum walking time (MWT)

Individuals with IC have limited exercise and walking capacity, and as such, the severity of disease and changes in condition are measured via walking ability (NICE, 2012). There have been a number of walking tests previously documented within the research. The most common of these are treadmill testing, graded treadmill tests and the 6-minute walk test. Other methods reported include shuttle walks, Global Positioning System (GPS) recording and unguided self-estimation (Le Faucheur et al., 2008).

Standardised methods of treadmill exercise testing have been developed. In PAD, there are two basic treadmill exercise protocols: the Constant Load Test and the Graded Test (Hiatt et al., 2014). The constant load test is performed on a treadmill with the speed set at a single rate (3.2 km/h) and a gradient of 10-12%. This approach has been questioned as not providing useful information in terms of functionally, as the set incline of 10–12% is quite extreme and often exceeds a patient's individual

ability. This makes the test impossible for them to complete (Hiatt et al., 2014). In contrast, the graded treadmill test begins at a speed of 3.2 km/h at a 0% incline. The grade is then increased by 2% every two minutes. With the progressive incline, each patient is taken to an individually defined exercise limit. The advantage of treadmill testing is that the assessment is standardised and reproducible (Brass et al., 2007). However, treadmill testing has been criticised as this does not represent walking in daily life (Perakyla et al., 1998, Watson et al., 1997, Parr and Derman, 2006), due to the requirement of the participant to maintain a constant rhythmic gait, to keep up with the constant pace set by the treadmill. The subject is also required to have dynamic balance to ensure safety on the treadmill (McDermott et al., 2014). Patients with PAD have impairments of balance and cognitive function (Gohil et al., 2013, Rafnsson et al., 2009), and these functions are required for a good balance and rhythmic gait on the treadmill (McDermott et al., 2014). The impairment of balance and cognitive function experienced by patients with PAD makes treadmill testing difficult, if not impossible, for some patients to complete.

The 6-minute walking test is an alternative to treadmill testing. The test is carried out according to a standardised protocol, including a script for instructions and feedback. Two cones are placed 30 metres apart, creating a 60-metre circuit. Participants are asked to cover the greatest distance possible in a 6-minute period. They are instructed to stop and rest if needed, but to resume walking after a self-determined rest break. This 6-minute walk test has been reported to be a more meaningful real-life test compared to treadmill testing, as it provides a more clinically relevant assessment (McDermott et al., 2014). However, there have been questions relating to the reliability due to patients' performance potentially being affected by a number of factors including environmental and assessor bias, and repeatability (Hiatt et al., 2014). Additionally there has been criticism that the forced walking pace attained during the test does not reproduce a real-life walking pace (Le Faucheur et al., 2008), and so may not provide the meaningful testing as claimed.

In general, these tests record two sets of distance measurement. The first measurement is the distance walked to the onset of claudication pain; the claudication pain. The second measurement is the distance covered to when the pain becomes so severe that the patient is forced to stop. This measure is known as the absolute claudication distance or the maximum walking distance.

It was felt that the important measurement in this study was real-life change in the patients' ability to walk. Therefore, a simple walking test was chosen for this study. Participants were asked to walk along a circuit formed through the corridors of Pinderfields Hospital (Wakefield, UK). They were instructed to walk at their normal speed, to report when they started to feel pain, and to continue

walking until the pain become unbearable and forced them to rest. The researcher walked with them around the circuit. The circuit was entirely indoors and flat with no inclines or stairs. The route varied at each assessment, so the participants did not have any prior knowledge of the distance they last walked. Time was recorded on a stop-watch, which was started on the participant's first step. PFWT was recorded as the time at which the participant first expressed pain and MWT was recorded as the time the participant was forced to stop walking. It should be noted that there are limitations with this method of testing due to issues related to reliability, comparability with other studies and repeatability. These limitations will be explored further in the discussion (Chapter 5). Both the PFWT and MWT test were stopped at eight minutes. If a participant was able to walk further than this, the maximum time in seconds (480 seconds) was recorded as censored data. Censoring applies specifically to time-to-event outcomes and is required when the value of a measurement or observation is only partially known and the event under observation is assumed to have occurred at some time past the point of stopping of the assessment.

Additionally, at each walking test the patient was asked whether it was the treated leg that forced them to stop walking. If this was not the case, the time at which they stopped walking/felt pain was recorded and this was also classed as censored data, meaning that the participant could at least walk for the time recorded. However, the participant may have been able to walk further, as the treated leg did not cause the stopping of the walking.

3.16.3 ABPI/systolic leg pressure

Ankle Brachial Pressure Index (ABPI) is the ratio of blood pressure at the ankle to the blood pressure of the brachial artery in the arm. ABPI is recommended to be measured in all patients with suspected PAD (Norgren et al., 2007, NICE, 2012). ABPI is a non-invasive test that measures the severity of arterial disease, and has been shown to have a 94% sensitivity and 99% specificity compared to angiogram proven disease (Bonham and Kelechi, 2008, Yao et al., 1969). The ABPI is performed using a Doppler probe, a sphygmomanometer and appropriate size cuff with the patient in the supine position after resting for 10 to 20 minutes. The systolic blood pressure is measured in both the brachial arteries (with the highest being used to calculated the ABPI) and in both legs, with pressure being recorded within the dorsalis pedis and posterior tibial. The systolic pressure is recorded as the pressure at which the first audible sound from the Doppler probe is heard. The ABPI is calculated separately for each leg, by dividing the highest of the two ankle systolic blood pressures by the higher of the two brachial blood pressures.

As ABPI is a ratio derived from two separate measures (brachial and ankle measurements), it potentially fails to isolate the specific change to the ankle/leg pressure. This is mainly due to its reliance on the brachial pressure, which makes subtle differences more difficult to identify. Therefore, systolic leg pressure measurement was also recorded and analysed in isolation to the ABPI in order to increase sensitivity of the measurement.

An ABPI ratio of 0.9 to 1.30 is normal for adults, whereas ratios less than 0.9 are indicative of PAD (NICE, 2012, Crawford et al., 2016). However, false negatives commonly occur in people who have calcification of the arterial wall, which creates non-compressible vessels and an artificially high reading (Crawford et al., 2016). This has lead previous research to question using ABPI <0.9 as a cut-off point as this may lead to underdiagnoses (McDermott et al., 2005, Allison et al., 2008). Therefore, ABPI alone was not specified in the inclusion/exclusion criteria for this study.

Participants' systolic brachial and leg pressures were recorded and used to calculate ABPI ratios. Where participants' leg pressures were incompressible, a pressure of 280 mmHg was recorded, as this is the maximum on the sphygmomanometer gauge. Measurements were recorded at baseline, week 4, week 8, week 12, week 16, week 24 and week 36.

3.16.4 Quality of life assessment

Intermittent Claudication (IC), without treatment, remains stable with symptoms neither improving nor deteriorating (Aquino et al., 2001). However, it can have a considerable impact on quality of life (NICE, 2012). The medical outcomes short-form 36 questionnaire (SF-36) was used in this study to assess participants' quality of life (Rand Health, 2016). SF-36 is the recommended generic health quality of life instrument to measure quality of life in PAD (Norgren et al., 2007). Furthermore, SF-36 has been widely used, and its validity has been proven at assessing the burden of disease and treatment benefits specifically in PAD (Amer et al., 2013, Regensteiner et al., 2008, McDermott et al., 2009).

The SF-36 is a generic rather than disease-specific quality of life questionnaire, which consists of 36 questions in eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health (Appendix 9). The questionnaire allows for yielding of scale scores for each of the eight domains, and two additional summary measurements of physical and mental health: the physical component summary and the mental component. Each domain has a scoring scale from 0 (worst quality of life) to 100 (best quality of life). Scores expressing the overall physical and mental health are calculated from the individual scales and are presented as the physical component scale

(PCS) and the mental component scale (MCS). Three domains (physical functioning, role limitations due to physical health, and bodily pain) contribute most to the scoring of the PCS; whereas social functioning, role limitations due to emotional problems and mental health contribute most to the scoring of the MCS measurement. These domains (general health perceptions, vitality and social functioning) correlate with both components. Higher scores of PCS and MCS indicate better health status.

A licence was purchased prior to the commencement of the study to use the SF-36 tool and scoring software. Information was collected using the questionnaire at baseline, week 12, week 16, week 24 and week 36. Participants completed the SF-36 without any help/instructions from the researcher. Results from the SF-36 questionnaire were entered into the Quality Metric Health Outcomes scoring software, which provided specific values of each parameter. The data was then pre-processed and exported to SPSS statistical software (Version 22.0) to facilitate statistical analysis. The results for each measure of SF-36 are presented as mean and standard deviation (SD). Norm-based scoring of SF-36 was used, as this allows for meaningful comparisons across scales. In norm-based scores, each scale is scored to have the same average (50) and the same standard deviation (10). Therefore, any group mean score below this can be interpreted as being below the average range for the general population. Standardisation of scale variability allows for much easier interpretation of exactly how far above or below the general population mean score is in standard deviation units.

The change in SF-36 measures with time were examined using statistical analysis. A series of repeated measures analysis of variance (ANOVA), including a Bonferroni-type adjustment to protect from type 1 error was performed. The significance level for a difference in each domain score between all-time points (p-value), and a standardised measure of effect magnitude (partial-η^2 statistic) were also derived.

3.16.5 Participant feedback

Participant feedback was deemed valuable as this can offer a useful, different perspective from the quality of life analysis data. Participants were asked to respond to three Likert-style ranked questions at the end of the 12-week therapy phase. The questions were:

1. How did you find using the product? - Options available were: "*very difficult*", "*difficult*", "*neutral*", "*easy*" or "*very easy*".

2. Have you been satisfied with the results so far? - Options available were: "*Very dissatisfied", "not satisfied", "neutral", "satisfied" and "very satisfied".*

3. When using the machine was it? – Options available were: *"painful", "mild discomfort", "neutral", "comfortable" or "very comfortable".*

3.17 Adverse events

Adverse events relate to any untoward medical occurrence during the study period, whether this is considered to be associated with the research/intervention or not. These events include any expected and unexpected harmful effect and includes physiological, social, economic or psychological harm. All adverse events in patients participating in clinical trials must be reported by the study sponsor and approving ethic committee. Serious adverse events, as classified by Health Research Authority (Health Research Authority, 2017) must be reported within 24 hours. Details of adverse events will be documented in the results chapter.

3.18 Data analysis

As discussed previously this feasibility study was undertaken to assess whether there was an association between the application of CVT to the lower limbs and changes in participants' PFWT and MWT. The following approach was undertaken to analyse the results:

Data was summarised descriptively with appropriate summary statistics presented (e.g. means and Interquartile range (IQR) for numerical variables; frequencies and percentages for categorical variables). Graphical summaries of key demographic variables were also derived where appropriate.

Specific analysis methods utilised for each part of the study are listed below.

3.18.1 Pain free walking time and maximum walking time

Any variation over time within PFWT and MWT is expressed as percentage changes, which allows for comparisons of effect size with other modalities for managing IC. Percentage changes have been reported in a number of other studies evaluating treatments for IC including: Gardner and Poehlman (1995), Salhiyyah et al. (2015), Standness et al. (2002), Parmenter et al. (2011) and Stevens et al. (2012).

Time-to-event (survival) analysis was performed using non-parametric methods on the outcomes of PFWT and MWT, measured over various time points throughout the period of active therapy (0-12 weeks) and the subsequent follow-up period (12-36 weeks). Kaplan-Meier survival graphs were constructed for all analyses. Kaplan-Meier methods are commonly used to analyse time-to-event data. From a determined starting time, they model the occurrence of a given event of interest, to determine

the time-dependent distribution of that event; which for this study was either commencement of pain or stopping of walking. Additionally, log-rank testing was undertaken to compare the distribution of the two-time points to detect any difference between the two groups. This is a non-parametric test to address the null hypothesis that there are no differences in time-to-event between the groups being studied, comparing all time points on the survival curve.

3.18.2 ABPI/systolic leg pressure

Comparisons between ABPI and systolic leg pressures were undertaken using paired samples t-testing. The paired samples t-test calculates the difference between pairs of measurements, each taken at different analysis time points, and determines the significance of these differences.

All data analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 22.

3.18.3 Participant compliance

The current guidelines for the management of PAD (NICE, 2012, SIGN, 2006) recommend initial treatment with supervised exercise programmes for individuals with IC. However, as previously discussed, there are difficulties in accessing such programmes, with strict patient exclusion criteria and problems with compliance: reported dropout rates are as high as 43% (Bendermacher et al., 2007, Cheetham et al., 2004, Kakkos et al., 2005, Patterson et al., 1997). The continuation of exercise participation is vital to maintain functional status and quality of life improvements (Warburton et al., 2006). Owing to the issues previously discussed of availability, acceptance and compliance with current recommended treatments (Kruidenier et al., 2009, Stewart and Lamont, 2007, Muller-Buhl et al., 2012, Nicolai et al., 2010), it was thought to be vital to assess participants' compliance with the CVT. The compliance with the CVT was monitored by means of a device counter within the machine. Perfect compliance was assessed as the device counter showing 168 (twice a day for 12 weeks). A 20% variation was still deemed to be compliant; however, this is an arbitrary figure as there was no previous evidence to support compliance with CVT. This score is based on the scale of 'good medication compliance' being defined as taking 80–120% of the prescribed medication (Jin et al., 2008).

3.19 Research time line

For any future studies, it is important to be able to estimate time frames for undertaking research projects, as this has a direct effect on the funding and allocation of staff. The research process for this study commenced with the enrolment into the PhD programme, commenced in April 2013; during the first year of study the research question and protocol were refined with appropriate ethical and

governance approvals obtained. The recruitment period commenced in July 2014 and continued until September 2015, with follow-up data collection completed in April 2016. The final year of the study was spent analysing the data and completing the thesis writing. Figure 3-2 provides a summary of timelines.

Figure 3-2 Research time lines

Proposed Date	Plan
April 2013	Enrolment
April – June 2013	Background reading – development of research question
July – September 2013	Development of research protocol – refining methodology
October – December 2013	Development of supporting documents and commence IRAS application form. Application completed to use SF-36 tool.
January 2014	Commencement of ethical approval application. Permission granted to use SF-36.
February 2014	Submission for school ethical approval - granted
Feb/March 2014	Submit for regional ethical approval and submitted for local R&D approval
April 2014	Approvals granted
May/June 2014	Site specific application completed and approval granted - contract between sponsor and NHS site signed
July 2014	Recruitment commenced
Sept 2015	Recruitment completed
April 2016	Follow-up data completed and study closed
May 2016	Data entry
June – July 2016	Data analysis using SPSS
August 2016	Completed abstract submission for scientific conference
Sept - Nov 2016	Writing up of project
Nov 2016	Abstract presented at Society Vascular Nurses annual conference and Vascular Society annual scientific meeting

3.20 Summary

This chapter has outlined the research methods used to assess the association of cycloidal vibration therapy in participants with intermittent claudication. Additionally, a timeline has been presented to allow the reader an understanding of the research process. The research methods used in this study provided data in order to assess the aims of the study:

- To explore the association of cycloidal vibration therapy with participants' pain free walking time and maximum walking time
- Establish optimal CVT intervention

- Establish whether any changes in walking distance are sustained after cycloidal vibration therapy is stopped
- To establish statistical variability of the primary outcomes

The results and analysis from the described methods will be discussed in the next chapter.

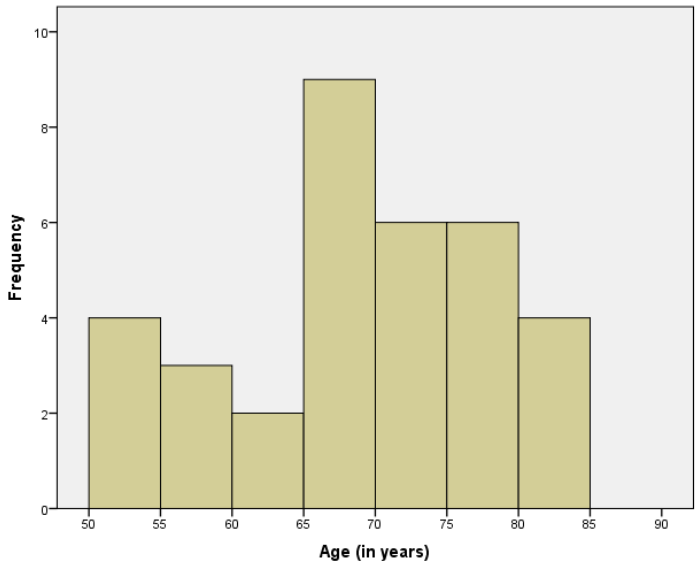
4 RESULTS

As discussed in previous chapters, suitable participants with a history of intermittent claudication were recruited following consent to participate in the research. Study protocols were followed and a total of 34 participants were recruited. The baseline data and results relating to the participants are presented in this chapter.

4.1 General participant baseline characteristics

Thirty (88.2%) of the participants were male; four participants (11.8%) were female. The male: female ratio was 7.5:1. All of the participants were white Caucasian. The age of participants ranged from 51 to 83 years, with mean age of 68 years (median 68.5 years), interquartile range (IQR) 60-75 years which indicates the degree of variability of the data set. The age distribution of participants is summarised graphically in Figure 4-1. The mean age of female participants was 65.5 years (median 62.5 years, IQR 57.8 - 76.3 years). The mean age of male participants was 68.5 years (median 69.5 years, IQR 63.8 - 75.0 years).

Figure 4-1 Participant age range histogram



4.1.1 Past medical history

Past medical history included: nine (26.5%) participants had history of diabetes; 23 (67.6%) had diagnosis of previous hypertension; one (2.9%) had previous cerebral vascular accident (CVA) or transient ischaemic attack (TIA); 12 (35.3%) were known to have ischaemic heart disease

(IHD)/Angina/Myocardial Infarction (MI). Twenty-three (67.6%) were previous smokers, six (17.6%) participants were current smokers and five (14.7%) had never smoked. Of the current smokers, the mean daily average intake was 10 cigarettes with a range of 5–15 cigarettes per day. There was no change to individual smoking habits through the period of follow-up. Participant demographics and co-morbidities are summarised in *Table 4-1*.

Table 4-1 Participants' demographics and co-morbidities

Variable	Frequency (valid %)
Gender	
Male	*30 (88.2%)*
Female	*4 (11.8%)*
Diabetes	
Yes	*9 (26.5%)*
No	*25 (73.5%)*
Hypertension	
Yes	*23 (67.6%)*
No	*11 (32.4%)*
History of CVA/TIA	
Yes	*1 (2.9%)*
No	*33 (97.1%)*
History of IHD/Angina/MI	
Yes	*12 (35.3%)*
No	*22 (64.7%)*
Smoking status	
Current	*6 (17.6%)*
Previous	*23 (67.6%)*
Never	*5 (14.7%)*

4.1.2 Best medical therapy/secondary disease prevention

The median systolic blood pressure on initial assessment was 160 mmHg (mean 164 mmHg), with a range of 114 to 195 mmHg. Despite this being an analysis of a single blood pressure reading per participant, rather than a series of blood pressure readings which is truly required to determine hypertension, 76.5% (26) of participants had a systolic blood pressure more than 140 mmHg. This indicates hypertension, which would require further investigation/management according to current guidelines (NICE, 2016b).

A total of 27 (79.4%) participants were receiving medication for hypertension. Four (11.7%) participants with systolic blood pressure greater than 140 mmHg were not receiving any hypertensive medication. Twenty-two (64.7%) participants were receiving antihypertensive medication, but were

either not well controlled on their medication, or were non-compliant, with systolic blood pressure remaining over 140 mmHg even with prescribed therapies.

Twenty-nine (85.3%) participants were on statin lipid lowering therapy at the time of enrolment. Twenty-nine (85.3%) participants were on antiplatelet or anticoagulant therapy at the time of enrolment, with 25 (86.2%) of these participants receiving aspirin or clopidogrel, and four (13.8%) receiving warfarin. The participants' hypertension and medication status is summarised in *Table 4-2*.

Table 4-2 Participant hypertension and medication status at baseline

Categorical Variable Name	Frequency (valid %)
Number of participant with systolic BP>140 mmHg	*26 (76.5%)*
Number of participant on hypertensive medication	*27 (79.4%)*
Number of participant not on medication	*4 (11.7%)*
Number of participant on medication with systolic BP>140 mmHg	*22 (64.7%)*
Number of participant on statins	*29(85.3%)*
Number of participant on antiplatelet therapy	*29(85.3%)*
Number of participant on warfarin	*4 (11.8%)*
Number of participant on aspirin/clopidogrel	*25 (73.5%)*
Numerical Variable	Median (Range)
Systolic blood pressure	*160 mmHg (114–195 mmHg)*

4.2 Arterial disease baseline information

4.2.1 Location of disease/pain

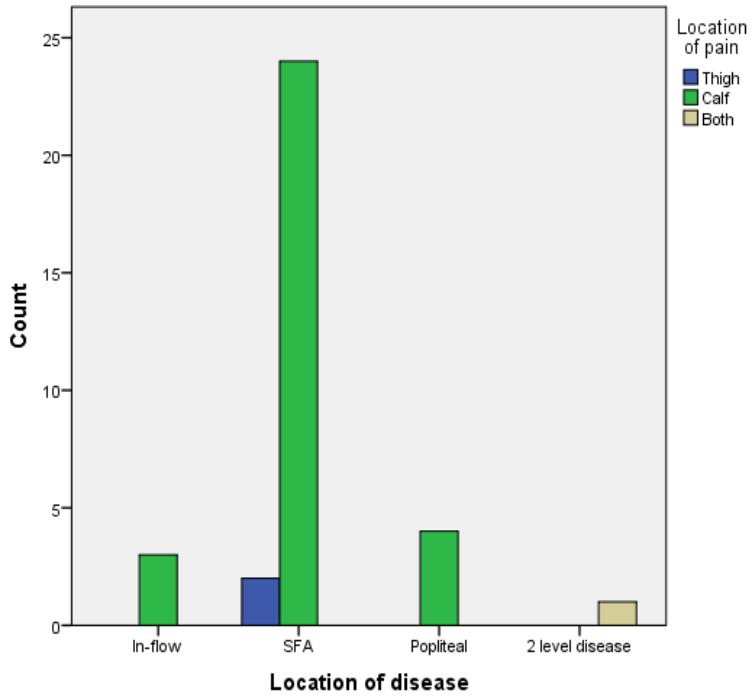
The majority of participants (31 out of 34; 91.2%) experienced claudication of their calf with two (5.9%) participants expressing thigh pain and one (2.9%) experiencing both thigh and calf claudication (Table 4-3). This directly related to the location of disease (Figure 4-2).

Twenty-six (76.5%) participants were suspected to have superficial femoral artery (SFA) disease, with the remainder having popliteal disease (four participants; 11.8%), inflow disease (three participants; 8.8%), and one participant (2.9%) having two level disease (meaning having disease in both the SFA or popliteal and the inflow). Location of disease had been confirmed with imaging for 32 (94.1%) participants, the most common imaging modality used was duplex ultra sound scanning (24: 70.6%), other modalities included MRA (5: 14.7%) and angiogram (3: 8.8%).

Table 4-3 Location of disease/pain

Category/variable Name	Frequency (valid %)
Location of pain	
Thigh	*2 (5.9%)*
Calf	*31(91.2%)*
Both	*1 (2.9%)*
Location of disease	
In flow	*3 (8.8%)*
SFA	*26 (76.5)*
Popliteal	*4 (11.8%)*
2 level disease	*1 (2.9%)*
Disease confirmation	
MRA	*5 (14.7%)*
Duplex	*24 (70.6%)*
Angiogram	*3 (8.8%)*
None	*2 (5.9%)*

Figure 4-2 Clustered bar chart showing location of disease and area of pain



4.2.2 Peripheral arterial disease history

Fifty percent (17) of participants were already known to have PAD, with the remaining 50% (17) being newly diagnosed. Of the 17 known participants, 11 (64.7%) had previous surgical or endovascular intervention. Of these 11 participants, nine had undergone angioplasty and two had common femoral endarterectomy or lower limb bypass surgery (Table 4-4).

Table 4-4 Participants' PAD history

Category/Variable Name	Frequency (Valid %)
Known/previous PAD	
Yes	*17 (50%)*
No	*17 (50%)*
Previous intervention	
PTA	*9 (26.5%)*
Surgery	*2 (5.9%)*
Conservative	*6 (17.6%)*
Not applicable	*17 (50%)*

4.2.3 Baseline claudication information

All participants as per inclusion criteria were claudicants. Seventeen (50%) had bilateral claudication, while the remaining 17 (50%) were symptomatic in one leg only. For participants experiencing bilateral claudication, the limb which the participant deemed the worse, in terms of walking distance, was treated with CVT, this was determined prior to enrolment in the study. It was decided only to treat one leg due to the time commitment required to undertake the CVT therapy. To treat both legs simultaneously would require treatment for two hours per day due to the device only being wide enough for one leg at a time. The median pain-free walking time was 82 seconds (mean 89 seconds), with a range of 35 seconds to 220 seconds (IQR 53 – 118 seconds). The median maximum walking time was 186 seconds (mean 168 seconds) with a range of 70 seconds to 450 seconds (IQR 128 – 224 seconds), (Table 4-5).

Table 4-5 Baseline claudication distance in time

	Baseline pain free walking time (seconds)	Baseline maximum walking time (seconds)
Mean	*89*	*186*
Median	*82*	*168*
Minimum	*35*	*70*
Maximum	*220*	*450*

4.2.4 Baseline Ankle Brachial Pressure Index (ABPI)

ABPI is the ratio of best ankle systolic pressure to systolic pressure in the brachial artery. The median ABPI in the treated limb at initial assessment was 0.63 (mean 0.63), with a range of 0.24 to 1.09, and IQR of 0.51 to 0.73. Two participants had incompressible arteries resulting from calcification of arterial vessel wall, so ABPI could not be calculated for these participants. The ABPI distribution in terms of severity is shown in Table 4-6.

Table 4-6 Baseline ABPI distribution

ABPI Group	Distribution Frequency (Valid %)
< 0.3	*2 (5.9%)*
0.3 – 0.49	*5 (14.7%)*
0.5 – 0.69	*15 (44.1%)*
0.7 – 0.89	*8 (23.5%)*
0.9 – 1.2	*2 (5.9%)*
>1.2	*2 (5.9%)*

4.2.5 Baseline Systolic leg pressure

The highest systolic pressure of the treated limb was recorded at initial assessment. The median systolic pressure was 110 mmHg (mean 110 mmHg), with a range of 40 mmHg to 280 mmHg, and an IQR of 86 mmHg to 120 mmHg.

4.2.6 Missing data

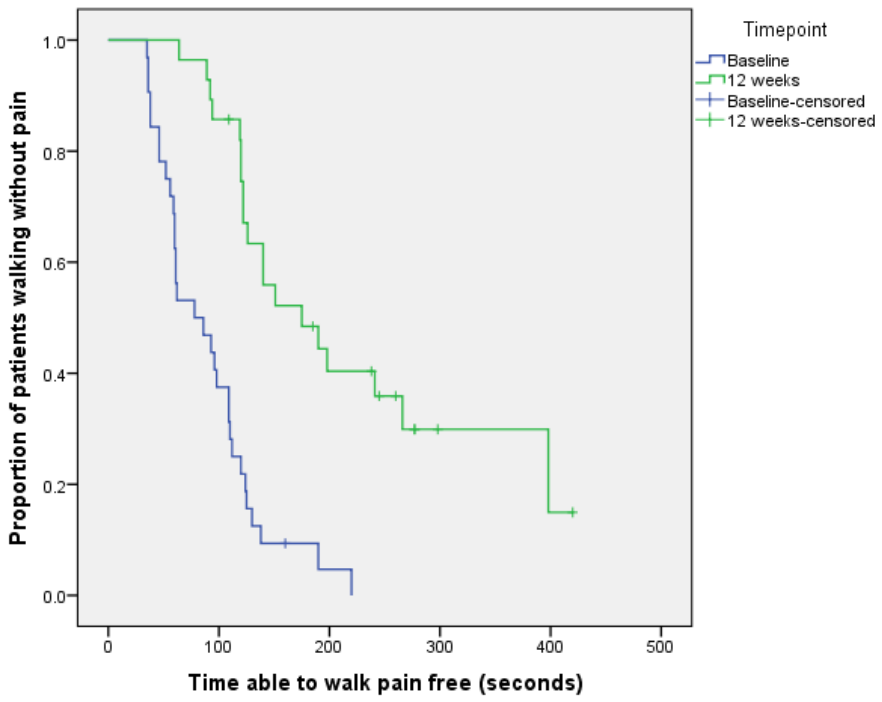
All 34 participants provided valid measurement of baseline systolic leg pressure. However, not all participants were able to complete every walking assessment. This was due to a variety of reasons, including: chest pain on exercise, fear of falling, and muscular skeletal/joint pain. The term ‘valid measurement’ will be used to describe the amount of data analysed within this research.

No participants left the study during the first 12-week activity therapy stage. However, 12 participants were lost during the long-term follow-up phase of the study.

4.3 Pain-free walking time therapy phase

The primary outcome measure of the study was the change in PFWT from baseline to 12 weeks (the end of the treatment phase), after each participant received vibration therapy for 30 minutes twice a day. Thirty participants (88%) provided valid measurement of PFWT at week 12; of these, 29 (97%) had an average improvement of 215% in PFWT from baseline. The range of change in PFWT from baseline to 12 weeks was -8% to 1005%. Kaplan-Meier analysis was conducted to compare the difference in time-to-event (i.e. when pain first felt) from baseline and week 12, (Figure 4-3). Log rank testing revealed a statistically significant difference, at the 5% significance level, between comparison time points at baseline and week 12, ($\chi^2_{(1)}$=25.6; p<0.001).

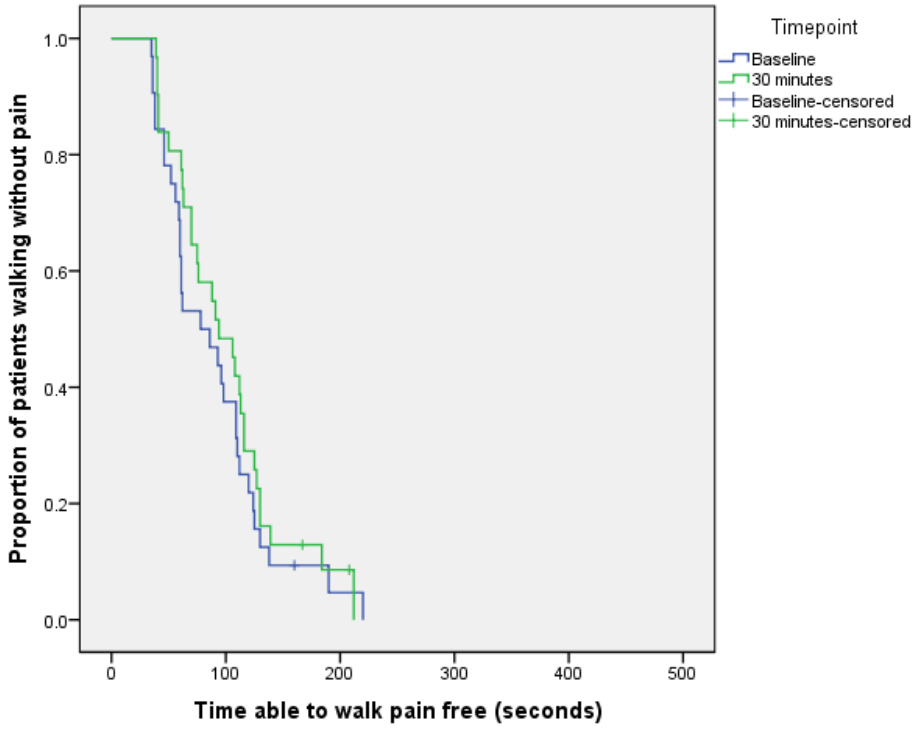
Figure 4-3 Time-to-event analysis of PFWT baseline and PFWT at week 12



As time-to-event analysis of PFWT baseline and PFWT at week 12 showed statistically significance (Figure 4-3), additional time-to-event analysis was undertaken to determine at which point the changes occurred. Carrying out this analysis would help in establishing the optimum length of treatment with CVT. Time-to-event analysis was undertaken in the data from 31 participants

comparing PFWT at baseline and at 30 minutes after first dose of vibration therapy, (Figure 4-4). Log rank testing was performed and indicated that there was no evidence for a statistically significant difference (at the 5% significance level) in PFWT between baseline and 30-minute post-test ($\chi^2_{(1)}$=0.675; *p*=0.411). This demonstrated that there is no evidence for any immediate benefits of CVT.

Figure 4-4 Time-to-event analysis of PFWT baseline and PFWT after a 30-minute single dose



Further time-to-event analysis was performed to compare PFWT at baseline with readings at week 4 (based on thirty valid measurements). The results of this analysis are shown in Figure 4-5. Log rank testing showed statistically significant difference, at the 5% significance level, between comparison time points baseline and week 4, ($\chi^2_{(1)}$=9.88; p=0.002).

Additional time-to-event analysis was undertaken to compare PFWT at baseline with readings at week 8 (based on 30 valid measurements, Figure 4-6). Log rank testing was carried out and this demonstrated a statistically significant difference at the 5% significance level between comparison of baseline and week 8 time points, ($\chi^2_{(1)}$=23.2; p<0.001). A comparison of Figure 4-5 and Figure 4-6 reveals that the effect is more pronounced at week 4 compared with week 8. The level of significance of the comparisons between baseline and 4, 8 and 12 weeks is such that each individual comparison

would still be considered to demonstrate statistically significance allowing for multiple comparison testing, using the Bonferroni procedure.

Figure 4-5 Time-to-event analysis of PFWT baseline and PFWT at week 4

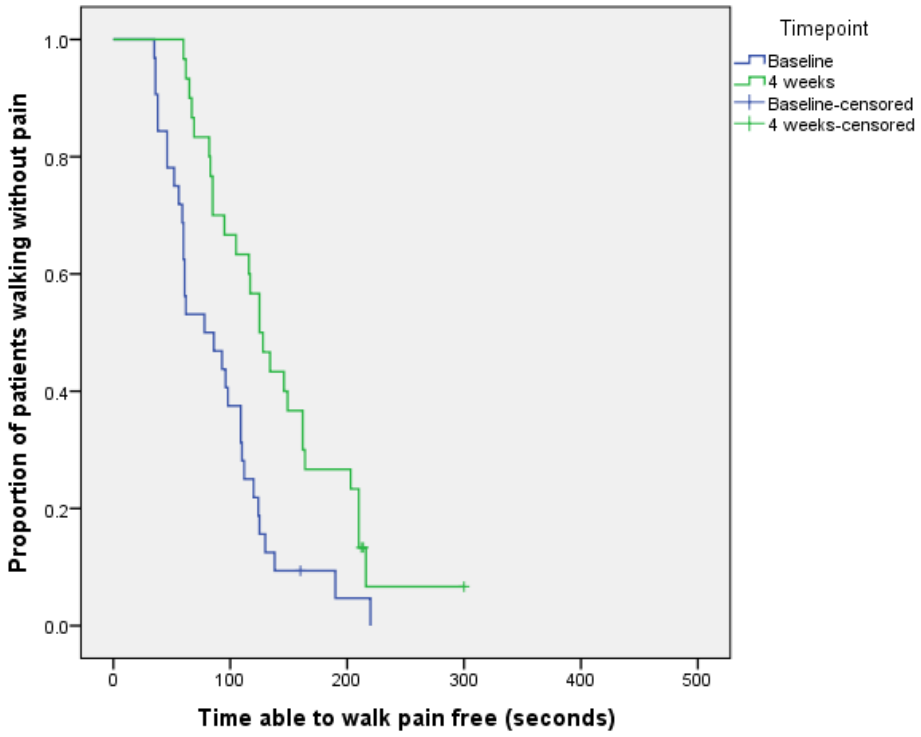
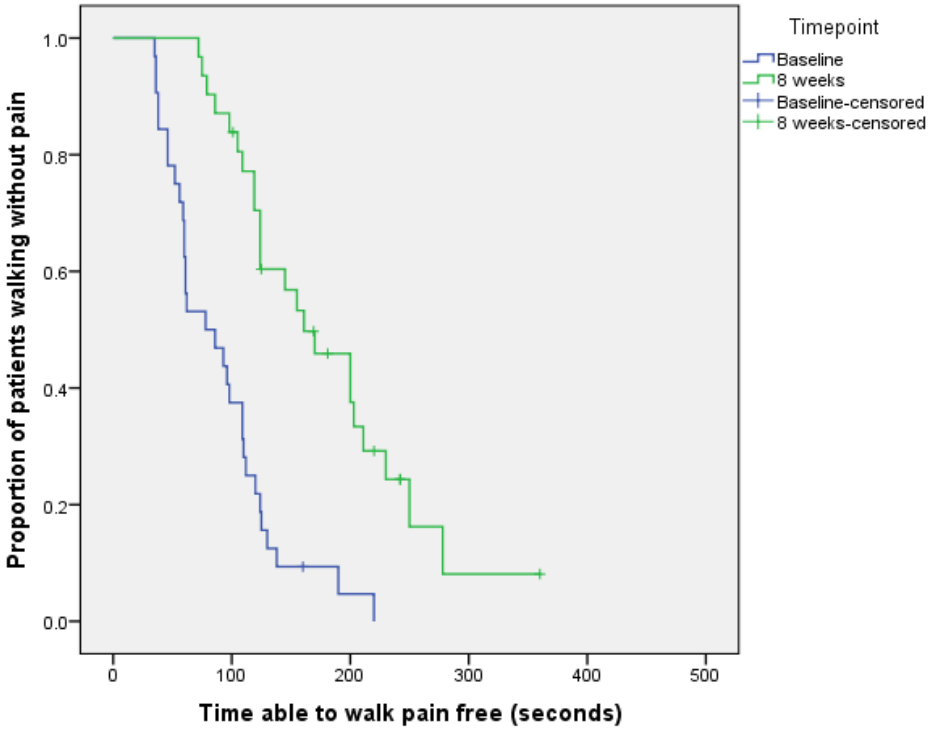
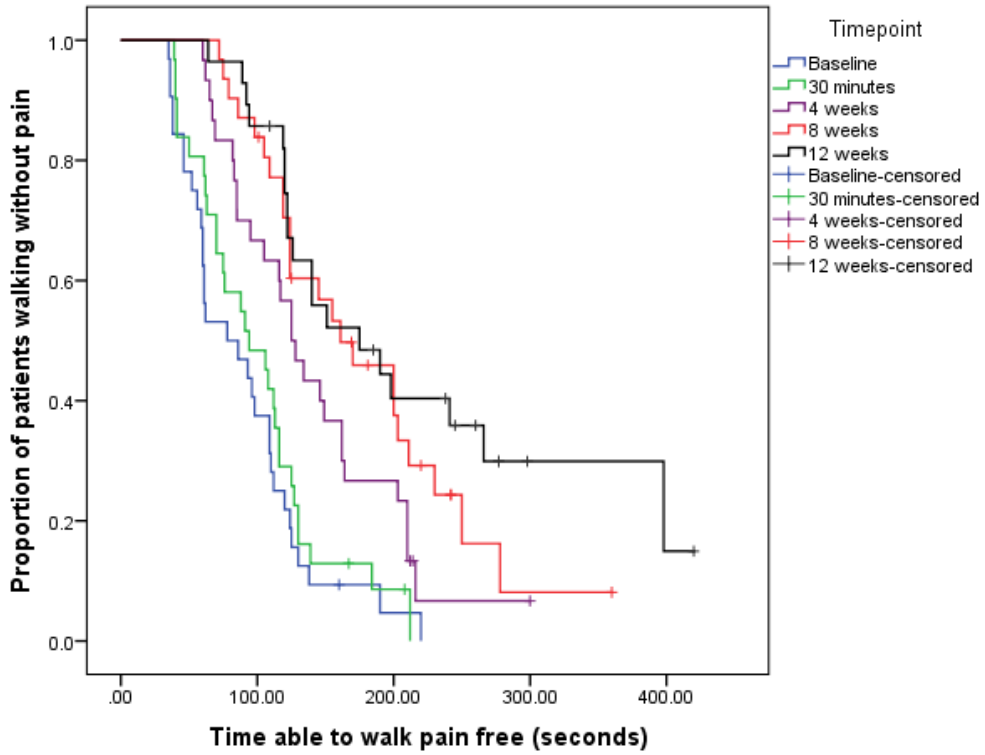


Figure 4-6 Time-to-event analysis of PFWT baseline and PFWT at week 8



An overall summary comparison of PFWT in time over a number of time points: baseline, 30 minutes, 4 weeks, 8 weeks and 12 weeks is illustrated in Figure 4-7.

Figure 4-7 Time-to-event analysis of PFWT at multiple time points



Comparisons of outcome of PFWT at baseline to weeks 4 and week 8 showed that the main difference occurred within the first four weeks of therapy, and that there was some further, but less evident, improvement by continuing the therapy to week 8. To further investigate this finding, additional time-to-event analysis was conducted to establish at what time point the main changes to PFWT was occurring. Comparison of PFWT at week 4 and week 8 (Figure 4-8), showed no evidence for a significant difference, ($\chi^2_{(1)}$=2.64; p=0.104). Similarly, comparison of PFWT in time at week 8 and week 12 again showed no evidence for a significant difference between comparison time points, ($\chi^2_{(1)}$=0.93; p=0.334), (Figure 4-9). Together this analysis demonstrates that the main impact on PFWT occurred in the first four weeks of treatment.

Figure 4-8 Time-to-event analysis of PFWT at week 4 and PFWT at week 8

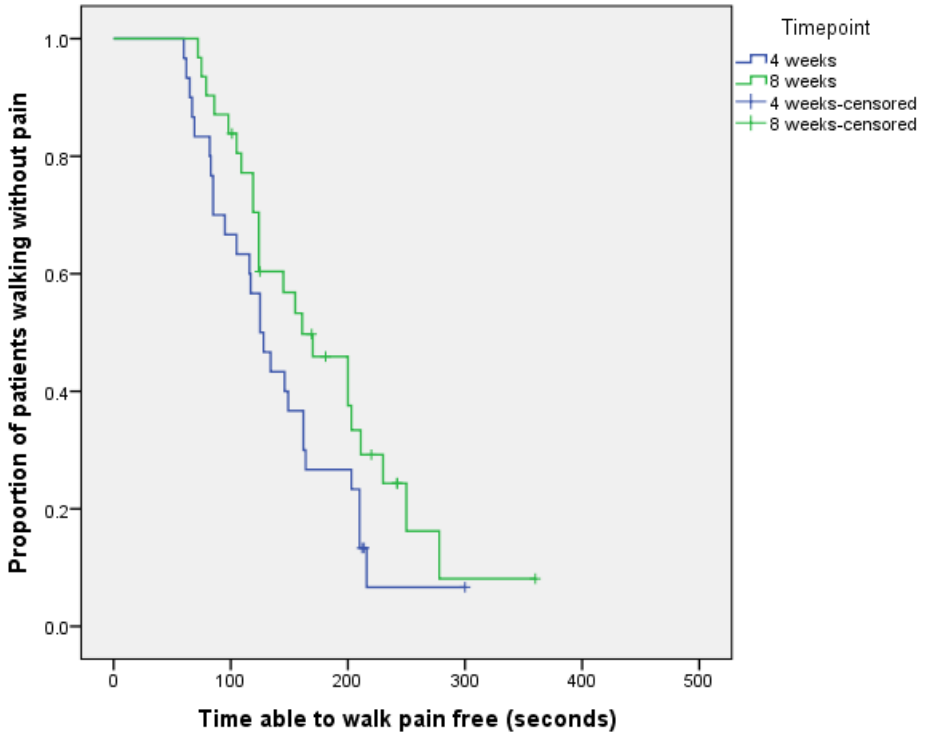
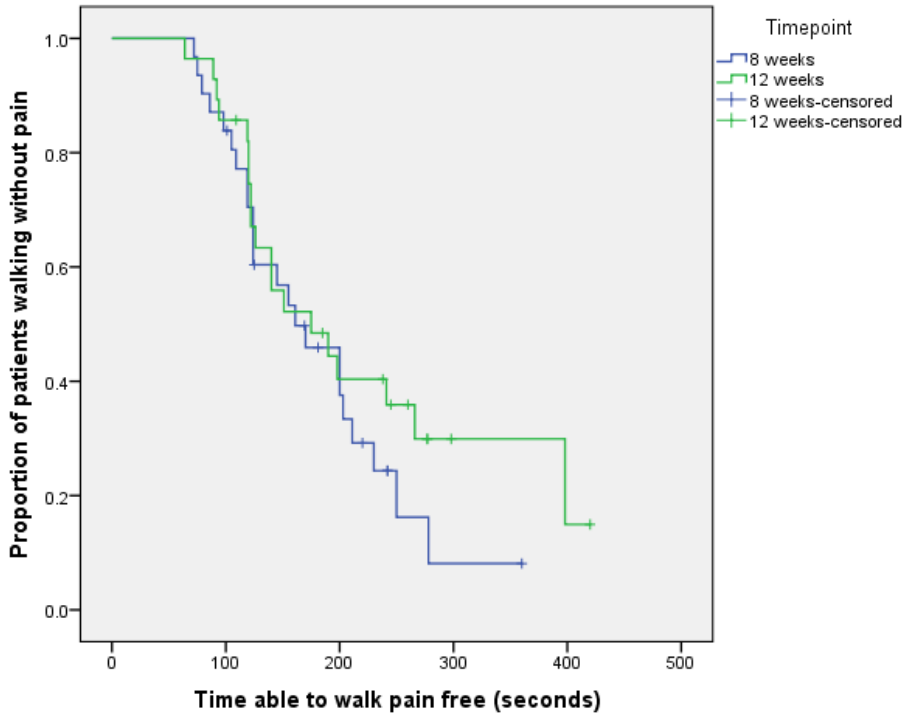


Figure 4-9 Time-to-event analysis of PFWT week 8 and PFWT at week 12



Dot plots offer an alternative method of illustrating the changes in PFWT over time; the mean pain-free walking times (with associated 95% confidence intervals) are illustrated in a dot plot Figure 4-10. This illustrates the monotonically increasing trend in pain-free walking time within the active therapy period from baseline to 12 weeks. The extent of separation of adjacent confidence intervals is greatest between baseline and 4 weeks, further demonstrating that the largest improvement occurs during this time interval. Table 4-7 shows change in mean PFWT at different time points.

Figure 4-10 Dot plot of PFWT as measured at various time points

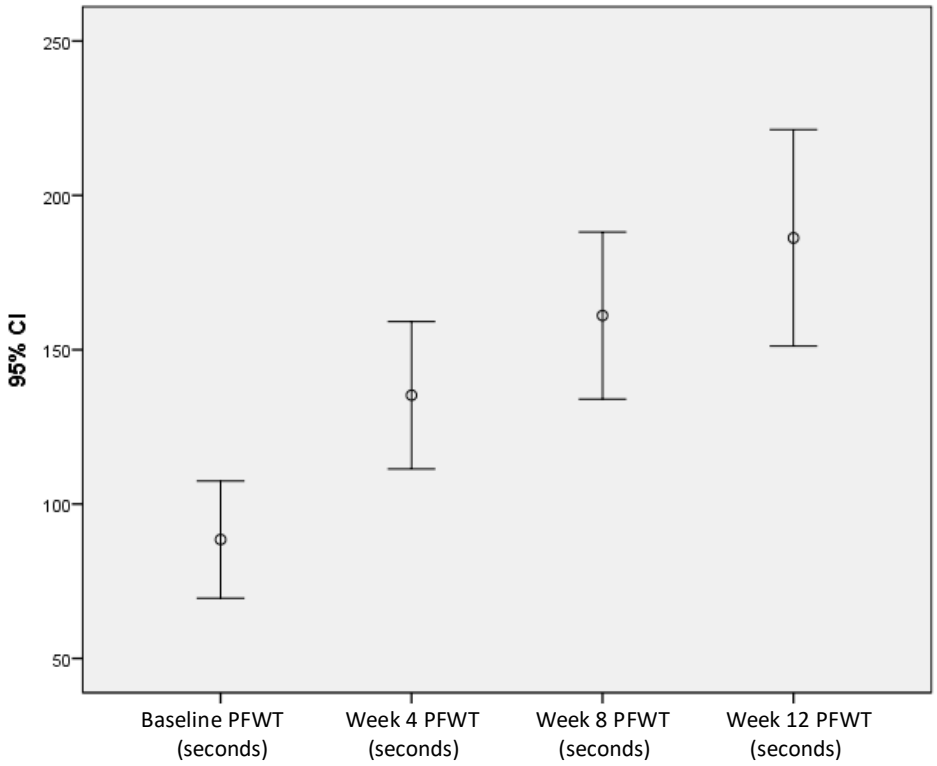


Table 4-7 PFWT measured at different time points

	Number	Minimum	Maximum	Mean	Std. Deviation
Baseline PFWT (seconds)	*31*	*35*	*220*	*88*	*46.7*
Week 4 PFWT (seconds)	*29*	*60*	*300*	*136*	*60.7*
Week 8 PFWT (seconds)	*30*	*72*	*360*	*161*	*68.0*
Week 12 PFWT (seconds)	*28*	*64*	*420*	*186*	*90.4*

4.4 Pain-free walking time follow-up phase

Participants received CVT for a total of 12 weeks. Following this treatment phase, participants were followed up at week 16, week 24 and finally at week 36. This was to assess if there would be any changes to participants' PFWT (either positive or negative) once the CVT was discontinued. Comparison of PFWT between week 12 to week 16 (based on 24 valid measurements), showed no evidence of a statistically significant difference between comparison time points, ($\chi^2_{(1)}$=0.28; p=0.593, Figure 4-11). Similarly, comparison of PFWT between week 12 and week 24 based on 18 valid measurements showed no evidence of a statistically significant difference between comparison time points, ($\chi^2_{(1)}$=0.83; p=0.361, Figure 4-12). A comparison of PFWT between week 12 and week 36, based on 18 valid measurements again did not show a statistically significant difference in PFWT. However, this result was only marginally above the level of 5% required for statistically significance, ($\chi^2_{(1)}$=3.75; p=0.053, Figure 4-13). While some substantive changes in PFWT measured between post-active therapy time-points exist, the lack of significance over this period suggests that the effect observed during the active therapy phase remains largely intact post-active therapy, and that changes during the post-active therapy phase are minor compared with the changes observed during the active therapy period.

To establish what these changes mean in terms of benefits to participants, a comparison of mean PFWT in time at baseline, week 12 and week 36 was undertaken, (Table 4-8, Figure 4-14). This analysis showed that participants' mean PFWT increased by 215% at week 12, and a further 55% to 270% at week 36 compared to baseline. This demonstrates that the main improvements occurred in the 12 weeks of active therapy with some additional improvements post active therapy. There is no evidence that the benefits achieved during active therapy diminishes over time post-therapy.

Figure 4-11 Time-to-event analysis of PFWT at week 12 and PFWT at week 16

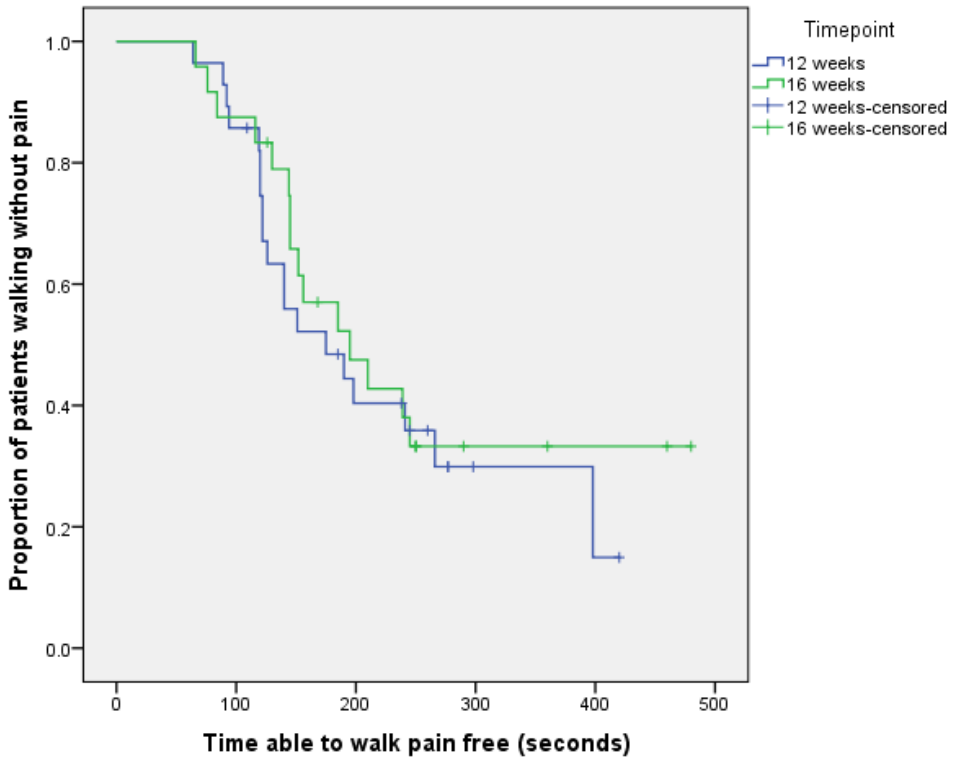


Figure 4-12 Time-to-event analysis of PFWT at week 12 and PFWT at week 24

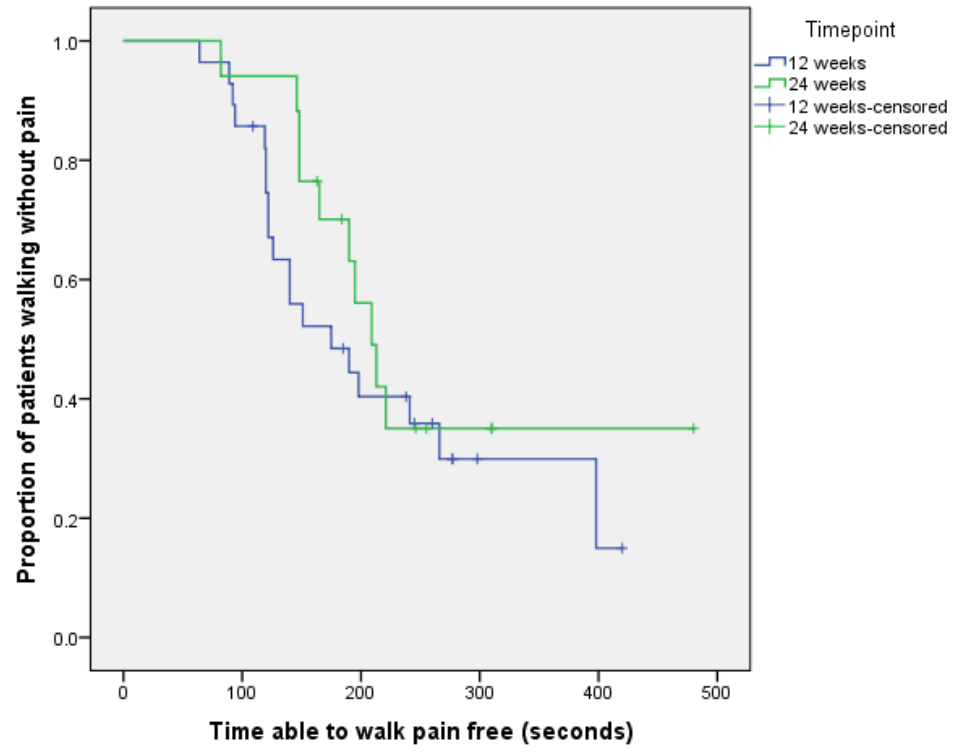


Figure 4-13 Time-to-event analysis of PFWT at week 12 and PFWT at week 36

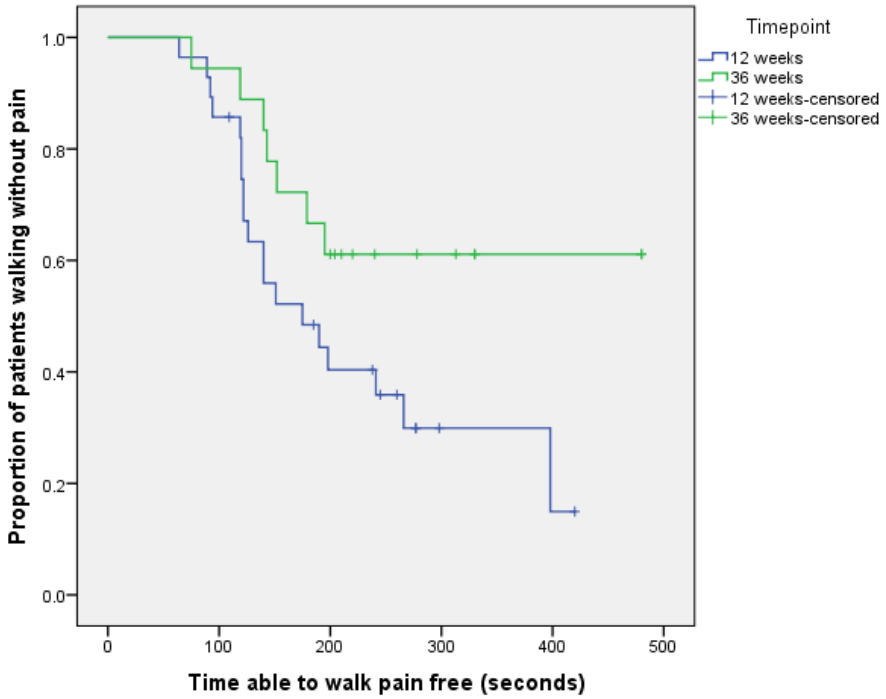


Figure 4-14 Time-to-event analysis of PFWT baseline, PFWT at week 12 and PFWT at week 36

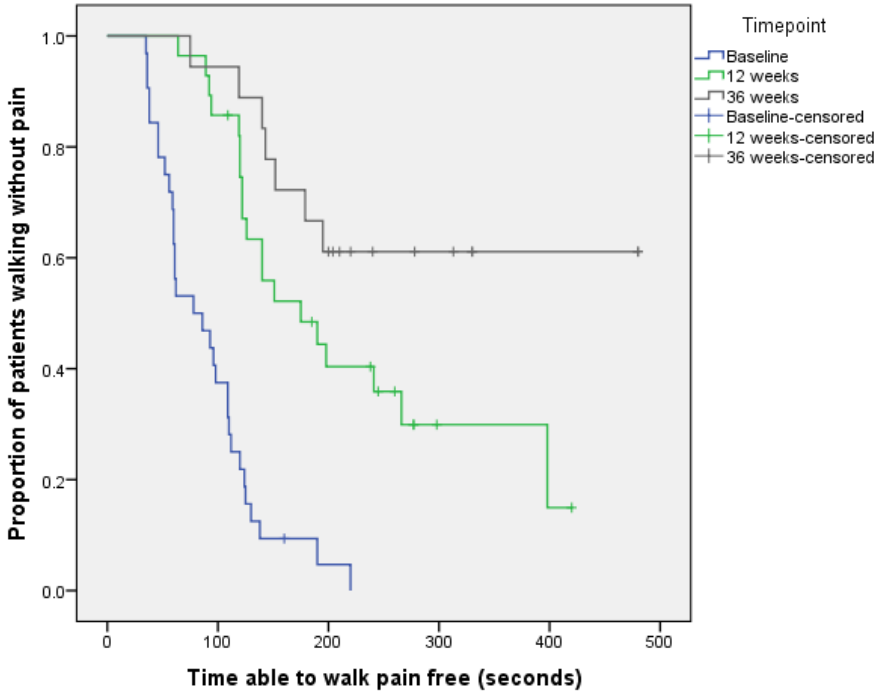


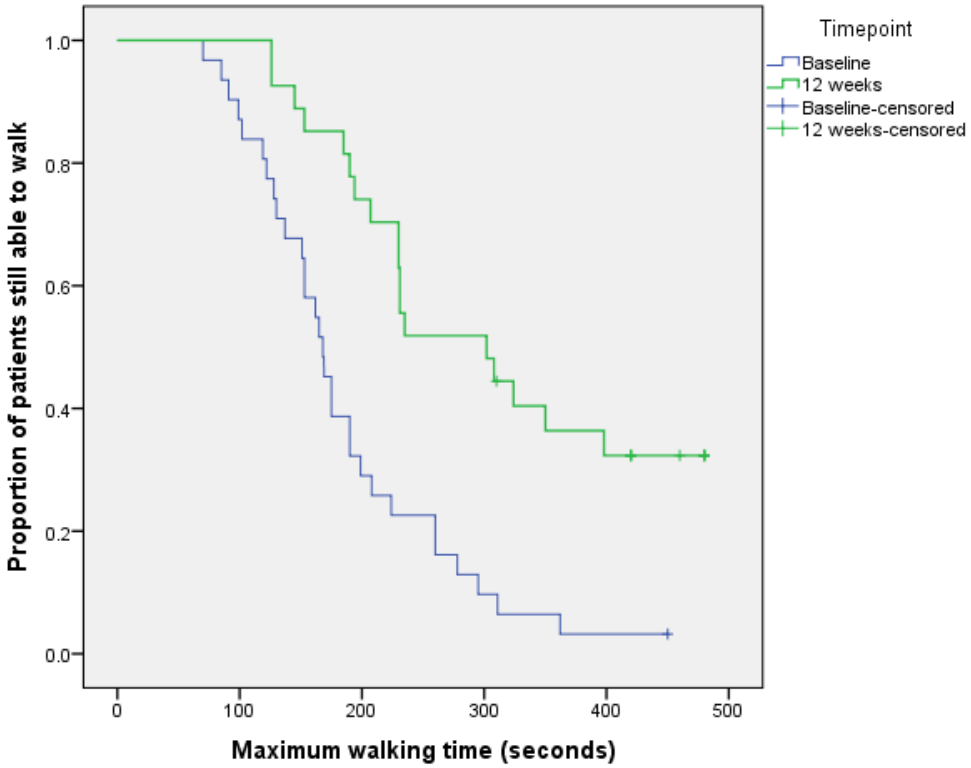
Table 4-8 Summary changes in mean of pain free walking time from baseline, week 12 and week 36

	Baseline pain free walking time (seconds)	Week 12 pain free walking time (seconds)	Week 36 pain free walking time (seconds)
Mean	*88*	*189*	*238*
Minimum	*35*	*64*	*75*
Maximum	*220*	*420*	*480*
25 percentile	*53*	*120*	*149*
75 percentile	*118*	*252*	*317*

4.5 Maximum walking time therapy phase

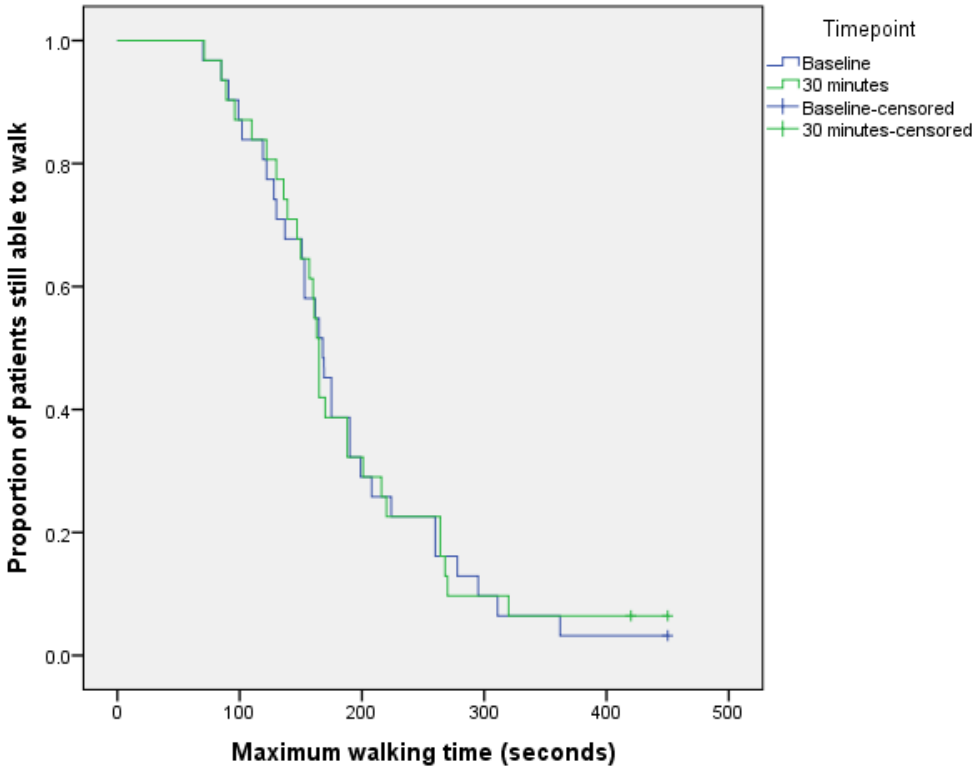
The second primary outcome measure of the study was the change in MWT measured in seconds at baseline and at 12 weeks; at the end of the treatment phase when the subject received vibration therapy for 30 minutes twice a day. Twenty-seven participants (79%) provided a valid measurement of MWT at week 12, and of these, 85% recorded an improvement in their MWT, with an average improvement of 161% and a range of -37 % to 488%. A comparison of differences in time-to-event (event being termination of walking due to pain), between baseline and week 12 showed that there was a statistically significant difference (at the 5% significance level) between comparison time points, ($\chi^2_{(1)}$=15.36; p<0.001, Figure 4-15).

Figure 4-15 Time-to-event analysis of MWT baseline and MWT at week 12



As the results highlighted in section 4.5 showed statistically significance, a further time-to-event analysis was undertaken to determine at which point the changes occurred. This further analysis would help to establish the optimum length of treatment with CVT. This included comparison of MWT from baseline and at 30 minutes following one dose of vibration therapy. Thirty-one valid measurements were analysed, illustrated in Figure 4-16. Log Rank testing of the data demonstrated no evidence of significant difference between comparison time points, ($\chi^2_{(1)}$=0.009; p=0.926), indicating that there are no immediate benefits of CVT.

Figure 4-16 Time-to-event analysis of MWT baseline and MWT at 30 minutes



Furthermore, comparison of MWT from baseline to 4 weeks based on 29 valid measurements, also showed no evidence of a statistically significant difference between comparison time points, ($\chi^2_{(1)}$=2.45; p=0.118), (Figure 4-17). However, comparison of MWT from baseline to 8 weeks (based on 30 valid measurement), did show a statistically significant difference between comparison time points, ($\chi^2_{(1)}$=11.02; p=<0.001), (Figure 4-18). Figure 4-19 shows summary of the time-to-event analysis of MWT at a number of different time points.

Figure 4-17 Time-to-event analysis of MWT baseline and MWT at week 4

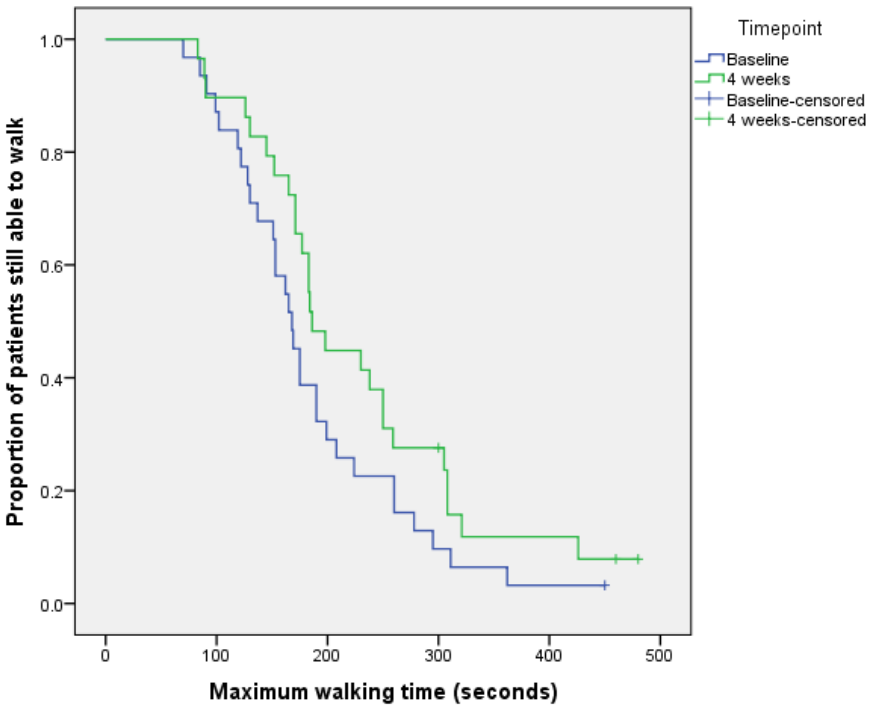


Figure 4-18 Time-to-event analysis of MWT baseline and MWT at week 8

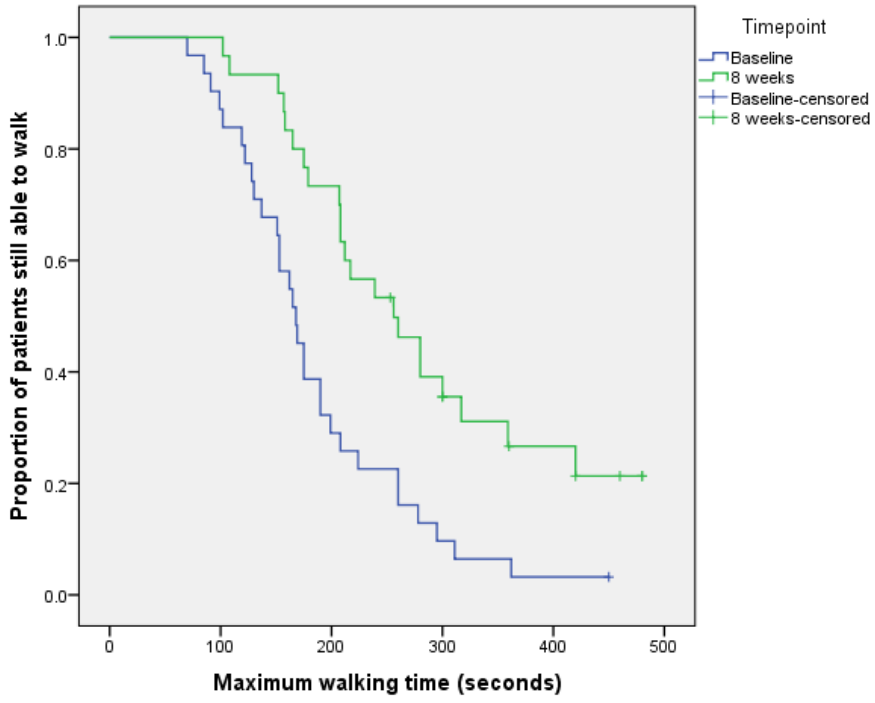
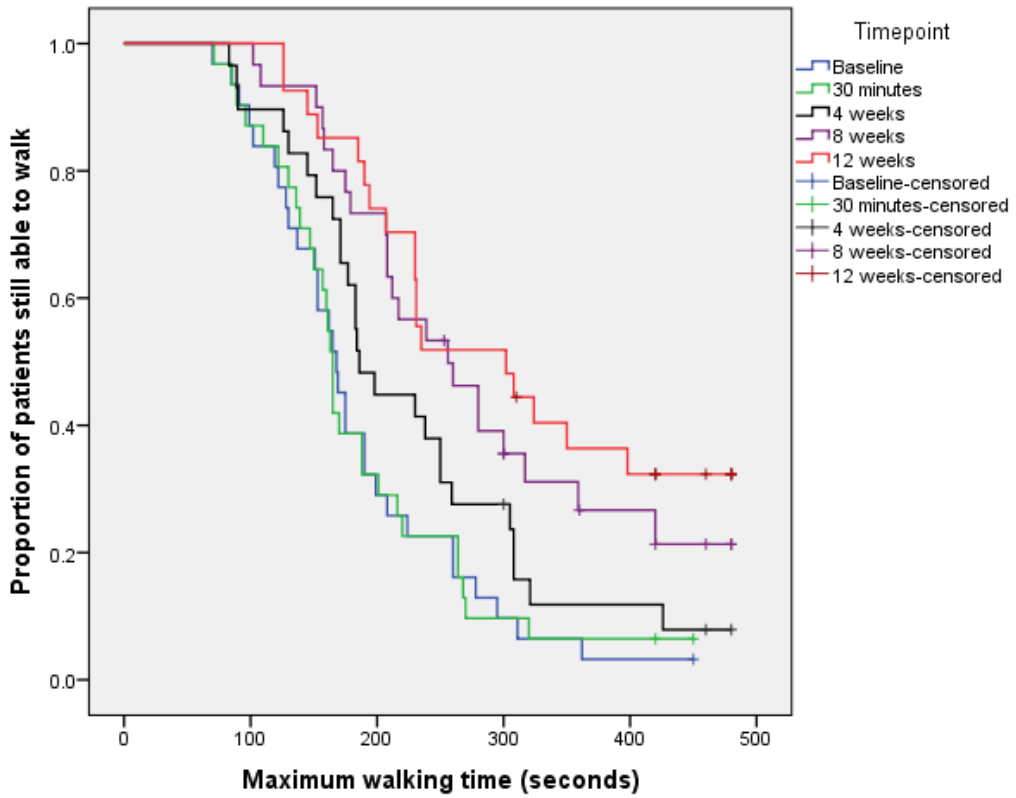


Figure 4-19 Time-to-event summary analysis of MWT at multiple time points



Mean maximum walking times (and associated 95% confidence intervals are illustrated in a dot plot (Figure 4-20), illustrating the monotonically increasing trend in maximum free walking time with number of weeks from baseline. Table 4-9 shows change in mean MWT at different time points.

Figure 4-20 Dot plot of MWT measured at multiple time points

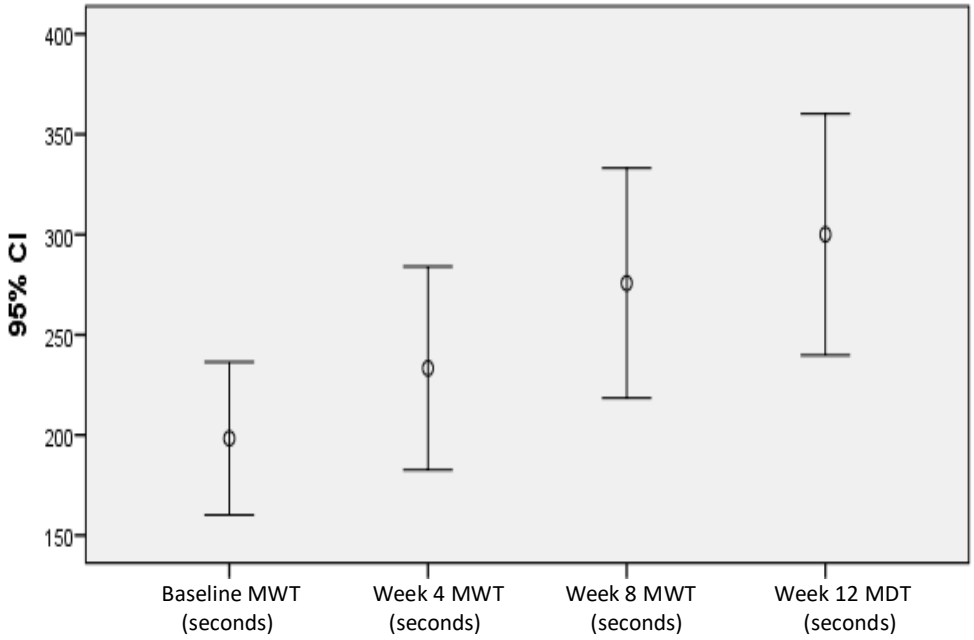


Table 4-9 MWT measured at different time points

	Number	Minimum	Maximum	Mean	Std. Deviation
Baseline MWT (seconds)	*30*	*70*	*450*	*186*	*87.0*
Week 4 MWT (seconds)	*28*	*83*	*480*	*224*	*105.0*
Week 8 MWT (seconds)	*29*	*102*	*480*	*266*	*108.6*
Week 12 MWT (seconds)	*26*	*126*	*480*	*294*	*118.8*

The results suggested that the main improvements in MWT occurred in the first eight weeks of therapy. In order to further investigate this finding, detailed analysis was conducted to assess at what time point the main changes to MWT were occurring. A comparison of MWT between week 4 and week 8 (Figure 4-21) showed no evidence for a significant difference between time points, ($\chi^2_{(1)}$=2.68; p=0.102). Likewise, a comparison of MWT between week 8 and week 12 again showed no evidence for a significant difference between comparison time points, ($\chi^2_{(1)}$=0.671; p=0.413), (Figure 4-22). The change to MWT reached a statistically significant difference (p=0.001) when comparing baseline to week 8 (Figure 4-18); this suggests that the main change in MWT occurred during the first eight weeks of treatment.

Figure 4-21 Time-to-event analysis of MWT at week 4 and MWT at week 8

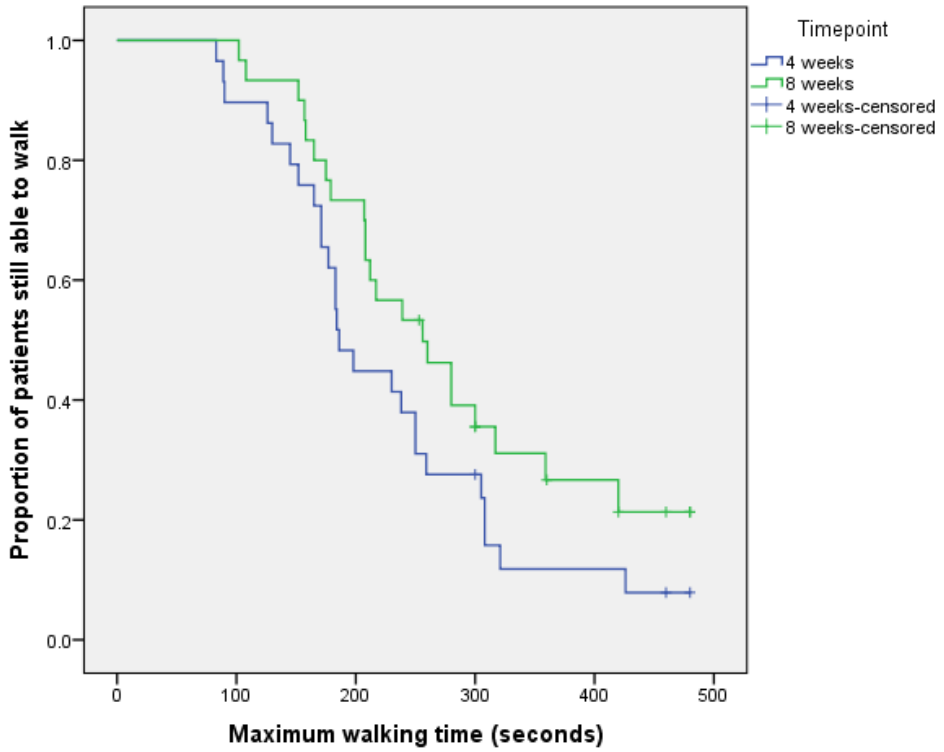
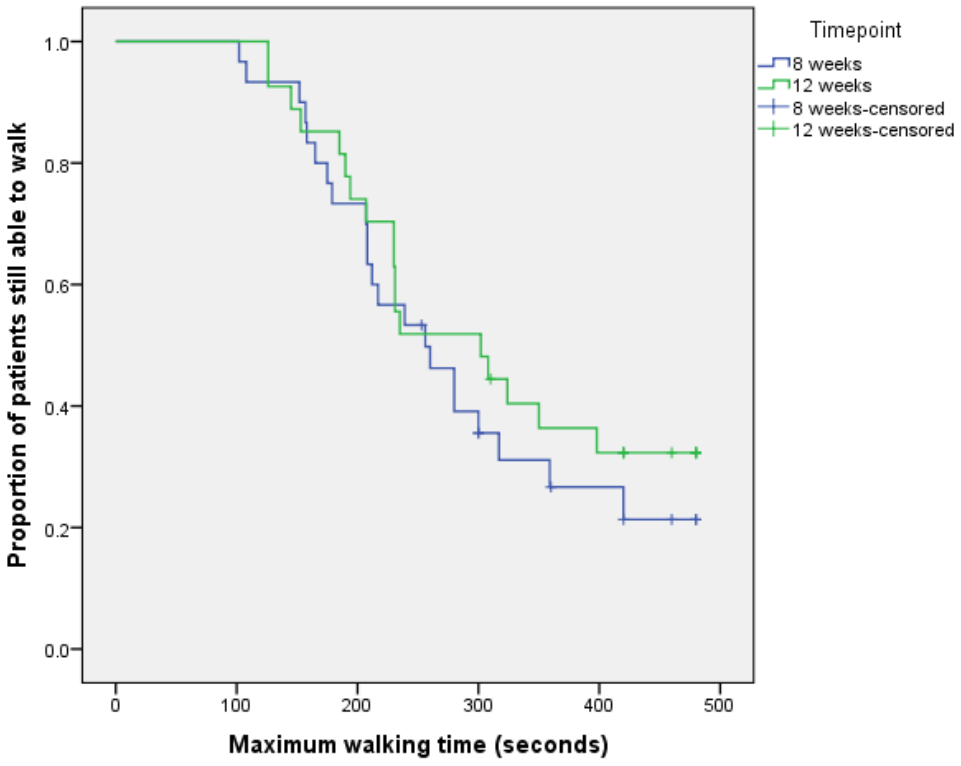


Figure 4-22 Time-to-event analysis of MWT at week 8 and MWT at week 12



4.6 Maximum walking time follow-up phase

Participants received CVT for 12 weeks (active therapy phase). Subsequent to the treatment phase, participants were followed up at week 16, week 24 and week 36. This was to assess if there were any changes to participants' MWT (either positive or negative) once the CVT was discontinued. Time-to-event analysis was conducted to compare MWT at 12 weeks with corresponding readings at week 16, week 24 and week 36. Results are illustrated in Figure 4-23, Figure 4-24, and Figure 4-25.Figure *4-25*

The results of this analysis showed no evidence of a statistically significant difference between comparison time points, points at week 12 and 16 (based on 24 valid measurements), ($\chi^2_{(1)}$=0.147; p=0.701, Figure 4-23), between week 12 and week 24 (based on 18 valid measurements), ($\chi^2_{(1)}$=0.780; p=0.377, Figure 4-24) and between week 12 and week 36 (19 valid measurements), ($\chi^2_{(1)}$=2.743; p=0.098, Figure 4-25).

Figure 4-23 Time-to-event analysis of MWT at week 12 and MWT at week 16

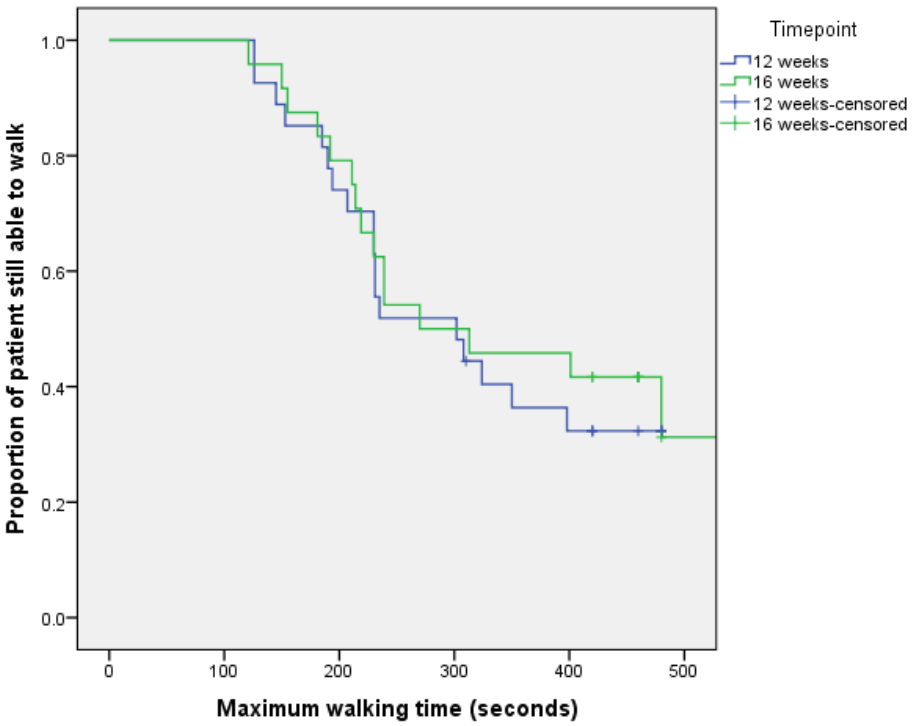


Figure 4-24 Time-to-event analysis of MWT at week 12 and MWT at week 24

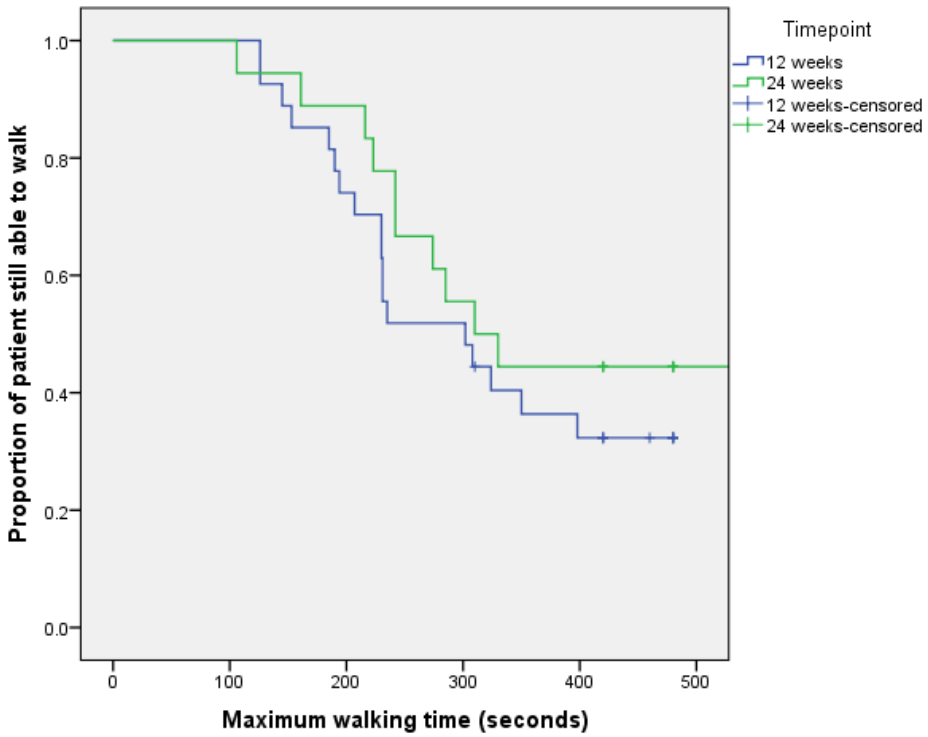
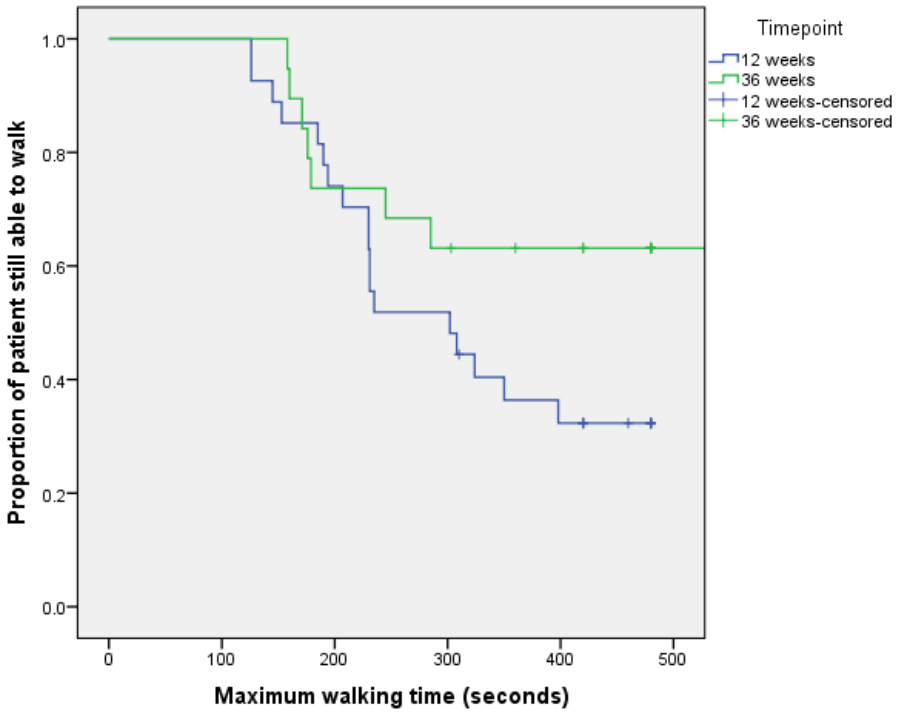


Figure 4-25 Time-to-event analysis of MWT at week 12 and MWT at week 36



An overall comparison of MWT from baseline, week 12 and week 36, shows the improvement in MWT from baseline to 12 weeks are sustained at week 36, (Figure 4-26). Table 4-10 shows the overall improvement in MWT in seconds from baseline, following 12 weeks of CVT and at follow-up at 36 weeks. The participants' mean MWT increased by 161% from baseline to week 12 and by 193% from baseline to week 36. This demonstrates that the main improvements occurred in the 12 weeks of active therapy, with some additional improvements post-active therapy. It is important to note that the benefits were sustained once the active therapy was stopped.

Figure 4-26 Time-to-event analysis of MWT baseline, MWT at week 12 and MWT at week 36

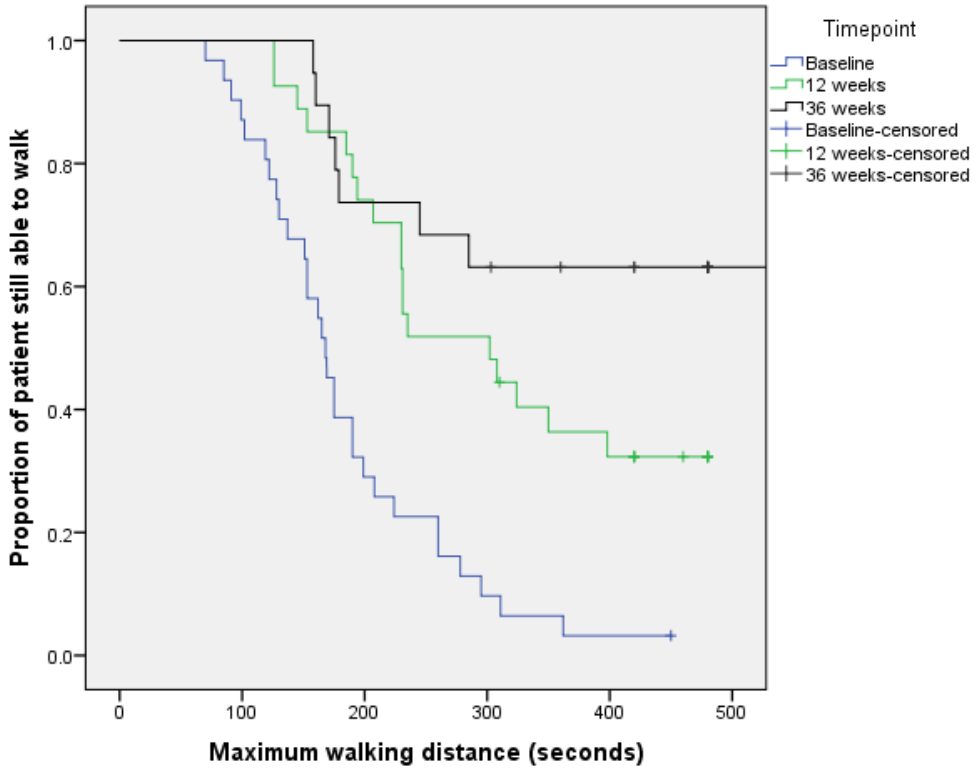


Table 4-10 Summary changes in mean of MWT from baseline, week 12 and week 36

	Baseline maximum walking time (seconds)	Week 12 maximum walking time (seconds)	Week 36 maximum walking time (seconds)
Mean	*186*	*300*	*359*
Minimum	*70*	*126*	*158*
Maximum	*450*	*480*	*600*
25 percentile	*128*	*194*	*179*
75 percentile	*224*	*420*	*480*

4.7 ABPI

One of the secondary outcomes of the study were changes in ABPI measurements/systolic leg pressure after 12 weeks CVT therapy compared with baseline. Analysis of changes in ABPI was undertaken by paired-samples t-testing, comparing means at different time intervals to assess the significance of change at the 5% significance level. Ninety-five per cent confidence intervals for the

changes were also reported. Thirty participants provided valid ABPI measurements to compare ABPI at baseline and at end of the treatment phase (week 12). The paired samples t-test showed evidence of a statistical difference between the groups (t_{29}=-2.008, p=0.046), (Table 4-11). However, looking at long-term change, 20 participants provided valid ABPI measurements to compare outcomes at baseline and week 36, showing no evidence of a statistically significant difference between the groups (t_{19}=-1.503, p=0.149), (Table 4-12).

Table 4-11 Paired t testing of comparison of ABPI at baseline and week 12

	Mean	Std. Deviation
Baseline ABPI in treated leg	*0.64*	*0.18*
Week 12 ABPI in treated leg	*0.71*	*0.21*

	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
Pair 1			Lower	Upper			
Baseline ABPI in treated leg Week 12 ABPI in treated leg	*-0.071*	*0.187*	*-0.141*	*-0.001*	*-2.088*	*29*	*0.046*

Table 4-12 Paired t testing of comparison of ABPI at baseline and week 36

	Mean	Std. Deviation
Baseline ABPI in treated leg	*0.63*	*0.18*
Week 36 ABPI in treated leg	*0.68*	*0.17*

	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
Pair 1			Lower	Upper			
Baseline ABPI in treated leg Week 36 ABPI in treated leg	*-0.05*	*0.149*	*-0.119*	*-0.019*	*-1.503*	*19*	*0.149*

4.8 Systolic leg pressure therapy phase

Twenty-four (71%) of participants had an increase in systolic leg pressure during the treatment phase, for two participants (5%) pressure remained static and eight participants (24%) had documented deterioration. In total, the average increase was 12%, ranging from -40% to 90%. Thirty-two participants provided valid measurements of systolic leg pressure at baseline and week 12, and paired

samples t-testing analysis was undertaken to assess the change in mean of systolic leg pressure (significance level was set to 0.05). This analysis revealed a statistically significant difference (t_{31}=-2.273, p=0.03) between systolic pressure of treated leg at baseline and at the end of treatment phase (week 12). These findings are illustrated in Table 4-13. In the untreated leg, there was no evidence of a statistically significant difference (t_{31}=-0.597, p=0.555) between pressure at baseline and at end of treatment phase week 12. This was based on valid measurements obtained from 32 participants (Table 4-14). The results show improvements in systolic leg pressure of the treated leg. This, combined with no change being seen over the same time period in the untreated leg (Table 4-14), suggests that the changes to systolic leg pressure are as a direct result of the CVT.

Table 4-13 Paired t testing comparison of systolic leg pressure of treated leg at baseline and week 12

	Mean	Std. Deviation
Baseline highest systolic pressure of treated leg	*111*	*47.7*
Week 12 highest systolic pressure of treated leg	*120*	*52.1*

Pair 1	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
			Lower	Upper			
Baseline highest systolic pressure of treated leg Week 12 highest systolic pressure of treated leg	*-8.531*	*21.234*	*-16.187*	*-0.875*	*-2.273*	*31*	*0.03*

Table 4-14 Paired t testing comparison of systolic pressure of untreated leg at baseline and week 12

	Mean	Std. Deviation
Baseline highest systolic pressure of untreated leg	*137*	*52.9*
Week 12 highest systolic pressure of untreated leg	*139*	*50.1*

Pair 1	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
			Lower	Upper			
Baseline highest systolic pressure of untreated leg Week 12 highest systolic pressure of untreated leg	*-2.375*	*22.498*	*-10.487*	*-5.737*	*-0.597*	*31*	*0.555*

A further secondary outcome of the study was to establish the length of treatment required with CVT to optimise the benefits. To establish at what time point the main changes to systolic leg pressure occurred, further paired samples t-test analysis of the data was undertaken. A comparison of systolic pressure at baseline and week 4 (Table 4-15) showed a statistically significant difference between pressure at these time points, (t_{32}=-3.746, p=0.01). Conversely, there was no evidence of a statistically significant difference (t_{32}=0.467, p =0.644) between systolic pressure of treated leg at week 4 compared and at the end of week 8, (Table 4-16). Similarly, there was no evidence of a statistically significant difference (t_{31}=0.07, p=0.945) between systolic pressure of treated leg at week 8 and at end of week 12, (Table 4-17). This implies that the main changes to the systolic pressure in the treated leg occurs in the first four weeks of treatment.

Table 4-15 Paired t testing comparison of systolic pressure of treated leg at baseline and week 4

	Mean	Std. Deviation
Pair 1		
Baseline highest systolic pressure of treated leg	*110*	*47.8*
Week 4 highest systolic pressure of treated leg	*122*	*49.1*

	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
Pair 1			Lower	Upper			
Baseline highest systolic pressure of treated leg Week 4 highest systolic pressure of treated leg	*-12.212*	*18.728*	*-18.853*	*-5.571*	*-3.746*	*32*	*0.001*

Table 4-16 Paired t testing comparison of systolic pressure of treated leg pressure at week 4 and week 8

	Mean	Std. Deviation
Pair 1		
Week 4 highest systolic pressure of treated leg	*122*	*49.1*
Week 8 highest systolic pressure of treated leg	*120*	*48.8*

	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
Pair 1			Lower	Upper			
Week 4 highest systolic pressure of treated leg Week 8 highest systolic pressure of treated leg	*2.636*	*32.445*	*-8.868*	*14.141*	*0.467*	*32*	*0.644*

Table 4-17 Paired t testing comparison of systolic pressure of treated leg at week 8 and week 12

	Mean	Std. Deviation
Pair 1		
Week 8 highest systolic pressure of treated leg	*120*	*49.6*
Week 12 highest systolic pressure of treated leg	*120*	*52.1*

Pair 1	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
			Lower	Upper			
Week 8 highest systolic pressure of treated leg Week 12 highest systolic pressure of treated leg	*-0.281*	*22.81*	*-8.504*	*7.941*	*0.07*	*31*	*0.945*

4.9 Systolic leg pressure follow-up phase

To assess whether the changes in systolic leg pressure were sustained once the active treatment phase was completed, long-term follow-up data was analysed. Twenty-seven participants provided valid systolic leg pressure measurements at week 16. Measurement of systolic leg pressure at week 16 were compared to measurement obtained at week 12, (Table 4-18), showing no evidence of a statistically significant difference between comparison time points, (t_{26}=1.14, p=0.265). Additionally, a comparison was made of systolic leg pressure of treated leg at week 12 and week 24 (based on valid measurements obtained from 21 participants), (Table 4-19). This interestingly showed evidence of a statistically significant difference between comparison time points, (t_{20}=2.361, p=0.028). This statistically significant change was due to a deterioration in comparison means 123 mmHg at week 12 and 116 mmHg at week 24. Further comparison of week 12 and week 36 (based on 20 participant valid measurements), (Table 4-20), returned to showing no evidence of significant difference between comparison time points, (t_{19}=1.139, p=0.269). This implies that the changes made in the first 12 weeks are sustained at week 36.

Table 4-18 Paired t testing comparison of systolic pressure of treated leg at week 12 and week 16

	Mean	Std. Deviation
Pair 1		
Week 12 highest systolic pressure of treated leg	*127*	*53.1*
Week 16 highest systolic pressure of treated leg	*124*	*53.7*

Pair 1	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
			Lower	Upper			
Week 12 highest systolic pressure of treated leg Week 16 highest systolic pressure of treated leg	*3.741*	*17.058*	*-3.007*	*10.489*	*1.14*	*26*	*0.265*

Table 4-19 Paired t testing comparison of systolic pressure of treated leg at week 12 and week 24

	Mean	Std. Deviation
Pair 1		
Week 12 highest systolic pressure of treated leg	*123*	*44.3*
Week 24 highest systolic pressure of treated leg	*116*	*44.6*

Pair 1	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
			Lower	Upper			
Week 12 highest systolic pressure of treated leg Week 24 highest systolic pressure of treated leg	*6.857*	*13.309*	*2.904*	*12.915*	*2.361*	*20*	*0.028*

Table 4-20 Paired t testing comparison of systolic pressure of treated leg at week 12 and week 36

	Mean	Std. Deviation
Pair 1		
Week 12 highest systolic pressure of treated leg	*109*	*32.1*
Week 36 highest systolic pressure of treated leg	*103*	*37.6*

Pair 1	Paired Differences				t	df	p-value
	Mean	Std. Deviation	95% Confidence interval for difference				
			Lower	Upper			
Week 12 highest systolic pressure of treated leg Week 36 highest systolic pressure of treated leg	*6.107*	*23.985*	*-5.118*	*17.332*	*1.139*	*19*	*0.269*

4.10 Cycloid vibration therapy positioning results

A component of this feasibility study was to determine at which location the device should be placed so as to optimise outcomes. The results showed that participants using the CVT device in the calf area had improved outcomes compared to those using the machine in the thigh (Table 4-21 and Table 4-22).

Table 4-21 Comparison of PFWT (seconds) outcomes and device location

Device location	Baseline pain free walking (seconds)	Week 4 pain free walking (seconds)	Week 8 pain free walking (seconds)	Week 12 Pain free walking (seconds)
Thigh				
Mean	*59*	*99*	*124*	*133.7*
Number	*8*	*8*	*8*	*7*
Std. Deviation	*19.2*	*36.3*	*39.9*	*43.5*
Calf				
Mean	*104*	*160*	*189*	*226*
Number	*16*	*14*	*15*	*14*
Std. Deviation	*52.3*	*67.0*	*77.0*	*99.9*
Total				
Mean	*89*	*138*	*166*	*195*
Number	*24*	*22*	*23*	*21*
Std. Deviation	*48.6*	*34.3*	*72.7*	*95.2*

Table 4-22 Comparison of MWT (seconds) outcomes and device location

Device location	Baseline maximum walking time (seconds)	Week 4 maximum walking time (seconds)	Week 8 maximum walking time (seconds)	Week 12 maximum walking time (seconds)
Thigh				
Mean	*172*	*189*	*251*	*234*
Number	*8*	*8*	*8*	*6*
Std. Deviation	*60.1*	*63.1*	*95.2*	*98.9*
Calf				
Mean	*199*	*259*	*287*	*333*
Number	*15*	*13*	*14*	*13*
Std. Deviation	*91.5*	*111.4*	*120.9*	*126.9*
Total				
Mean	*190*	*233*	*274*	*300*
Number	*24*	*21*	*22*	*19*
Std. Deviation	*81.6*	*100.4*	*111.3*	*124.9*

4.11 Quality of life analysis results

Analysis of results from SF-36 data showed the overall grand mean of physical component summary scores was 42.7; the overall grand mean of mental component summary scores was 50.1. These summary scores are an expression of participants' overall physical and mental health and are calculated from the individual scales of specific health domains. All scales contribute in different proportions to the scoring of both physical component summary and mental component summary (Lins and Carvalho, 2016). The calculation of the component summary scales uses specific algorithms and is completed by the SF-36 software. Three domains (physical functioning, role limitations due to physical health, and bodily pain) contribute most to the scoring of the physical component summary score; whereas social functioning, role limitations due to emotional problems and mental health contribute most to the scoring of the mental component summary score. These domains (general health perceptions, vitality and social functioning) correlate with both components. All the results from SF-36 data analysis are based on norm-based scoring and this is an important factor to remember when interpreting the data. Traditional scoring of SF-36 used a linear scale from 0-100 and the higher the score the better quality of life, but this had limitations, as there was no comparison with the general population. To simplify the interpretation of the data, norm based scoring was introduced (Burholt and Nash, 2011). In norm-based scores, each scale is scored to have the same average (50) and the same standard deviation (10). Therefore, any group mean score below this can be interpreted as being below the average range for the general population. This standardisation allows for much easier interpretation of exactly how far above or below the general population mean score and this allows for meaningful comparisons across scales.

Repeated measures ANOVA were undertaken for all SF-36 health domains and both component summary scales evaluated at measured time points (Table 4-23). This revealed evidence for a statistically significant difference within physical functioning scores over the study period ($p=0.03$). However, this may not be considered significant under the application of a Bonferroni or similar correction for multiple testing. There was no evidence of statistically significant changes within any of the other domains, including the physical component summary score (Table 4-23). Increases from baseline were noted in all of the physical domains at the end of active therapy period (week 12), with the exception of 'general health', in which a negligible deterioration was observed. The largest increase over the period of active therapy was seen in physical functioning and physical component summary scores.

The improvements seen in the physical scores at the end of the active treatment phase do start to regress throughout the follow-up phase; however, compared to baseline, improvements in physical functioning, role physical and physical component summary scores are still evident at week 36 (Figure 4-27).

In relation to mental health scoring, within the majority of measures there was noted deterioration in scoring from baseline to week 12, with the exception of the 'role emotional' domain, in which small improvements were seen. Throughout the follow-up period, the mental health scoring measures fluctuated; however, at the end of the study at week 36, there was evidence in a reduction in all measures, including the mental component summary (Figure 4-28).

Table 4-23 SF-36 analysis over time points

	Baseline mean (SD)	Week 12 mean (SD)	Week 16 mean (SD)	Week 24 mean (SD)	Week 36 mean (SD)	p - value	Partial η^2
Physical Functioning (PF)	35.34 (8.93)	44.52 (9.11)	39.93 (10.07)	39.30 (11.04)	39.55 (12.37)	0.03	0.46
Role Physical (RP)	40.90 (15.36)	43.68 (9.39)	44.13 (11.71)	44.58 (12.56)	47.27 (11.94)	0.50	0.18
Bodily Pain (BP)	44.90 (14.86)	46.75 (12.38)	44.59 (9.63)	43.93(14.22)	44.01 (10.80)	0.77	0.10
General Health (GH)	49.85 (9.59)	49.66 (11.31)	48.95 (12.71)	52.23 (11.47)	45.43 (12.79)	0.05	0.43
Physical Component Summary (PCS)	39.30 (11.67)	45.07 (8.68)	42.58 (10.65)	43.16 (11.11)	43.40 (11.11)	0.26	0.27
Vitality (VT)	50.81 (7.45)	48.44 (13.05)	50.22 (7.69)	50.22 (11.58)	47.85 (12.35)	0.82	0.09
Social Functioning (SF)	48.56 (10.33)	41.05 (18.92)	46.06 (14.39)	43.55 (16.05)	41.05 (18.92)	0.23	0.35
Role Emotional (RE)	44.33 (13.84)	46.42 (11.90)	44.33 (10.32)	42.92 (13.79)	40.85 (14.48)	0.46	0.19
Mental Health (MH)	52.04 (8.02)	49.82 (13.54)	50.86 (9.61)	51.91 (11.04)	48.12 (11.75)	0.55	0.16
Mental Health Component Summary (MCS)	53.90 (9.44)	48.81 (15.93)	51.15 (10.97)	50.61 (12.15)	46.04 (14.09)	0.26	0.27

Figure 4-27 Estimated Marginal Means: Physical Component Summary (PCS)

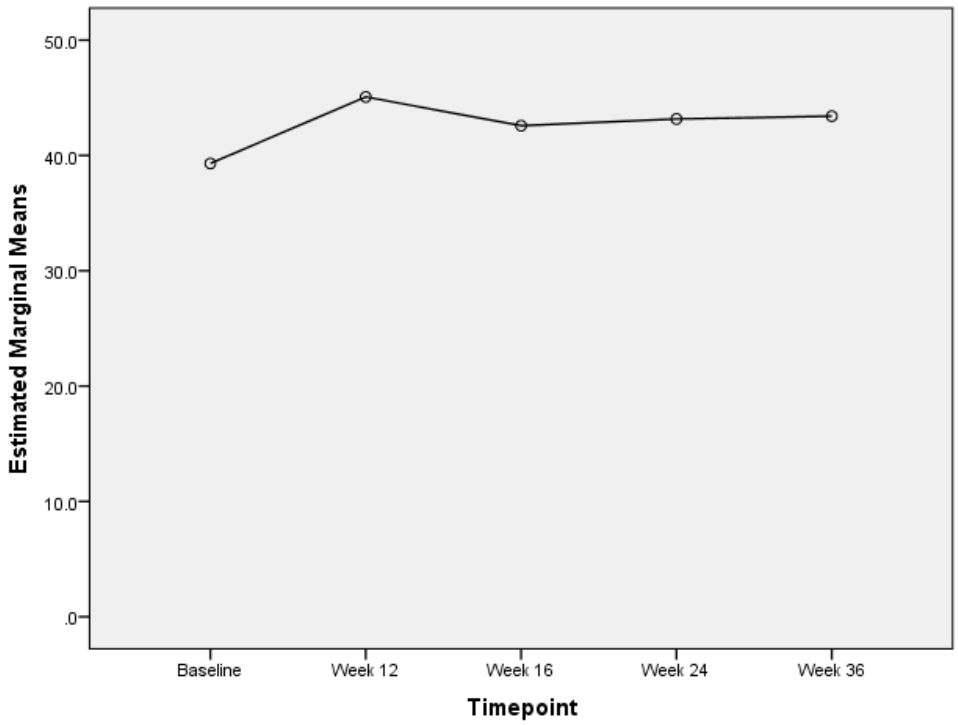
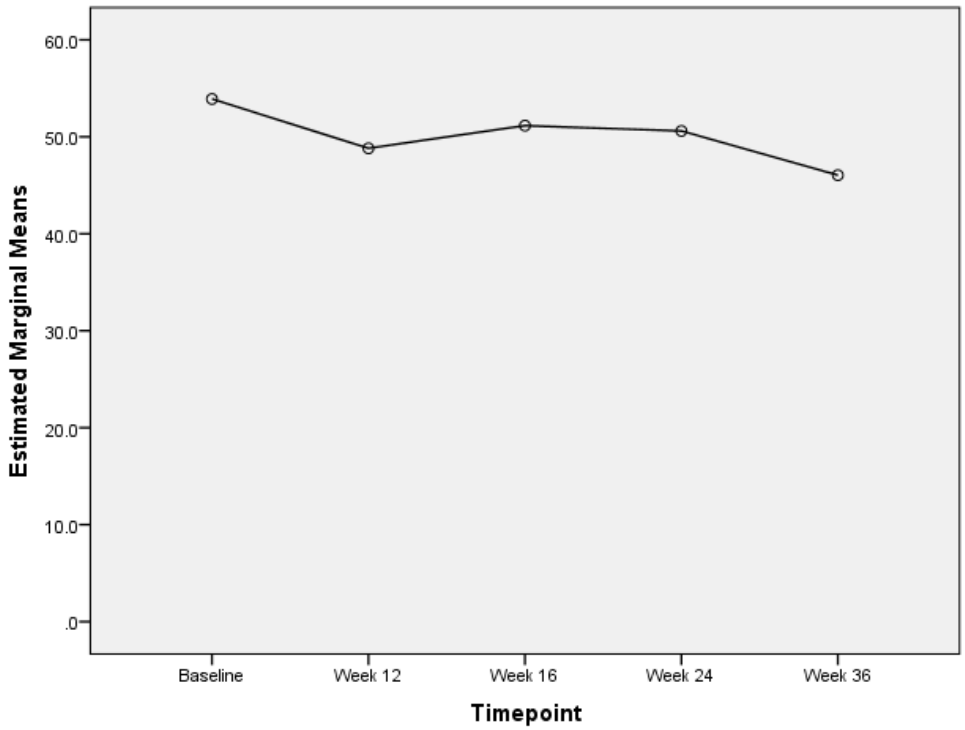


Figure 4-28 Estimated Marginal Means: Mental Health Component Summary



4.12 Participant compliance

Thirty-four valid measurements were recorded, mean usage of the CVT machine was 154, with a range of 116 to 197. As previously discussed in Section 3.18.3, compliance was set at the level of 168 (+/- 20%), 26 (76%) of participants were compliant with the treatment and eight (24%) had usage outside of this set allowance. There were no participant drop outs during the treatment phase.

4.13 Participant feedback

Participants were asked three questions at week 12 to provide valuable feedback on the acceptability of CVT:

1. How did you find using the product? - Options available were: "*Very difficult"*, "*difficult"*, "*neutral"*, "*easy"* or "*very easy"*. Twenty-one (62%) of patients found the machine "easy" to use, 13 (38%) found the machine "very easy", no participant reported the machine as being "difficult", "very difficult" or "neutral".

2. Have you been satisfied with the results so far? - Options available were: "*Very dissatisfied", "not satisfied", "neutral", "satisfied" and "very satisfied"*. No participant indicated they were "very dissatisfied" or "not satisfied", four (12%) indicated they were "very satisfied", 18 (53%) were "satisfied" with the results and 12 (35%) specified a "neutral" response.

3. When using the machine was it? – Options available were: "*Painful", "mild discomfort", "neutral", "comfortable" or "very comfortable"?* No participant indicated that they found the machine "painful", one participant (3%) indicated they had "mild discomfort" when using the machine, three (9%) provided a "neutral" response, 19 (56%) found the machine "comfortable" to use and 11 (32%) answered that they found the machine "very comfortable".

4.14 Adverse events

During the walking test one participant fell. This resulted in bruising to face. The participant was assessed in Accident and Emergency and no further treatment was required. This adverse event was reported to the study sponsor, the research governance team, and the local ethics committee. The participant continued in the trial but did not take part in any further walking assessments. Data from this participant was still included in the study analysis.

4.15 Summary

The study recruited 34 participants with intermittent claudication, to investigate the original research question: to critically explore the association of cycloidal vibration therapy in participants with intermittent claudication, with primary outcome measures of changes from baseline of pain free and maximum walking time after 12 weeks of CVT. The results demonstrate improvements in PFWT and MWT at 12 weeks which were sustained at week 36. This improved walking ability resulted in improved quality of life, measured by physical functioning scores. Additionally, participants' lower limb perfusion had increased, both ABPI and systolic leg pressure showed statistical evidence of improvements, and these changes in lower limb perfusion were not seen in the untreated limb.

The results address the aims of this feasibility study which were to:

- To explore the association of cycloidal vibration therapy with participants' pain free walking time and maximum walking time
- Establish optimal CVT intervention
- To establish whether any changes in walking distance are sustained after cycloidal vibration therapy is stopped
- To establish statistical variability of the primary outcomes

The findings of these results and their limitations will be discussed in the next chapter.

5 DISCUSSION

The aims of this feasibility study were to:

- To explore the association of cycloidal vibration therapy in participants' PFWT and MWT
- To establish optimal CVT intervention
- To establish whether any changes in walking distance are sustained after cycloidal vibration therapy is stopped
- To establish statistical variability of the primary outcomes

The objectives of the study were to:

- To observe changes in participants' PFWT and MWT
- To establish whether any change in participants' lower limb perfusion occurs
- To determine the duration of treatment required to achieve maximum benefits
- To determine the most effective physical location of vibration therapy
- To determine measurement/equipment suitability to assess a degree of change in clinical and functional status
- To determine the final study protocol

This chapter discusses the study findings and potential implications for further research and clinical practice. The strengths and limitations of the study are highlighted. To aid clarity the findings are discussed in the order they were presented in chapter 4.

5.1 General baseline characteristics of participants

5.1.1 Age

The patient profile in this study is similar to that documented in previously conducted studies (Cheetham et al., 2004, Kakkos et al., 2005, Savage et al., 2001). The average age of the participants was 68 years (interquartile range (IQR) 60-75 years). The youngest participant was aged 51 years and the oldest was aged 83 years. PAD prevalence increases with age, below the age of 60 years PAD is present in less than 3% of the population. However, this increases to between 15-20% for those aged over 70 years (Selvin and Erlinger, 2004). Therefore, the average age of patients within this research

is typical of the population with PAD. This provides reassurance that the findings from the study are relevant to clinical practice.

5.1.2 Gender

Substantially more males (n=30) than females (n=4) constituted the study's sample. Historically, being male was thought to be a predictive factor of developing PAD. The Framingham study, which started in the United States of America (USA) in 1948 and includes more than 5,000 subjects, is the longest and largest published cardiovascular cohort study examining PAD, and found that males were twice as likely as females to be affected (Murabito et al., 1997). As a result of this early study, being male still remains a risk factor of developing PAD within the American Heart Association guidelines (Hirsch et al., 2006). However, the data on which these guidelines were based is over thirty years old. More recent studies report conflicting results to these early studies, with global prevalence in women being similar or even higher than that of men (Sigvant et al., 2007, Diehm et al., 2004). Interestingly, even though the prevalence of PAD is now considered to be equal between the sexes, there is a significant gender-based difference with asymptomatic disease ($p<0.03$) with prevalences of 13% in females and 9% in males (Teodorescu et al., 2013). This increased rate of asymptomatic disease in females has been discussed in a number of previous papers (McDermott et al., 2000a, Brevetti et al., 2008, Hirsch et al., 2001) and may explain the reason for lower rate of females being included in research trials, since the absence of pain will primarily result in fewer females presenting to their GP. Also, should PAD be discovered incidentally, the patient would not be referred to vascular centres due to the lack of related symptoms. These factors contribute to a lower proportion of females within the vascular claudication clinic where the participants for this research were recruited. The disproportionate number of male participants in PAD research may be accounted for by the majority of vascular research initiatives recruiting patients within vascular out-patient settings.

5.1.3 Ethnicity

One potential limitation in the population demographics of this study was that all of the participants were white Caucasians, despite the evidence that the presence of PAD is greater in non-Caucasian groups (Balarajan, 1991, Criqui et al., 2005, Meadows et al., 2009). The increased prevalence in non-Caucasians may be explained by the greater incidence of risk factors such as diabetes, smoking, hypertension and obesity in this ethnic group. However, ethnicity in isolation of any other factors has been shown to be a strong and independent risk factor for the development of PAD (Criqui et al., 2005). Untangling the factors which lead to an increased prevalence in specific ethnic groups is therefore extremely difficult.

As mentioned above, the prevalence of PAD is higher in non-Caucasian ethnic groups but, once diagnosed, ethnicity does not appear to be an independent factor relating to long-term outcomes. Meadows et al. (2009) examined two-year outcomes for multiple ethnic groups with PAD, and found that there were no differences in all-cause mortality among ethnic groups or any significant differences in rates of angioplasty intervention between groups. Therefore, even though this research into CVT only contained Caucasian participants, there is no evidence to suggest that the changes, in terms of walking benefit, would be any different in patients from other ethnic origins. However, for any future research investigating CVT in PAD patients, strategies for improving recruitment from ethnic minorities need to be considered. These strategies could include: targeting areas with high concentrations of ethnic minorities, engaging with community/faith leaders, ensuring all research documentation is in a variety of languages and that translators are available for patients who are not fluent in English.

5.1.4 Past medical history

The majority of participants had documented past medical history which is associated with the development of PAD. Over two thirds of participants (n=23, 68%) had history of hypertension; nine participants (26.5%) had history of diabetes; one participant (2.9%) had previous cerebral vascular accident (CVA) or transient ischaemic attack (TIA); 12 participants (35.3%) were known to have ischaemic heart disease (IHD)/angina/myocardial Infarction (MI). As previously discussed in section 1.8.2, there are strong links between the presence of cardiovascular disease and PAD (Criqui and Aboyans, 2015). Apart from hypertension, the prevalence of these risk factors in the study sample was similar to that of previous studies in similar groups of patients (Dopheide et al., 2016, Collins et al., 2005, Lane et al., 2014).

The number of participants in this research with hypertension was higher when compared to other studies. The prevalence of hypertension (on presentation) in patients with IC has previously been reported as between 35% to 55% (Singer and Kite, 2008, Clement and Debuyzere, 2007, Hirsch et al., 2001, Makin et al., 2001, Dopheide et al., 2016). It is known that hypertension is the most common risk factor for developing cardiovascular disease (Bennett et al., 2008). The link between hypertension and PAD is clear, due to the fact that hypertension contributes to the pathogenesis and progression of atherosclerotic disease (Alexander, 1995). Additionally, hypertension alone is associated with a 2.6-fold increase in adjusted risk for developing PAD (St-Pierre et al., 2010). It is unclear why there is a high proportion of participants within the study sample who had hypertension. One reason for this increased prevalence may be the small participant numbers involved, which may amplify the

concentration of patients with hypertension. Alternatively, the elevated proportion of participants with hypertension could be a reflection of the specific population from which the recruitment was undertaken, as the occurrence of cardiovascular disease within Yorkshire (where this research was undertaken) is 4% higher than the national average (Bhatnagar et al., 2015).

5.1.5 Smoking

Amongst patients with PAD, an estimated 80% report current or previous smoking (Meyers et al., 2009, Smith et al., 1990). Within the current study sample, 85.2% were either active smokers (n=6, 17.6%) or previous smokers (n=23, 67.5%). These are only slightly higher than the reported levels in other studies, and can be accounted for by the slightly higher prevalence of smoking within the geographical location of this study (24.8% of all adults), compared to the national statistic of 19.5% of all adults (Wakefield Council, 2014).

Smoking is a well recognised risk factor for the development of arterial disease (Norgren et al., 2007). The single greatest opportunity to improve health and reduce premature deaths is the modification of smoking behaviour (Black III, 2010). In one study (St-Pierre et al., 2010), smoking cessation decreased the long-term risk of amputation and secondary cardiovascular events. After one year of complete smoking cessation, the risks of progression of PAD returned to that of patients who had never smoked (St-Pierre et al., 2010). There is debate within the literature as to whether smoking cessation alone leads to improvement in symptoms of IC. Dickinson et al. (2008) stated that smoking cessation improves long-term outcomes and improves walking distance. However, previous studies (Girolami et al., 1999) question the findings of Dickinson et al. (2008). Girolami et al. (1999) disputed the true mechanisms of improvement to walking distance, stating that successful smoking cessation is associated with other lifestyle changes, and any favourable results in improved walking ability could be a result of other factors, as opposed to the smoking cessation in isolation.

Nevertheless, whether smoking cessation or confounding factors are responsible for the improvements the act of smoking cessation does result in rapid improvement of severe PAD symptoms and increased walking distance (Powell et al., 1997, Quick and Cotton, 1982, Fowkes et al., 1992). Therefore, any patients who had successfully stopped smoking during the period of this study could have reported improvements in symptoms which were attributable to stopping smoking. Prior to recruitment to this research, study participants were seen and assessed in a vascular specialist clinic. During this clinic appointment, the diagnosis of PAD was established, and risk factor management was commenced, which included smoking cessation advice and signposting to smoking cessation services. Consequently, during the duration of the research, the participants' smoking status

may have changed, and this have could resulted in a positive impact on their ability to walk. To monitor this, smoking status was reported at baseline, and at each follow-up visit the participants were questioned as to whether there had been any changes in their smoking status. The participants were not encouraged further to stop smoking, and a record of their status was documented at each follow-up visit. During the follow-up period, no participants changed their smoking habits, so any improvements in symptoms were not related to smoking cessation.

5.2 Best medical therapy

Despite increasing awareness and high prevalence of PAD within the community, there remains inadequacies in risk factor management in primary care (Zeymer et al., 2008, Oka et al., 2012). As previously discussed in Chapter 1.9.1, because of the strong association between PAD and cardiovascular mortality, patients with PAD require 'best medical therapy'. This is a term used to describe a range of approaches including the prescribing of antiplatelet agent and statin therapy, and modification of any risk factors. 'Best medical therapy' is designed to reduce the progression of disease and prevent secondary cardiovascular events. The results of this study demonstrate there are still areas of improvement needed within primary care to ensure patients have adequate '*best medical therapy*'. Five (15%) participants were not prescribed any form of statin lipid-lowering therapy at the time of enrolment, and five (15%) participants were not prescribed any antiplatelet/anticoagulant therapy. These results highlight that improvements to medical management are still required; this lack of appropriate medical management is a lost opportunity in aiding the prevention of secondary cardiovascular disease/events.

The initial demographic of the participants revealed evidence of a failure to identify or optimise hypertension. On initial review, 26 (76.5%) participants had a systolic blood pressure above 140 mmHg, indicating hypertension. However, it is acknowledged that this hypertension assessment is based on a single blood pressure reading, whereas the diagnosis of hypertension usually requires a series of blood pressure measurements over a number of time points (NICE, 2016b). The need for multiple blood pressure measurement is required, as a single blood pressure reading may be elevated for a number of reasons, including stress, anxiety, or 'white coat syndrome', and may not necessarily mean that the patient has sustained hypertension.

Of greater concern is that out of the 27 (79.4%) participants who were receiving medication for a previous diagnosis of hypertension, 22 (81%) remained hypertensive with a systolic blood pressure greater than 140 mmHg. This is indicative of poorly controlled hypertension as a result of inadequate/wrong medication or non-compliance with treatment. Hypertension is the most common

modifiable risk factor in the development of cardiovascular disease (Oparil and Schmieder, 2015), and despite the plethora of evidence for hypertension and the variety of treatment options available, optimisation of blood pressure remains a challenge (Heagerty, 2006).

Non-adherence to the antihypertensive agent within drug monitoring studies have highlighted that between 25-65% of patients are non-compliant with hypertensive medication (Tomaszewski et al., 2014, Jung et al., 2013, Ceral et al., 2011). However, practitioners should refrain from labelling patients as non-compliant. Rather, care and advice should be focused on the patient-practitioner relationship, aiming to improve adherence through the promotion of positive health outcomes (Gould and Mitty, 2010). Practitioners should also reaffirm with the patient that optimisation of blood pressure control reduces the incidence of stroke, myocardial infarction or heart failure; reduction of 35–40%, 20–25% and above 50% respectively have been found in these conditions (Neal et al., 2000). Even a small reduction in systolic blood pressure has been identified to have significant health benefits. Estimates indicates that when a patient has a systolic blood pressure between 140–159 mmHg and are able to sustain a reduction of just 12 mmHg, over a 10-year period one death in every 11 patients treated will be prevented; and that if another cardiovascular disease, such as PAD, is already present, this ratio improves to one life saved for every nine patients treated (Ogden et al., 2000).

5.3 Arterial disease baseline information

The majority of participants (31; 91.2%) experienced claudication of their calf, with only two (5.9%) participants expressing thigh pain and one (2.9%) experiencing both thigh and calf claudication. Norgren et al. (2007) highlighted that the calf is the most common location for claudication, affecting 3-5% of the adult population, whereas thigh claudication is relatively rare.

Thirty participants (88%) had suspected superficial femoral artery disease (SFA) or popliteal artery disease. The location of disease had been confirmed by radiological imaging in 32 (94.1%) participants, with the most common imaging modality being duplex ultra sound scanning (24 participants; 70.6%). The requirement for imaging was not part of the research protocol. However, many participants (32; 94.1%) had undergone imaging as part of the normal clinical pathway prior to recruitment to this study, the imaging provided evidence of the presence of arterial disease. In two patients, there was no form of imaging undertaken. Subsequently, the diagnosis of arterial disease was based on practitioner assessment through assessment of patients' symptoms and clinical findings. For future studies, it is recommended that imaging should be undertaken as this adds a level of confirmation and assurance to the practitioners' diagnosis.

Half of the participants (17) were newly diagnosed with PAD; the remaining 17 had been previously diagnosed with PAD. Of the 17 participants with known PAD, 11 (64.7%) had undergone previous surgical or endovascular intervention. However, their symptoms had recurred or the intervention had not resulted in improvement in symptoms, highlighting that long-term success of both surgical and endovascular intervention cannot be guaranteed. Numerous follow-up studies of patients who have undergone surgical or endovascular intervention report that patency rates at two years can vary immensely: femoral popliteal bypass is recorded to be around 49%, endovascular stenting 67%, and balloon angioplasty as low as 37% (Met et al., 2008, Schillinger et al., 2006, Malas et al., 2014). If the re-vascularised artery is no longer patent, this will result in the return of patients' symptoms. Additionally, it is important to remember that frequently the severity of infra-popliteal disease abolishes most, if not all, of the named vessels, making mechanical revascularisation impossible (White and Gray, 2007). For the reasons of both practicality and long-term benefits, alternative treatment methods, such as CVT, to improve walking distance in patients with claudication may hold advantages.

5.4 Baseline claudication information

Half (17) of the participants were experiencing bilateral claudication at the outset of the study, which affects gait and walking distance more severely than unilateral claudication (Chen et al., 2008). Bilateral claudication is well described within the literature. However, its prevalence has not specifically been documented (Ballotta et al., 2003). Participants of the current study who were experiencing bilateral claudication were asked to identify the worse leg in terms of walking distance. This limb was treated with CVT. This was a subjective decision by the patients, and so there was no assurance that the CVT was indeed being applied to the leg which limited walking distance. Arguably, the non-treated leg may have affected accurate measurement of improved walking distance, as this may have continued to limit exercise. To take account of this, at each follow-up visit the patient was asked whether it was the treated leg that forced them to stop walking. If this was not the case, the time at which they stopped walking/felt pain was recorded and classed as 'censored data', meaning that the participant could at least walk for the time recorded. However, the participant may have been able to walk further, as the treated leg did not cause the stopping of the walking.

For the participants with bilateral claudication, it was decided to only treat one leg, due to the time commitment required to undertake the CVT therapy. To have both legs treated would have required treatment for two hours per day, due to the device being wide enough for only one leg at a time. Due to the high prevalence of bilateral symptoms (50% in this study sample), it would be worthwhile

considering whether a device which was wide enough for both legs was feasible to design and operate. This would allow treatment of both legs simultaneously, eliminating the additional time currently required to treat both legs.

The median pain-free walking time at baseline was 82 seconds (range of 35 seconds to 220 seconds) and the median maximum walking time at baseline was 186 seconds (range of 70 seconds to 450 seconds). This emphasises the true impact of IC on patients' walking ability. Two participants could not complete the baseline walking assessment, due to chest pains whilst undertaking the assessment. These same two participants failed to complete walking test at any of the follow-up assessments. They were, however, able to provide measurement for ABPI/systolic pressure included in the data analysis. For future studies, it may be helpful to add 'able to perform walking assessment' as part of the inclusion criteria, to ensure that data can be collected from all participants recruited.

5.5 Baseline ABPI measurement

The median ABPI in the treated limb at initial assessment was 0.63 (range of 0.24 to 1.09). As previously discussed in section 1.7.1, an ABPI below 0.9 is diagnostic of PAD (Norgren et al., 2007). Thirty participants (88%) had an ABPI below the 0.9 level, additionally, in isolation a reduction in ABPI has been found to be an independent predictor of mortality, with the lower the ABPI the greater the risk of death (Leng et al., 1996, Gardner et al., 2008, Mlacak et al., 2006, Criqui and Aboyans, 2015, Feringa et al., 2006, McKenna et al., 1991, McDermott et al., 1994). The average ABPI of participants within this study highlights the increased risk of earlier mortality faced by patients with IC. Two participants had incompressible arteries resulting from calcification of arterial vessel wall, so their ABPI could not be calculated. In patients with arterial calcification, the ABPI becomes impractical and non-diagnostic (Al-Qaisi et al., 2009). In these two participants, the presence of arterial disease was confirmed using imaging. Two (5.9%) participants had a normal level of ABPI, however, they had evidence of PAD on imaging. ABPI measurements in this study were taken at rest. The sensitivity of resting ABPI measurement in patients with low grade stenosis has been questioned (Stein et al., 2006). Carter (1972) points out that the use of post-exercise ABPI measurement can unmask patients with mild PAD. Post-exercise ABPI has been shown to have a slightly greater correlation of detecting PAD. When compared to Duplex ultra sound scanning, post-exercise ABPI detected 85% of cases compared to 83% in the rested ABPI group (Allen et al., 1996). Nevertheless, there are limitations with post-exercise ABPI including: the availability of exercise area; difficulties when patients have bilateral disease (as the most symptomatic limb will be a limiting factor); and it may not be appropriate/possible in patients with poor mobility or comorbidities. Both resting ABPI and post-

exercise ABPI have been used in previous studies exploring claudication (Cunningham et al., 2012, Murphy et al., 2012, Bronas et al., 2011, Treat-Jacobson et al., 2009). Taking into account that the detection rate is only slightly increased in the post exercise ABPI group and the limitations in general with ABPI and specifically with exercise ABPI, resting ABPI does seem appropriate for any future studies, especially if a form of imaging is required at recruitment, so that PAD will be confirmed on imaging, and not alone through ABPI assessment.

5.6 Baseline systolic leg pressure

Baseline systolic pressure was recorded due to the limitations with ABPI as explored in Chapter 3. The main limitation of ABPI is thought to be due to ABPI being a ratio derived from two separate measures (brachial and ankle measurements). Therefore, ABPI potentially fails to isolate the specific change to the ankle/leg pressure. This is mainly due to its reliance on the brachial pressure, which makes subtle differences questionably more difficult to identify. For these reasons, systolic leg pressure measurement was also recorded and analysed separately from ABPI. Systolic leg pressure in isolation has been reported in previous studies investigating treatments for IC (Khurana et al., 2013, PACK investigators, 1989). However, the number of papers including systolic leg pressure are considerably lower than those reporting ABPI. The sensitivity of ABPI to detect progression or improvements in disease has been questioned by Caruana et al. (2005). They found that the magnitude, as well as time scales, over which increases to ABPI occur following intervention depend upon the extent of the underlying disease, as well as the type and extent of the intervention. Even after femoral-popliteal bypass surgery, where arterial flow is fully restored, one would expect a near instantaneous rise in ABPI to normal value but in fact it can up to four hours before ABPI reaches normal values (Caruana et al., 2005). Furthermore, evidence supports the hypothesis that ABPI may continue to raise for several months following successful bypass surgery (Caruana et al., 2005). The ability of ABPI to identify improved perfusion through collateral vessels has also been examined. Caruana et al. (2005) states that the effects of collateralisation would be under-represented by changes in ABPI. It could therefore be questioned whether systolic leg pressure would be sensitive enough to pick up changes in collateralisation, as this relies on similar methods of measure to ABPI. However, due to systolic leg pressure being an independent value and not divided by the brachial systolic pressure, it may be more appropriate for studies investigating improvement in claudication symptoms through the mechanism of collateral formation.

5.7 Recruitment

The recruitment of participants into this current study was slower than expected, taking 14 months to recruit 34 patients. Problems with recruitment to research projects is not uncommon (Badger and Werrett, 2005). Over the study period, many patients were screened for recruitment into this study, with many failing to meet the inclusion criteria. The most common causes were either: that the disease was greater than Fontaine's classification stage II A or stage II B (patients were experiencing rest pain or ulceration); or that there were absent or reduced femoral pulses. Another reason that anticipated recruitment was slower than expected could be that the United Kingdom funding system places health care budgets within local primary care groups. As a result, referrals into secondary care are not certain and are often dependent on General Practitioner decision-making. This could result in reduced referral rates for patients with simple claudication (Greenhalgh, 2008).

During the recruitment phase, 22 potential participants declined to participate in the research, even though they did meet the initial screening with the inclusion and exclusion criteria. The most common reason for not wanting to be involved included: 15 patients (68%) were 'not interested' in taking part in a research trial, three patients (14%) wanted to be listed for intervention, and two patients (9%) were concerned about the number of follow-up appointments and the need to return to the out-patients clinic monthly. One patient did not provide a reason. Guidon and McGee (2013b) highlight that recruiting patients with PAD into research is challenging. In their randomised trial comparing supervised exercise with standard care, they screened 548 patients, with only 44 being eventually recruited, a recruitment rate of only 8%. The reasons for such low recruitment rates are down to the frequency of comorbidities and lack of patient motivation (Barbosa et al., 2015, Bartelink et al., 2004). The rate of recruitment into this study was on average 2.4 participants per month, with 61% of patients approached agreeing to participate. It is acknowledged that the rate of recruitment may have been affected by the fact that the research was carried out by one individual rather than a research team. Time restrictions were associated with the research being conducted by a single researcher; having a team of researchers would have allowed for more potential participants to be approached and screened in a range of appropriate vascular clinics. However, these experiences provide an understanding as to how to effectively plan the recruitment phase in future research studies for this population. Strategies should include opening research to more vascular centres, involving GP surgeries in the recruitment, and advertising the research directly to the patient through the media.

5.8 Primary outcomes

5.8.1 Change in pain-free walking time between baseline and week 12

The primary outcome measure of this study was the change in PFWT from baseline to 12 weeks (i.e. the end of the treatment phase), after the subject received vibration therapy for 30 minutes twice a day. All participants received CVT. The main comparative analysis was concerned with the comparison of the PFWT from baseline to 12 weeks and MWT over the same time frames. Of the 30 participants (88%) who provided valid measurements, 29 (97%) improved their PFWT, with an average improvement of 215% in PFWT from baseline. However, the range of change in PFWT from baseline to 12 weeks was -8% to 1005%, meaning that for one participant, PFWT actually decreased by 8%. Four patients were unable to complete the walking test at 12 weeks, and it was not possible to assess whether their walking distance improved, remained the same or deteriorated. Statistical analysis showed significant difference from baseline to week 12 ($\chi^2_{(1)}$=25.6; p<0.001) (Figure 4-3). These results were surprisingly convincing considering the low numbers of participants and were not expected due to this being a feasibility study.

The average increase in PFWT was 215%, this level of improvement is comparable to previous findings from other research investigating exercise therapy for the treatment interventions for IC. Stewart et al. (2002) reported average improvement of 120% from supervised exercise. Furthermore, a systematic review of the evidence for the Cochrane group by Lane et al. (2014) showed supervised exercise has a positive effect on walking ability in the range of 50% up to 200%. The level of improvements found within this study is at the higher end of this scale.

This study measured walking time rather than distance, whilst previous studies investigating treatments of IC report either walking time in minutes/seconds (McDermott et al., 2008, Hiatt et al., 1994, Mika et al., 2005) or walking distance in metres (Collins et al., 2005, Guidon and McGee, 2013a, Kakkos et al., 2005, McDermott et al., 2009). There are though practical advantages in measuring time rather than distance, as this is easier to undertake, does not require a measured walking circuit and arguably provides a more accurate measurement of walking ability as dependent on individuals walking speed.

5.8.2 Change in maximum walking time between baseline and week 12

The second primary outcome measure of the study was the change in MWT from baseline and at 12 weeks. Twenty-three (67%) participants had a recorded improvement in their MWT, with an average improvement of 161%. However, in four participants (12%) there was a decrease in their MWT. The

range of change in MWT was -37 % to 488%. For those that were able to complete the walking test, the results showed a statistically significant difference between comparison time points at baseline and week 12 ($\chi^2_{(1)}$=15.36; p<0.001) (Figure 4-15). The level of improvement of 161% remains within the scale of improvements seen with exercise programmes (Lane et al., 2014). One participant recorded a 488% improvement in MWT, which is greater than the effects seen with exercise. The number of participants who could not provide data related to their maximum walking time (due to either not being able to take part or the test having to be stopped as a result of chest pain, muscular skeletal pain, breathlessness or being unsteady on feet) highlights the comorbidities and poor general health of this patient group.

Natural improvements to walking distance are not expected. Aquino et al. (2001) published a large series study of over 1244 patients following them for a period of 15 years, and showed that without treatment, patients with claudication have an average decline in walking distance of 9.2 yards per year. The reason why there was an improvement in PFWT and MWT is unclear. There may be an association with CVT, but this cannot be proven or disproven in this feasibility study. To accept the hypothesis that CVT improves PFWT and MWT in patients with IC requires further research in the form of a randomised controlled trial. There are many other variables within the research which may explain these results, including the choice of measurement for walking, researcher/participant relationships, and placebo effect. These will be discussed further within the limitations of this study.

Equally, the reason why four participants were found to have a reduction in walking ability is also uncertain. The degree of deterioration was up to a decrease of -37% in walking ability compared to baseline. The participants recruited did have a varying degree of symptom severity and this could have influenced the findings: some patients had severe limitation in their ability to walk distance, where others were able to walk further. The participants who had a deterioration in walking ability were those that had the shortest walking times at the start of the study. It may be useful in future studies to stratify patients into different categories, according to their PFWT, to try to investigate this further.

5.9 Secondary outcomes

A number of secondary outcomes were measured as part of this study. Discussions relating to these are presented below.

5.9.1 Change in walking time between baseline and week 36

It was important to assess whether any changes seen within the treatment phase were sustained once the CVT had been discontinued, as long-term sustainment of improvement is essential for any

potential treatment of IC. Comparison of PFWT data from week 12, at the end of treatment phase, to time points at: week 16 ($\chi^2_{(1)}$=0.28; p=0.593) (Figure 4-11); week 24 ($\chi^2_{(1)}$=0.83; p=0.361) (Figure 4-12) and week 36 ($\chi^2_{(1)}$=3.75; p=0.053) (Figure 4-13), showed no evidence of statistical differences. This lack of significance over this time period suggests that the effect observed during the active therapy phase remains largely intact post-active therapy. This provides encouragement that the benefits seen are not short-lived and are more likely to be due to the formation of collateral vessels, rather than related solely to increased level of nitric oxide and subsequent reactionary vasodilation.

Similar results were seen in MWT: time-to-event analysis compared MWT at 12 weeks with corresponding readings at week 16 ($\chi^2_{(1)}$=0.147; p=0.701 (Figure 4-23), week 24 ($\chi^2_{(1)}$=0.780; p=0.377) (Figure 4-24) and week 36 ($\chi^2_{(1)}$=2.743; p=0.098) (Figure 4-24).Figure *4-25*

The results again showed no evidence of a statistically significant difference between comparison time points, suggesting that the benefits observed at the end of week 12 are sustained.

The impact on patients' walking ability is a paramount outcome for any treatment for IC. This is best expressed in percentage improvements in walking ability. At the end of week 12, participants' mean PFWT had increased by 215% and continued to improve by week 36, with mean improvement in PFWT increasing by 270% compared at week 36 compared to baseline. Similar improvements were seen with participants' mean MWT increasing by 161% from baseline at week 12 and 193% at week 36. This demonstrates that the main improvements occurred in the 12 weeks of active therapy, with some additional improvements post active therapy. Importantly there was no evidence that the change diminished over time.

5.9.2 Overall changes to walking ability

It is interesting to see that improvements continued once CVT therapy had stopped. However, these changes during the post-active therapy phase are smaller compared with the changes observed during the active therapy period. This effect could be explained by patients being able to walk further and, therefore, potentially more likely to exercise more, as they would no longer be experiencing intense pain at short distance. This increase in level of daily activity would improve the natural rate of collateralisation and continue the patient's upwards trajectory of improvement.

Consideration must be given to the expected natural improvements in functionality amongst participants with PAD and IC over time, especially due to the absence of a control group in this study. Patients with IC who do not undergo any form of treatment can show stabilisation or even improvements of leg symptoms over time (McDermott, 2013). However, this is thought not to be due

to an increase in blood flow, but to be due to patients slowing their walking speed and limiting walking activity in order to avoid leg symptoms (McDermott, 2013). When formally assessing patients, who reported improvements in symptoms using the 6-minute walking test, McDermott et al. (2010) found no evidence of increased walking ability over a 7 year period, instead, finding evidence of a functional decline in walking ability. The majority of claudicants (70-80%) stabilised over a five-year period, with 10-20% going on to show worsening symptoms and 5-10% developing critical limb ischaemia (Leng et al., 1996, Hirsch et al., 2006). Even if patients' walking distance appears to be stabilised, there was, on average, a slight decline in walking distance of 8.4 metres per year (Aquino et al., 2001). Therefore, natural improvements are unlikely to explain the results seen in this study. Consequently, it is feasible that the observed improvements seen are due to the CVT intervention. However, this has not been proven and the precise mechanism of improvement is unknown.

In this study, a number of participants failed to complete the walking tests. This reinforced the difficulties with this group of patients being able to participate in exercise therapy. For future studies, it would be worthwhile to undertake a form of cardiovascular screening to ensure that potential candidates are able to fully participate in the research. However, this process of screening has limitations, as this will result in a study group which is not truly representative of the whole claudication group, as it will exclude patients with the most severe limitations on walking distance and those with multiple co-morbidities.

Within the treatment phase of this study, no participants dropped out of the study. Conversely, during the follow-up phase there were issues with drops outs/missing data/failure to attend follow-up visits. The amount of missing data increased over the time of the follow-up period, affecting the number of valid measurements analysed to formulate the long-term follow-up data. At week 12, 30 measurements were analysed and this number dropped to 24 measurements at week 16. The number of valid measurements then fell again to only 18 measurements by week 24 and week 36. As previously discussed, not all the missing data within this study was due to attrition, as some data was missing due to participants not being able to complete the walking. There were though 12 participants who dropped out before the final 36-week follow-up, a long-term dropout rate of 33%. The level of missing follow-up data may compromise the validity of the long-term results of this study, as there is no way of telling whether the patients who dropped out of the study are different to those who remained. It is suggested that a 5% loss in follow-up leads to an element of bias within the research, whereas a greater than 20% drop out poses a serious threat to the validity of any findings (Sacket et al., 1997). However, it is important to remember that even small portions of patients lost to follow-up can cause significant bias (Bhandari et al., 2001). The reason for the increase in missing data is thought to be

multifactorial. One of the issues could be the number of follow-up visits required. Participants were followed up on four separate occasions once the therapy had stopped. Potentially, this number of follow-up visits were not required and participants could have lost motivation to attend the appointments once the therapy had stopped. For future studies, it would be worthwhile to consider reducing the frequency of follow-up visits to reduce attrition, and reviewing other strategies to improve long-term follow-up compliance. However, it is important to remember that the number of follow-up visits required is often dictated by the information required by the study; however, there needs to be a balance between the need to generate meaningful data and limiting the attrition rate.

Three participants withdrew from the study at week 16 to undergo an angioplasty, as they were unsatisfied with the results of the CVT and their symptoms continued to negatively impact on their day-to-day living. Each of these three participants had an improvement in either their PFWT or MWT; however, the real term improvements ranged from 37 seconds to 59 seconds. In one case, this amounted to a doubling of walking distance, but even at this level of improvement the participant was still only able to walk maximum of two minutes without having to stop. This level of inability to walk was severely impacting the patient's ability to work and therefore the patient proceeded with angioplasty. It is important to remember that one treatment option will never be a success for all patients, as patient expectations vary greatly and the impact of IC on patients' quality of life is very individualised.

When assessing PFWT and MWT the test was stopped at eight minutes. If a participant was able to walk further than this, the maximum time in seconds (480 seconds) was recorded as a censored observation. The limiting of the walking test to a maximum of eight minutes was enforced due to practical limitations, taking into account the length of the walking circuit and the availability of time. This approach does not allow for the documentation of the actual PFWT or MWT in all participants; therefore, it is impossible to assess the true level of improvements in all participants. However, it could be argued that if a patient can walk for more than eight minutes without a break, then their claudication may not be severely impacting on their walking ability as such would not require any immediate treatment intervention.

5.9.3 Changes in ABPI measurements

Further secondary outcomes of the study were the changes to ABPI measurements/systolic leg pressure after 12 weeks of CVT therapy. The analysis of changes in ABPI by paired-samples t-testing showed evidence of a statistically significant difference between ABPI at baseline and at the end of

week 12 (t_{29}=-2.008, p=0.046), (Table 4-11). However, there was no evidence of a statistically significant difference, either improvement or deterioration between baseline and week 36 (t_{19}=-1.503, p=0.149) (Table 4-12). The analysis of long-term data was only based on 20 participants, compared to 30 participants who provided data for the comparison from baseline to week 12. It is possible that the reason why there was no statistical evidence of long-term improvement to ABPI at week 36 is the substantial reduction in valid measurements due to participant numbers dropping from 30 to 20. However, it is also feasible that the improvements in ABPI seen at week 12 are not sustained once the CVT is discontinued.

5.9.4 Changes in systolic leg pressure

As previously discussed, in section 3.16.3, it is proposed that the measurement of systolic leg pressure may be more sensitive at detecting subtle changes in blood flow than ABPI measurement. At the end of week 12, 24 (71%) participants had an increase in systolic pressure, pressure remained static in two participants (5%), and in eight participants (24%) there was documented deterioration in systolic pressure. The change in systolic pressure over the 12 weeks was an average increase of 12% compared to the baseline. However, there was great variability in the change to systolic pressure with the range being from -40% to +90%. The reasons for this variation and perceived reduction could be as a result of fluctuations in blood pressure. These fluctuations in blood pressure are normal, necessary and response-adaptive. Systolic blood pressure is the peak force within the arteries at the end of the cardiac cycle, when the ventricles contract; hence systolic pressure is directly related to cardiac output volume which causes the variation in blood pressure.

Systolic blood pressure is known to vary in response to a number of factors including: physical activity, sleep, emotional stimuli, mechanical forces affecting the sympathetic nervous system and non-neural mediators, as well as the timing of antihypertensive medication (Narkiewicz et al., 2002, Guiseppe, 2012). A variation of systolic blood pressure of between 10-15 mmHg throughout the daytime is normal (Rothwell, 2011). Similarly, the variation of systolic blood pressure across a number of different clinic appointments is reported as being on average 10–20 mmHg in the non-hypertensive population (Klungel et al., 2000). It is conceivable that this variation will be greater in the hypertensive group, who made up a large part of the study group. This natural variation in systolic blood pressure over time questions the significance of the findings related to leg systolic blood pressure, and argues against the specificity of systolic leg pressure changes.

Conversely, paired samples t-testing analysis of the change in mean to systolic leg pressure at baseline and week 12 revealed a statistically significant difference in the treated leg (t_{31}=-2.273, p=0.03) (Table

4-13) but in the untreated leg there was no evidence of a statistically significant difference (t_{31}=-0.597, p=0.555) (Table 4-14). This strengthens the possibility of the changes being seen in the treated leg being a valid finding and not, as previously suggested, as a result of fluctuation in systolic blood pressure. It is possible the improvements seen during and after the active therapy may be due to the placebo effect. The placebo effect is a pervasive phenomenon (Hróbjartsson and Norup, 2003), where patients' belief in the treatment can result in clinical improvements. If the participants believed in the treatment, this may have made them feel better so they could have felt that they could actually walk further resulting in increased performance. However, the changes seen in systolic leg pressure are physiological changes that cannot be explained by self-belief. Malani and Houser (2008) suggests that placebos have been reported to have the ability to produce objective physiology changes, but these cases have all been in relation to research into chronic pain, anxiety or fatigue. All of these are areas of health where patients' mind and beliefs will impact on their symptoms. The improvements seen in the systolic leg pressure in this study cannot be explained by the placebo effect; this, combined with the evidence of no change occurring in the untreated limb, implies that the changes to systolic leg pressure are a direct result of CVT.

Furthermore, the changes to systolic leg pressure seen at week 12 appear to be sustained when reviewing the long-term follow-up data. Twenty-seven participants provided valid systolic leg pressure measurements at week 16 and there was no statistically significant difference between this time and week 12 measurements (t_{26}=1.14, p=0.265) (Table 4-18). This suggests that the changes seen at week 12 remain present once the therapy is stopped. However, at week 24 there was evidence of a statistically significant deterioration in comparison with mean values recorded at week 12 (t_{20}=2.361, p=0.028) (Table 4-19). This deterioration was not evident at week 36 where there was no evidence of significant difference between comparison time points at week 12 and week 36 (t_{19}=1.139, p=0.269) (Table 4-20). This implies that the changes made in the first 12 weeks appear to be sustained at week 16, reduce at week 24, but recover again at week 36. It has to be taken into account that there was a gradual reduction in the number of participants who provided valid data throughout the long-term follow-up. This may have impacted on the statistical results, as there does appear to be an overall reduction in mean recorded values over time: at week 12 the mean systolic pressure was 127 mmHg, and at week 36 this had reduced to 103 mmHg. For future studies, the number of potential long-term follow-up drop-outs will need to be considered in order for the study to be appropriately powered, ensuring that the data generated is able to provide firm conclusions about the long-term effects of CVT.

5.9.5 Vibration positioning

A component of this feasibility study was to determine at which location the CVT device should be placed to optimise outcomes. The results demonstrated that participants using the CVT device in the calf area had improved outcomes compared to those using the machine in the thigh (Table 4-21, Table 4-22). However, there were limited numbers in the thigh group: only eight participants used the device on this area, whereas twice as many participants used the machine at the level of the calf. Both groups had improvements in their PFWT and MWT, but the effect was more pronounced in the calf group. The machine was originally designed to be used on the lower leg, and the ergonomics of the machine did make it more difficult to use at the level of the thigh. The reason behind consideration of which is the most effective position to use the CVT machine is related to the potential mode of action of the CVT. It has been proposed that by using the CVT directly around the area of arterial disease (i.e. the thigh region in patients with SFA disease who were experiencing calf claudication), the effect of increasing nitric oxide at level of the stenosis/occlusion would be maximised. This would capitalise on the stimulation of angiogenesis. The results did not agree with this proposal, as those patients who had CVT applied to their calf (the area below the level of disease) had a greater improvement in PFWT and MWT. In previous PAD animal modelling, which showed an increase in blood flow and levels of nitric oxide (Lievens and Van den Brande, 2004, Lievens, 2011), the whole animal was placed on the vibration plate. This made it impossible to assess the impact of positioning of the vibration. Research on healthy humans has been undertaken by Button et al. (2007) who investigated the effect of multidirectional mechanical vibration on peripheral circulation. Their study showed improvements in blood flow in the vibration group compared to the control group. In this study, however, the vibration was applied to the buttocks and the foot/ankle region, with blood flow being measured in the lower limb. Again, it is difficult to assess the impact relative to the location of vibration. As previously mentioned, the CVT machine is ergonomically designed to be applied on the lower limb, and this study has shown that the positioning of the machine under the calf appears to be more beneficial. Therefore, it is suggested that for any future studies, the machine is applied to the calf areas irrespective of the level of disease.

5.9.6 SF-36 quality of life questionnaire

SF-36 has been widely used within PAD research, and its validity has been proven at assessing the burden of disease and treatment benefits specifically in PAD (Amer et al., 2013, Regensteiner et al., 2008, McDermott et al., 2009). Compared to population norms, it is accepted that patients with PAD have a significantly reduced quality of life (Izquierdo-Porrera et al., 2005). Furthermore, patients with

IC in a community setting have also been found to have impaired health related quality of life (Dumville et al., 2004). When patients are experiencing IC, it is not only their physical functioning that is affected by the lower limb symptoms, but a PAD diagnosis and its associated symptoms can also affect patients' psychological well-being and mental health (McDermott et al., 2003, Breek et al., 2002).

In this study, the overall grand mean of physical component summary scores was 42.7; and the overall grand mean of mental component summary scores was 50.1. Remembering that with norm-based scoring an average score is 50, anything above this level is better than national average, whilst anything below is worse than national average for the general population. The results indicated that overall the participants had average mental component summary scores but lower than average physical component scores. This is unsurprising when considering the nature of PAD and the limitation which IC places on patients' physical abilities.

Analysis of the score data revealed evidence for a statistically significant difference within physical functioning scores evaluated at the measured time points (p=0.03), (Table 4-23). However, this may not be considered significant under the application of a Bonferroni or similar correction for multiple testing. Physical functioning at baseline was 35.34 (SD 8.93) increasing at the end of active therapy, week 12, to 44.52 (SD 9.11), over the follow-up period there was a decline in scores; however, at week 36 the scores were 39.55 (SD 12.37), which is still an increase from the starting baseline. Physical functioning scores are calculated by the participants answering questions about how their health limits activities. Examples of the type of questions asked in the questionnaire include: "How easy do you find vigorous activities?"; "Does your health limit you in walking more than one mile, more than several hundred yards or more than one hundred yards?". It is therefore not surprising that, relating to PAD, it is the physical functioning where improvements in quality of life are likely to be seen. In the physical component summary, which is made up by combining three other scales (physical functioning, role limitations due to physical health, and bodily pain) there was noted improvement over time (39.30 (SD 11.67) at baseline, to 45.07 (SD 8.68) at week 12 and 43.40 (SD 11.11) at week 36), but this was not statistically significant (p=0.26).

The improvements seen in the physical scores at the end of the active treatment phase do start to regress throughout the follow-up phase; however, compared to baseline, improvements in physical functioning, role physical and physical component summary scores are still evident at week 36, with the improvement in physical functioning being statistically significant. However, there is a possibility that if longer follow-up had been undertaken over time, the benefits seen could have eroded.

As part of an investigation of the improvement in quality of life through the use of exercise programmes, Guidon and McGee (2010) found that physical functioning was the most sensitive measure in relation to PAD. This review of the literature reported that 11 out of 16 studies demonstrated an improvement in physical functioning scores. However, this increase in score did not always relate to an improvement in overall physical component summary scores. This finding is consistent with the findings of this current study. Significant improvements have, however, been reported in physical component summary scores in a number of other studies (Patterson et al., 1997, Collins et al., 2005, Nicolai et al., 2010), and it is possible that the small numbers of participants within this feasibility study hindered the overall physical component summary score from reaching statistically significance.

Within the study period there was a non-significant decline in general health scores. This indicates that the participants perceived their general health to be deteriorating, despite the evidence that their physical ability was improving. Additionally, the psychological and emotional consequence of PAD is clear within the results. Both the social functioning and role emotional scores were below average at the start of the study. Throughout the study period there was some fluctuation in measurements. However, by the end of the study both measures had reduced from 48.46 to 41.05 for social functioning, and 44.33 to 40.85 for role emotional. The mental health component summary score, which is devised from results of scores from social functioning, role limitations due to emotional problems and mental health, also showed a reduction over the time of the study. At baseline, mental health component summary was 53.90, indicating better than average scores; however, over the duration of the study this decreased to a below national average score of 46.04, although the changes were not statistically significant. A possible explanation for this reduction in mental health components of quality of life could be the overall impact of other coexisting diseases and the awareness of increased morbidity/mortality rates. Patients with IC are known to have worse quality of life than members of the general population, and this includes all aspects of their lives which are affected, not just physical functioning and pain (Pell, 1995).

As previously discussed, SF-36 has been used in a number of previous studies investigating IC. However, generic health related quality of life measures, such as SF-36, are theoretically less responsive to change compared to disease-specific measures (Vemulapalli et al., 2015). Additionally, due to the overall reduction in quality of life seen in patients with PAD, identifying improvements related to intervention through generic tools can be difficult. In studies which use disease-specific quality of life tools, statistical improvements have been demonstrated, whereas SF-36 failed to identify any change (Hoeks et al., 2009). The sensitivity of SF-36 may be seen as a limitation in this

study. Alternative measures of generic quality of life are available, including the EQ-5D instrument. However, the most frequently used quality-of-life evaluation tool in PAD studies is SF-36 (Poku et al., 2016). Additionally, SF-36 has been shown to provide a greater level of sensitivity, compared to EQ-5D, when used in the PAD population (Poku et al., 2016).

Disease-related questionnaires have been formulated specifically for the measurement of quality of life in patients with IC. The most frequently used within the literature are the Kings College Hospital vascular quality of life questionnaire (VascuQol), and the walking impairment questionnaire (WIQ) (Poku et al., 2016). Key advantage of disease-specific instruments is the focus on specific symptoms of the disease. Hoeks et al. (2009) state that disease-specific instruments have a greater sensitivity and responsiveness to clinical change, and therefore may be more sensitive in measuring treatment benefits compared to generic tools. However, Hoeks et al. (2009) go on to highlight that there may be still some value for generic quality of life assessments, especially when comparing health status across difference diseases.

There are, however, limitations with disease-specific tools, as they provide a measure of condition-specific mobility relevant to IC but do not include any general quality of life measure to ascertain the impact of PAD in general. Poku et al. (2016) state that the SF-36 holds advantages over disease-specific quality of life tools, as the domains within SF-36 provide a broader measure of quality of life and include further questioning in important domains of pain and mobility. One major benefit of SF-36 is that the questionnaire is self-administered. The WIQ can also be self-completed; however, evidence suggests that the number of errors occurring during self-completion was unacceptably high (Mahe et al., 2011).

There appear to be advantages of both disease-specific and general quality-of-life assessment; therefore, it is unsurprising that a number of studies use both a disease-specific and a general measure (Treat-Jacobson et al., 2009, Izquierdo-Porrera et al., 2005, Mazari et al., 2010, Dawson et al., 2000). For future studies, it would be worth considering using both general and disease-specific quality of life tools. This dual method is encouraged by Vemulapalli et al. (2015), who state that using both disease-specific and general quality-of-life measures increases validity of findings.

5.9.7 Treatment compliance

Patients' compliance to any treatment is important, as non-compliance is associated with increased costs and lack of potential treatment benefits (Haynes et al., 1996). In terms of treatment for claudication there are problems with adherence to the currently recommended supervised exercise programmes (Muller-Buhl et al., 2012, Kruidenier et al., 2009, Treat-Jacobson et al., 2009, Nicolai et

al., 2010). Therefore, monitoring compliance with alternative treatments is vital. Within this study, the participants were provided with the device to use at home and the general compliance with CVT was high. There were no participants who dropped out during the treatment phase. This indicates the high degree of participant acceptability of the treatment, which is in stark contrast to supervised exercise programmes, where attrition loss during the treatment phase is very common (Muller-Buhl et al., 2012). The high compliance to CVT is a great advantage to ensure resources are used appropriately and to maximise treatment benefits.

Individual participant use of the CVT machine was recorded within the machine device counter, this allowed usage to be monitored. As previously discussed in section 3.18.3, if participants fully adhered to the recommended twice a day usage for a period of 12 weeks, the device counter should read 168. A degree of variation was allowed in the form of a 20% leeway either side of the 100% compliant value of 168. This degree of variation was based on methodology for medication compliance (Jin et al., 2008). It is acknowledged that compliance in relation to medication is different to compliance with treatments such as CVT, but in the absence of data relating to the degree of appropriate variation of use in relation to non-medication treatments, the 20% leeway of compliance was deemed appropriate. At this level, 26 participants (76%) were said to be compliant with the CVT treatment. Eight participants (24%) had usage outside this level, but interestingly half of these participants had a higher level of usage than that recommended. It is possible that these participants were using the machine more frequently than was recommended. Alternatively, this finding could have been because participants were also using the device on the opposite leg. This could have been the case in participants with bilateral claudication, especially if they believed the CVT was benefiting their symptoms. There could also have been justifiable reasons for the increased use that were unrelated to the clinical study. For example, power cuts or having to break and restart the treatment due to interruptions, or requirements to use the bathroom could also account for increased levels of usage. In these situations, it would mean that the machine would have had to be restarted and this would result in the appearance of increased use.

Unfortunately, there is no assurance through this measure that the participants have actually used the machine, as the device counter simply counted how many times the machine had been turned on and therapy started. The participants could have set the machine going and not applied the therapy to their limbs, or applied the therapy but for a shorter period of time then recommended. The device counter is a crude measurement of usage rather than compliance and has limitations as discussed; however, it does provide some level of information.

5.9.8 Participant feedback

Patient feedback is vitally important within today's NHS, and the patient's voice is now seen as an integral part of treatment decision-making (Department of Health, 2012). To gain feedback from the participants about their experience of CVT, they were asked to respond to three questions:

1. How did you find using the product? - Options available were: "v*ery difficult"*, "*difficult"*, "*neutral"*, "*easy"* or "*very easy"*.

2. Have you been satisfied with the results so far? - Options available were: "*very dissatisfied", "not satisfied", "neutral", "satisfied" and "very satisfied"*.

3. When using the machine was it? – Options available were: *"painful", "mild discomfort", "neutral", "comfortable" or "very comfortable"?*

In terms of ease of use, all the participants found the CVT machine either "easy" or "very easy" to use, with no reports of any participants having any difficulties. This is an important consideration for any treatments where the individual will be applying the therapy in their home setting, as home treatments need to be simple to use for all. One of the issues and reasons why patients are reluctant to undertake exercise therapy is the fact that the exercise stimulates pain. This discomfort is something that is unattractive to many patients. Therefore, gaining the opinion from the participants about how comfortable the CVT was to use was vital. The bulk of the participants (33, 97%) found the CVT either "neutral", "comfortable" or "very comfortable", and only one participant (3%) indicated that they experienced "mild discomfort" when using the machine. This indicated that for the majority, CVT is a comfortable treatment option. This is a huge benefit of CVT when compared to supervised exercise, where all the patients who attend experience a degree of pain due to the nature of inducing intermittent claudication (Brunelle and Mulgrew, 2016).

The participants were also asked how satisfied they had been with the results at the end of week 12. None of the participants indicated that they were either "very dissatisfied" or "not satisfied" with the results, 12 (35%) specified a "neutral" response and 65% (22) of the participants stated they were "satisfied" or "very satisfied" with the results. Of those who indicated they were "very satisfied", they verbally acknowledged that they felt 'cured' and 'had their life back'. These simple questions provide some feedback of the experience of CVT, but lack research validity. To further explore participants feeling of CVT qualitative research is required. Nevertheless, this data has provided important information that CVT therapy is easy to use, comfortable and generally the participants were satisfied with the results.

5.10 Adverse events

During one of the walking tests a participant stumbled and fell, which resulted in bruising to her face. The participant was elderly and rather frail and the fall affected her confidence; she had issues with a fear of falling following this incident. There were no other adverse effects during the trial. It is important that during research any exposure to danger/adverse effects to participants is limited. Patients with IC have a risk of falling due to impaired balance (Gohil et al., 2013, Rafnsson et al., 2009). However, the extent to which balance is affected varies. To ensure that participants are not exposed to harm, it is suggested that for any future research, where some form of walking testing is required, it would be beneficial to introduce a 'risk of falling assessment' at the participant screening stage. These are commonly used within hospital settings, especially within elderly care settings. This assessment may help to determine whether the participant is at high risk of falling and therefore may not be suitable for inclusion in the trial. This would help to eliminate any future adverse research events.

5.11 Immediate benefits

The mechanism of how CVT could improve symptoms of IC, as previously discussed in section 2.5, is not fully understood. One of the mechanisms hypothesised is that physical forces from the CVT, which is known to increase nitric oxide production, leading to vasodilation and improved blood flow (Lievens and Van den Brande, 2004, Maloney-Hinds et al., 2009, Ryan et al., 2000), results in increased muscle perfusion and therefore should improve walking ability. However, this effect of vasodilation has only been documented during or immediately after a period of vibration (Lievens and Van den Brande, 2004). Therefore, this should result only in short-lived improvements in walking ability and not sustained longer-term benefits. To assess whether there were any immediate effects from the CVT at the initial visit, baseline information was gathered from the participants, and then CVT was applied in the clinical setting for a period of 30 minutes. Immediately following this application, the walking test was repeated. The results showed no evidence of a statistically significant difference (at the 5% significance level) in PFWT ($\chi^2_{(1)}$=0.675; p=0.411) (Figure 4-4) or MWT ($\chi^2_{(1)}$=0.009; p=0.926) (Figure 4-16) between baseline and after 30 minutes of vibration. This demonstrated no evidence for any immediate benefits of CVT, disputing the proposal that vasodilation from the CVT in isolation leads to improvements in walking ability.

5.12 Length of CVT treatment

A further objective of this feasibility study was to determine the duration of treatment required to achieve maximum benefits. Throughout the active treatment phase, information was obtained every four weeks. The results showed that, compared to baseline measurements, there was a statistically significant difference in PFWT after 4 weeks ($\chi^2_{(1)}$=9.88; p=0.002) (Figure 4-5). Further improvements were seen in PFWT at week 8 ($\chi^2_{(1)}$=23.2; p<0.001) (Figure 4-6) and these improvements continued in PFWT at week 12, ($\chi^2_{(1)}$=0.675; *p*=0.411) (Figure 4-3). Whilst investigating changes in MWT, there was no evidence of statistically significant difference between baseline and week 4 time points, ($\chi^2_{(1)}$=2.45; p=0.118) (Figure 4-17). However, comparison of MWT from baseline to 8 weeks did show a statistically significant difference ($\chi^2_{(1)}$=11.02; p<0.001) (Figure 4-18), and these improvements in MWT continued at week 12 ($\chi^2_{(1)}$=0.009; p=0.926) (Figure 4-16).

The most predominant effect of change to PFWT was seen within the first four weeks of therapy, whereas in relation to MWT, the results suggested that the main improvements occurred in the first eight weeks of therapy. There may have been further improvements if the vibration therapy was continued longer than 12 weeks; however, over time the degree of improvements diminished, with the largest improvements in PFWT being in the first four weeks of therapy, and the largest improvements in MWT within the first eight weeks. It could therefore be argued that the treatment time may be reduced to eight weeks. This could potentially improve the appeal of CVT as a treatment option for patients.

5.13 Cardiovascular health improvements

Intermittent claudication contributes to the major cardiovascular burden facing the NHS (Bhatnagar et al., 2016). Exercise is known to contribute towards improved overall activity. This increase in activity is associated with enhanced physical function, reduction in cardiovascular events and overall reduction in morbidity/mortality (Garg et al., 2009). However, to gain these improvement in outcomes, patients need to engage and adhere to exercise therapy. It is known that there are difficulties with accessing supervised exercise programmes for patients with IC (Shalhoub et al., 2009), and that simple exercise advice from clinicians does not increase the amount of patient-directed walking (Bartelink et al., 2004, Makris et al., 2012). Additionally, there are problems with engagement, as individuals with IC can lack the motivation to commit sufficiently to exercise therapy (Galea et al., 2008, Guidon and McGee, 2013b). Generally, patients with PAD do not participate in any form of sustained physical activity. Garg et al. (2006) found that patients with PAD are in the lowest quartile

level of physical activity in daily life. Gardner et al. (2008) went further by describing patients with IC as sedentary, as many of them avoid any form of physical activity.

Even taking into account the difficulties with exercise, the overall cardiovascular benefits of exercise should not be understated, as the biggest threat to patients with IC is increased risk of cardiovascular events and early death. Spronk et al. (2005) noted that there was an absence of long-term (i.e. one year or more) outcomes for the benefits of supervised exercise for patients with IC and that taking part in exercise programmes reduced the overall risk of cardiovascular events. Gardner et al. (2008) scrutinised levels of general physical activity in patients with IC and classified them as sedentary or physically active. Patients self-rated their level of actively and were classed as sedentary if they indicated that they avoided physical activity or only undertook light physical activity occasionally. If the patients indicated they undertook moderate physical activity regularly they were classed as physically active. Looking at five-year mortality rates, Gardner et al. (2008) found that those who engaged in physical activity had a lower mortality rate when compared to the sedentary group, and that the protective effect of physical activity remained present, even after adjusting for other known predictive factors of mortality, including age, ABPI and BMI. This suggests that even moderate levels of physical activity are beneficial to patients with IC in terms of overall mortality reduction. Therefore, it is logical that if patients undertake a supervised exercise programme, this would improve the amount of physical activity, the general level of fitness and increase cardiovascular reserve. This should result in a decreased risk of secondary cardiovascular events and improve all-cause mortality rates.

With CVT there is no such mechanism for improvements to overall cardiovascular health. This is an important consideration and a significant limitation of treatment with CVT, as patients with IC are more likely to die of cardiovascular events rather than problems related to their PAD. However, if it is conceivable that patient symptoms of IC improve through the use of CVT, then their general ability to walk will improve. This may stimulate increased levels of physical activity which would then result in enhanced cardiovascular fitness. Gardner et al. (2008) emphasise that even small increases in physical activity levels may benefit the health of patients with IC and reduce their overall mortality risk.

5.14 Barriers to supervised exercise programmes

As previously discussed, there are many barriers to patients undertaking a supervised exercise programmes. These include: the lack of provision of supervised exercise programmes (Stewart and Lamont, 2001, Shalhoub et al., 2009); difficulties in patients accessing local services (Harwood et al., 2016); a general unwillingness to participate (Stewart et al., 2008, Muller-Buhl et al., 2012); high drop-

out rates (Kruidenier et al., 2009) and low completion rates of the recommended 12-week programme (Treat-Jacobson et al., 2009). Additionally, a proportion of patients with IC cannot be referred to undertake exercise therapy (Kruidenier et al., 2009), due to the presence of concomitant disease or comorbidities, such as ischaemic heart disease or diabetic foot complications, where increasing cardiovascular physical exercise through walking may expose the patient to harm.

CVT as a treatment for IC would eliminate many of these issues/barriers. If adopted as a treatment option by the NHS, CVT could be available through simple community prescription (FP10). This would mean that the GP could prescribe the CVT machine, eliminating current difficulties with accessing services and the lack of provision of supervised exercise. As CVT is a therapy that is applied on the limb whilst resting and does not require any physical effort, it is suitable for patients with many other concomitant diseases. This study has shown that CVT is highly acceptable to patients, with 100% of participants completing the 12-week course. This is extremely favourable compared to supervised exercise, where dropout rates have been reported at between 30% and 53% (Kruidenier et al., 2009, Nicolai et al., 2010). Eliminating these obstacles, and therefore increasing the number of patients who can access/participate in treatment for IC, is a huge advantage.

5.15 Cost

Supervised exercise programmes are the recommended first-line treatment option for patients with IC (NICE, 2012). The cost of providing these services (based on three hours per week supervised exercise) has been calculated at £2,306 for the year (Lee et al., 2007). If each session is fully utilised the cost of an individual patient participating in a three-month supervised exercise programme can be as low as £48.06 per patient (Lee et al., 2007). This figure is substantially lower that the projected costs within NICE guidance, which estimate the cost of a 12-week supervision exercise programme to be around £255 per person (NICE, 2014). However, Kakkos et al. (2005) report that the costs could be as much as £500 per patient for a full three-month programme. The variation in costs could be explained by different methods of providing supervised exercise programmes, such as stand-alone programmes or those that are delivered together with cardiac rehabilitation programmes. There is also variation in whether exercise programmes are provided by qualified physiotherapists within hospital gymnasiums or out of hospital in general health centres with the session run by physical trainers rather than physiotherapists. All of these factors can influence the costs.

Quality-adjusted life years (QALY) analysis has been undertaken by a number of investigators and highlights that supervised exercise programmes are cost-effective in terms of QALYs gained (Lee et al., 2007, van Asselt et al., 2011, van den Houten et al., 2016). However, the cost of CVT is unclear. CVT is

currently used within some NHS organisations for the management of lower limb ulceration/oedema management/cellulitis (Johnson et al., 2007). In these cases, the machines are provided on loan for free by Vibrant Medical (the manufacturer of the Vibropulse machine) and the NHS only purchases consumables for the machine. The consumables required include a large absorbent pad which is placed over the sleeve of the machine to capture any exudate from the limb/wound. These covers are single use only and the manufacturer of the machine gains revenue from the re-prescribing/purchasing of these disposable single-use covers. Covers are not required for patients with PAD, as there is no issue with leakage from wounds or infection control, since the skin in patients with PAD is generally intact. The manufacturers of the Vibropulse machine are exploring ways in which CVT could be accessed for patients with PAD. Through communication with Vibrant Medical, the estimated cost of the machine to purchase will be around £180-£200 and they are investigating the possibility of whether CVT could be added to the national drug tariff allowing practitioners to prescribe this therapy in the same way they currently prescribe drugs or appliances. If this is the case, CVT therapy may be a cheaper alternative to supervised exercise programmes. However, there will need to be further studies, ideally randomised control studies, to assess the impact of CVT and these should ideally include evaluation of cost effectiveness and impact on QALYs.

5.16 Recurrence of disease

The return of symptoms is an issue with many of the current treatments for IC (Met et al., 2008, Schillinger et al., 2006, Malas et al., 2014). Within the follow-up timeframe of this current study, there was no evidence of deterioration in walking distance once the therapy was stopped. However, as discussed previously, there are questions about the validity of the long-term results. Additionally, the participants were only followed up for 36 weeks, so longer term information is not available. If the CVT machine is dispensed on community prescription, the machine would be in the possession of the patient and, therefore, if symptoms were to recur, patients could use the CVT machine again. This would not result in additional costs to the NHS. This re-use option is unique to CVT and is not available with supervised exercise or endovascular/surgical revascularisation.

5.17 Statistical approach

5.17.1 Time-to-event analysis limitations

The time-to-event analysis was undertaken due to the expected skewness associated with time recordings, plus the presence of censored data, which occurs when the value of the measurement is only partially known and this was deemed appropriate as time-to-event analysis removes the bias of

censored data events (Collett, 2003). However, one unavoidable limitation of all time-to-event analyses concerns the precision of estimates associated with data obtained from the end of the analysis period. In the current investigation, the proportion of patients successfully completing the walking tests was generally under 50% and under 20% in some cases; i.e. fewer than 10 patients. Hence the uncertainty associated with the accuracy with which these estimates can be obtained increases throughout the eight-minute walking period.

5.17.2 Multiple testing

Uncorrected multiple statistical testing increases the chances of Type 1 statistical error (i.e. the spurious inference of statistical significance). In the current investigation, multiple testing arises from the use of more than one outcome measure (PFWT and MWT), from the analysis of outcomes measured at multiple time points, from the use of a separate testing procedure (the t-test procedure) to measure changes in ABPI/systolic leg pressure, and the analysis of both treated and untreated legs in this procedure.

In general, control of familywise error rates in these situations can be achieved by methods such as the application of the Bonferroni correction, in which *p*-values obtained from individual tests are multiplied by the number of tests conducted which are considered to be *a priori* primary outcomes. However, the Bonferroni method may be over-conservative, particularly when applied to large tranches of analyses.

The current investigation, as a feasibility study, was not generally powered to detect significant effects, and as such the inferences of significance or otherwise were not a key objective of the study. Hence in general, the application of Bonferroni corrections or similar is not considered appropriate in the current investigation; furthermore, analyses conducted based on interim time points, and all tests of ABPI/leg pressure would be considered to be secondary analyses in a full-scale study, and hence should not affect inferences obtained from primary analyses.

Despite the low power of the study, it may be observed from inspection of log-rank statistics that the level of significance of the comparisons between baseline and 4, 8 and 12 weeks is such that each individual comparison would still be considered to demonstrate statistical significance allowing for multiple comparison testing, using the Bonferroni procedure applied across all time-to-event studies.

5.18 Study limitations

The study has several possible limitations. One limitation is the choice of a simple walking test to measure walking time both PFWT and MWT. This method of testing has limitations due to issues with

reliability, comparability with other studies and repeatability. The majority of published studies use a form of treadmill testing to help reduce some of the variables, improving the repeatability and validity of the walking assessment. The use of a simple walking test in this current study does introduce a potential for data collection bias due to the issues with repeatability.

It is well established that the researcher conducting a study can impact the research. This, however, is a more common phenomenon within qualitative research (Al-Natour, 2011). Within this current study, the researcher walked around the walking circuit with the participant to ensure safety and to document the time of pain and time of stopping. There is a question whether the presence of the researcher during the walking test may have influenced the result. The researcher tried to limit conversation to a minimum, but did ask questions such as "Are you OK?" and "Let me know when you have any pain or need to stop". This could be considered a leading question, as such resulting in reporting bias. Additionally, there is a potential for the 'Hawthorne effect' to influence the outcomes. The 'Hawthorne effect' is well-documented within clinical research, it refers to the ways that individuals taking part in research may modify an aspect of their behaviour in response to their awareness of being observed (McCambridge et al., 2014). Within this current research, the participants may have acted differently, perhaps walking further, due to the fact that they were being observed or indirectly encouraged.

The potential for observer bias is also acknowledged, as the researcher was not blinded and had prior knowledge of the research aims, disease status and intervention. As such, these can all influence data recording (Delgado-Rodríguez and Llorca, 2004). The researcher tried to minimise the risk of bias by following standardised protocol for enrolment and follow-up. The potential of reporting bias and observer bias could be reduced by implementing blinding to future studies.

A further limitation is due to the study being conducted at a single NHS site with a single researcher who designed, delivered, collected data and analysed the results. This was inevitable since the research was conducted by a single researcher as part of the PhD process. This does reduce the generalisability of the findings. However, as this was a feasibility study, the research was not intended to evaluate outcomes nor infer generalisability.

A feasibility study was required as the literature search (Chapter 2) identified that there was a lack of robust information in relation to the effects of CVT in relation to the symptomatic management of IC. The purpose of a feasibility study is to evaluate proposed research methods and research integrity. This is an essential step in evaluating study design and aids the contextualisation and

conceptualisation of research proposals. However, by the essence of a feasibility study it is a requirement but also a limitation.

The number of participants included in this study was generally small and the challenges faced in terms of slower recruitment and loss of patients to follow-up are similar to other studies in this patient population (Hobbs and Bradbury, 2003). A large proportion of trials included in the Cochrane review of exercise of IC had small sample sizes, with the majority (15 out of 22 studies) containing sample sizes of between 20 and 49 (Watson et al., 2008). This current study was of a feasibility design so the sample size is not a major limitation, as the intervention was not being evaluated and the focus was on the research design.

A further limitation is the number of missing data points. As discussed, a number of participants could not complete walking tests due to multiple reasons and this led to a reduced number of measurement points. This may have affected the analysis. Patients who suffer claudication are known to have many additional factors that influence their ability to walk and with PAD the more severe the disease progression the more likely patents are to have issues in completing walking tests (Ehrman et al., 2013). A number of other research studies used a walking test as part of the screening process on recruitment, so that if the patient could not complete the walking test they were excluded from the research (Mahé et al., 2011, Treat-Jacobson et al., 2009, Fouasson-Chailloux et al., 2015, Sanderson et al., 2006). However, this process naturally excludes patients with the most severe PAD, and those with major associated health diseases, which makes them unsuitable/unsafe to complete walking tests. This does question the generalisability of the results, as studies following this process are excluding a cohort of patients who potentially are the most severe/complex. The present study did not exclude patients on this basis, so does provide a real-life view of the whole spectrum of patients with IC. However, it did have limitations in terms of outcome measurements.

Additionally, there were issues with failure to attend follow-up visits. A third of the participants (12, 33%) dropped out of the study prior to the final week-36 follow-up visit. It is impossible to tell whether the participants who dropped out of the study were any different to those who remained in follow-up. This void of information does question the validity of the long-term findings of this study. It may be that the number of follow-up visits could have been seen as excessive, as after the therapy was stopped, a further three follow-up visits were included in the research protocol. The final one of these visits was nearly nine months after commencing the study. The number of visits, and time elapsed between visits, could have played a part in why participants failed to attend. Additionally, if the participants felt they were able to walk further, they may have seen the visit as irrelevant as they were

now no longer troubled by IC. Conversely, if the participants felt the therapy had not provided them with any benefits, they may have reached the conclusion that the follow-up visits were a waste of their time.

5.19 Summary

This chapter discussed the findings of this study and outlined their relevance in clinical and research practice. The main findings of the study showed a potential association between cycloidal vibration therapy and improvements in participants' symptoms of intermittent claudication. The results also revealed an improvement in systolic blood flow in the treated limb, which was not identified in the untreated leg, and provides some evidence of an association between improvements and CVT. There are several limitations of this research which have been described and explored. However, this feasibility study has provided vital information which will aid the formulation of a research protocol enabling a study to be performed to investigate whether CVT improves patients' symptoms of IC.

A summary of the findings of the study will be outlined in the next chapter, taking into consideration theoretical implications and providing suggestions for further research.

6 CONCLUSION

This chapter summarises the findings of the study described and discussed within the thesis, considering theoretical implications and providing suggestions for further research. The impact of the findings within the management of intermittent claudication (IC) will be highlighted. The aims of this feasibility study were to:

- To explore the association of cycloid vibration therapy (CVT) in participants' pain free walking time (PFWT) and maximum walking time (MWT)
- To establish optimal CVT intervention
- To establish whether any changes in walking distance are sustained after CVT is stopped
- To establish statistical variability of the primary outcomes

The objectives of this study were to:

- To observe changes in participants' PFWT and MWT
- To establish whether any change in participants' lower limb perfusion occurs
- To determine the duration of treatment required to achieve maximum benefits
- To determine the most effective physical location of vibration therapy
- To determine measurement/equipment suitability to assess a degree of change in clinical and functional status
- To determine the final study protocol

6.1 Summary of study findings

The aim of this research and resultant thesis was to explore the relationship between CVT and PAD and to establish the feasibility of using CVT to improve patients' symptoms of IC. The results of this study highlight that following 12 weeks of active treatment there were improvements demonstrated in participants' PFWT. The degree of improvement in PFWT reached statistical significance ($\chi^2_{(1)}$=25.6; p<0.001, Figure 4-3), even though the study was of a feasibility design and hence not powered accordingly to detect significant effects. Despite this, evidence for statistically significant differences in certain parameters in this study was revealed. This finding likely reflects the substantive improvements seen in participants PFWT. On average, participants' PFWT increased by 215% from

baseline, and this level of improvement is comparable to improvements seen from other treatment options such as supervised exercise (Stewart et al., 2002).

Improvements were also seen in participants' MWT. The differences at week 12 from baseline were showed to be statistically significant ($\chi^2_{(1)}$=15.36; p<0.001, Figure 4-15). There was on average an 161% improvement in MWT. This level of increase remains within the scale of improvements seen with exercise programmes (Lane et al., 2014).

As well as showing no significant reduction in the benefits seen during the active therapy, the results of this study also show that the improvements seen within the treatment phase were continued once the CVT therapy had been discontinued. This long-term sustainment in improvements provides essential reassurance that the benefits seen in the treatment phase are not short-term.

It has been emphasised that whilst the reason for the improvements in both PFWT and MWT remains unclear, it has been established that there may be an association between the improvements and CVT. However, whether CVT is responsible for these improvements cannot be proven or disproven in this feasibility study. To increase confidence in the hypothesis that CVT improves PFWT and MWT in patients with IC, requires further research in the form of a randomised controlled trial, as there are many other variables within the research which may contribute to the results, as discussed within the study limitations (section 5.18).

Further significant effects were observed during the analysis of certain secondary outcomes, again suggesting a substantive effect of the therapy. Assessment of change in participants' lower limb perfusion showed evidence of a statistically significant difference between ABPI at baseline and at the end of week 12 (t_{29}=-2.008, p=0.046), (Table 4-11). Furthermore, statistically significant changes were seen in the treated leg when comparing systolic leg pressure at baseline and week 12 (t_{31}=-2.273, p=0.03, Table 4-13). However, in the untreated leg there was no evidence of a statistically significant difference (t_{31}=-0.597, p=0.555, Table 4-14). This physiological change established that improvements seen in walking distance are more likely to be due to improvement in blood supply rather than the result of a placebo effect.

The results showed a positive improvement in participants' quality of life, with their overall physical functioning scores improving from 35.34 (SD 8.93) at baseline, increasing at the end of active therapy to 44.52 (SD 9.11). However, during the follow-up period, there was a decline in scores at week 36; the physical functioning scores were 39.55 (SD 12.37), which is an increase from the starting baseline.

The potentional duration of treatment required to achieve maximum benefits has been considered. The results showed that the main improvement in PFWT occurred within the first four weeks of therapy, and that there was some further, but less evident, improvement by continuing the therapy to week 12 (Figure 4-10). Furthermore, analysis of the changes in MWT confirmed that the main improvement occurred in the first eight weeks of therapy, with again some, but less evident, improvements up to week 12 (Figure 4-20). These results provide evidence that the duration of CVT should be at least eight weeks in order to optimise outcomes.

This research has shown that improvement in symtoms have been seen when the CVT device is placed on the calf area, irrespective of the location of disease. The results demonstrated that participants using the CVT device in the calf area had improved outcomes compared to those using the machine in the thigh (Table 4-21, Table 4-22). However, there were limited numbers in the thigh group: only eight participants used the device on this area, whereas twice as many participants used the machine at the level of the calf. Both groups had improvements in their PFWT and MWT, but the effect was more pronounced in the calf group. This may be due to the machine being ergonomically designed to be used on the lower leg, which made it more difficult to use at the level of the thigh. It is suggested that for any future research the CVT machine is positioned on the calf.

A further objective of this feasibility study was to determine measurement/equipment suitability to assess a degree of change in clinical and functional status. As previously discussed, within section 5.18, there are some limitations in the measurement systems in this study. However, there has been some valuable insight gained from this feasibility study. For further studies, it is suggested that a standardised walking test is used to reduce some of the variables and improve repeatability and validity of the walking assessment. After reviewing the advantages and disadvantages of available walking assessments in section 3.16.2, it is suggested that for further studies the six-minute walk test may provide a method of assessing real life walking ability which provides a degree of measured repeatability. The alternative is the use of treadmill testing. However, this has the potential to limit patient recruitment to future studies, due to the inability of many patients to undertake treadmill testing. In this particular study, a large number of patients would not have been able to take part in treadmill testing due to physical issues.

The use of ABPI assessment and the measurement of systolic leg pressure are recommended for further studies. In this current study, both measurements proved to be sensitive in assessing changes in lower limb perfusion pressure, and the comparison between the treated and untreated leg provided evidence of physiological changes.

Quality of life assessment is important for any future studies into patients with IC. Participants within this study showed an overall improvement in physical functioning scores of the SF-36 instrument. However, other domains of quality of life in this scale failed to show any significant changes. The sensitivity of the SF-36 instrument has been discussed as a potential limitation to this study (Section 5.18). Disease-related questionnaires have been formulated and may hold advantages over SF-36, as disease-specific instruments focus on specific symptoms of IC and, therefore, may have a greater sensitivity and responsiveness to clinical change (Hoeks et al., 2009).

However, disease-specific quality of life tools may also have limitations as they provide a measure of condition-specific measures but do not include any general quality of life measures. This would mean that, although a disease-specific tool provides a measure of condition-specific mobility relevant to IC, it would be difficult to ascertain the impact of PAD more generally. There appear to be advantages of both disease-specific and general quality-of-life assessment. For future studies, it would be worth considering using both general and disease-specific quality of life tools to increase the validity of the findings.

6.2 Feasibility findings

Feasibility studies are an important step in evaluating study design and to aid in the contextualisation and conceptualisation of research proposals. This feasibility study centred on refining the research protocol and procedures including intervention delivery, evaluation process, measurements and follow-up requirements and has answered vital questions which were required to be able to formulate further research.

This feasibility study has assessed the variability of the primary outcome measure. This information is required to estimate sample sizes needed for any future studies. Additionally, it has clarified the optimum characteristics of proposed intervention and outcome measures, including: positioning of device; the length of treatment and the appropriate measurement methods.

Furthermore, the study has provided new information into the number of eligible participants with IC who are willing to participate in research into CVT. Sixty-one per cent of patients who were approached and met the inclusion/exclusion criteria agreed to participate in this research. On average the rate of recruitment was 2.4 participants per month from a standard size district general hospital. The completion rates and number recruited per month provided a level of detailed information which is required, for future studies, to estimate time required to undertake recruitment/research.

Additionally, this study has provided evidence of the acceptability of the research protocol and indications of some changes which should be considered, including removing the requirement for repeated measurements at 30-minute post-initial treatment, and reducing the number of follow-up visits required. Reducing the number of follow up visits could help limit the attrition rate whilst still generating meaningful data.

Finally, this study has highlighted the difficulty of attrition loss within the follow-up period. The extent of attrition loss has been defined and further exploration is needed on how this loss might be mitigated for further studies. The information gained from this study, in terms of numbers lost to follow-up, needs to be taken into account for any further research when performing sample size calculations in order to maximise the power of the data generated, ensuring that firm conclusions for the treatment of IC with CVT can be made with future research.

In this study, a number of participants failed to complete the walking tests. Difficulties were encountered in completion of the walking test due to significant co-morbidity from coexisting cardiovascular disease, the elderly population and issues with balance/increased risk of falling. This reinforced the difficulties with this group of patients being able to participate in exercise therapy. For future studies, it would be worthwhile amending the inclusion/exclusion criteria so that potential participants are required to undertake a form of cardiovascular screening/walking assessment to ensure that all potential candidates are able to fully participate in the research. However, this process of screening has limitations, as this will result in a study group which is not truly representative of the whole claudication group and it may exclude patients with the most severe limitations on walking distance and those with multiple co-morbidities. Nevertheless, acknowledging the limitations of this approach by defining precise populations (that may not fully reflect the whole IC group) will provide detailed information on outcomes and any results could be extrapolated to the wider population. Alternative solutions on how participants with IC who are unable to complete a formal walking test can be included within research should be explored. This could include stratifying participants into different categories, according to the severity of their PFWT/ability to walk, to try to investigate this group of patients further.

No participants dropped out during the treatment phase. This indicates the high degree of participant acceptability of the treatment, which is in stark contrast to supervised exercise programmes, where attrition loss during the treatment phase is very common (Muller-Buhl et al., 2012). The high compliance to CVT is a great advantage to ensure resources are used appropriately and to maximise treatment benefits.

6.3 Study implication for clinical practice

The current recommended first-line treatment for patients with IC is supervised exercise (NICE, 2012). However, access to supervised exercise programmes is limited. A survey of UK vascular specialists completed in 2008, prior to the introduction of the NICE guidelines, indicated that 72% of respondents claimed they did not have access to supervised exercise programmes for patients with IC (Shalhoub et al., 2009). When supervised exercise programmes were unavailable, patients were given simple verbal exercise advice or were provided with written information leaflets. Even after the introduction of NICE guidelines in 2012 (NICE, 2012) there still remains variation across the country as to whether patients can access supervised exercise programmes. A survey undertaken in 2016, four years after the introduction of the NICE guidelines, demonstrated that 59% of vascular units continue to have no access to a supervised exercise programmes (Harwood et al., 2016). Furthermore, it has been highlighted that the provision of supervised exercise is mostly within hub arterial centres (normally larger teaching hospital/trauma centres) and not locally within vascular spoke hospitals, providing a degree of postcode lottery as to whether patients can access this recommended first line treatment. This variation across the country results in inequitable patient care.

Even if patients can access supervised exercise programmes there are difficulties in completing the required programme. This is due to a number of factors, including: the requirement of pain, the presence of concomitant disease and a general lack of motivation in patients to engage or complete the programme (Garg et al., 2009). Other known treatment options for IC such as endovascular or surgical interventions also have major limitations. Endovascular or surgical interventions require patients to undergo a surgical procedure and therefore there is a requirement to accept the associated risks. Additionally, these treatment options are obviously costly compared to out-of-hospital treatments. Owing to these difficulties and limitations of exercise and surgical/endovascular intervention, there is a gap in the current treatment options.

The impact of supervised exercise is clear and it is proven to improve patients' symptoms of IC (Lane et al., 2014). It is rather bewildering and, at the same time, frustrating that the first-line recommended treatment which is proven to improve patients' symptoms is something that is unavailable to all. The provision of supervised exercise programmes is locally decided within commissioning units. If patients cannot access supervised exercise programmes there are no other non-invasive alternatives. This questions whether there needs to be an alternative provision, such as CVT, which is not dependent on commissioning of services. Currently within the local NHS vascular services at Mid Yorkshire NHS Trust, there is no access to supervised exercise programmes. Mid Yorkshire NHS Trust is a 'spoke' hospital

within a larger vascular network. Services are commissioned as part of a 'hub and spoke' model, with the hub being the Leeds Vascular Institute. Together the services have a catchment area of over 800,000 and even within the larger vascular network there still is no provision of supervised exercise programmes for patients with IC. This results in limited treatment options for patients within this catchment area. CVT could potentially provide a solution to these issues, as CVT treatment could be accessed via prescription and applied at home, therefore would not require commissioning.

This study has identified that there is a potential for the use of CVT in the treatment of IC. The advantages of CVT over other treatment methods are substantial and include being a treatment that is: easy to access, completely pain free, applied in patients' homes, with no therapy associated risk to the patient, and not limited by concomitant disease presence. Future research is required to establish the concept of CVT impacting on symptoms of IC and to increase understanding of mechanisms of improvement. However, if CVT is proven to be a suitable and effective treatment, there is a potential that it could revolutionise the care of patients with IC.

This study was not designed to prove whether CVT is an effective treatment for IC. It was designed to establish the feasibility of using CVT in patients with IC. However, this research did show that a high proportion of patients had an improvement in their symptoms, which may or may not be associated with the use of CVT. The main aim of any treatment given by a health professional is to improve patients' symptoms and ease suffering, so in this case CVT has been highly effective. Whether the mechanisms of improvements are due to the CVT or simply due to placebo has not been investigated in this feasibility study. To be able to prove whether CVT has a physical effect and is an effective treatment for IC requires further investigation.

6.4 Study conclusion

PAD is a common chronic condition and is associated with increased cardiovascular morbidity and mortality (Criqui and Aboyans, 2015). The global aging phenomenon will further increase the burden of cardiovascular disease, including PAD (Selvin and Erlinger, 2004). It is accepted that PAD affects patients' quality of life and that the primary treatment goal is to relieve pain, improve quality of life, reduce the incidence of secondary cardiovascular disease/events and prolong survival. A common symptom of PAD is IC.

Existing treatments to reduce symptoms of IC include medication, exercise, angioplasty or bypass surgery (Cassar, 2006). Exercise therapy can be in the form of simple advice asking the patient to regularly walk through the pain. However, this form of unsupervised exercise fails to address the

barriers to walking faced by patients with IC (Stewart and Lamont, 2007). Supervised exercise has been shown to offer improvements in patients' symptoms of IC and help with some of the barriers to exercise such as fear and motivation (Stewart et al., 2008). However, even though supervised exercise is an effective treatment it is often underused due to lack of availability and many patients being unwilling or unsuitable to participate. This study has established that CVT is a potentially viable alternative treatment to supervised exercise which eliminates many of the factors which hinder supervised exercise from being used.

Existing treatments for IC have been extensively researched. There is emerging evidence of the effects of CVT on the improvement of nitric oxide production, improved blood flow and increased rate of angiogenesis (Ichioka et al., 2011, Maloney-Hinds et al., 2009, Button et al., 2007). This increased blood perfusion would reduce symptoms of IC. This is the first study investigating the feasibility of using CVT as a treatment for IC and has provided novel information relating to length/positioning of treatment, potential association between CVT and improved symptoms and described research methodology required for future research. In conclusion, this study has established the feasibility of using CVT to improve patients' symptoms of IC.

6.5 Recommendations for future research

This research has highlighted a number of issues which warrant future research. This feasibility study focused on refining the study protocol and while the results confirm the concept of using CVT in patients with IC, it was never designed to establish the true effect of CVT or to assess the extent of impact. This requires further investigation with a more robust research design. Further research should examine the effectiveness of CVT, ideally in a multi-centre randomised controlled trial design, potentially using a placebo dummy machine, using a greater number of researchers to recruit and collect the data. This should include a health economic evaluation which can be compared to current treatment options. This would provide valuable information about the translation and transition of CVT into everyday healthcare.

Following this, comparatives studies would be useful in comparing outcomes from CVT with currently recommended supervised exercise programmes, assessing acceptability of intervention, compliance to therapy and overall benefits in walking ability.

All treatments for IC should aim to improve both patients' symptoms of IC and to reduce overall morbidity. Future research should consider whether CVT affects patients' motivation/ability to walk

further and whether this is linked to improvement in general cardiovascular fitness and aiding reduction in overall morbidity and mortality rates.

7 Appendices

7.1 Appendix - NIHR approval letter

NHS
Health Research Authority
NRES Committee Yorkshire & The Humber - South Yorkshire
North East REC Centre
Unit 002, TEDCO Business Centre
Rolling Mill Road
Jarrow
Tyne and Wear
NE32 3DT

Telephone: 0191 428 3561

08 April 2014

Mrs Leanne Atkin
Vascular Nurse Specialist
Mid Yorks NHS Trust
Pinderfields Hospital
Aberford Road
Wakefield
WF1 4DG

Dear Mrs Atkin

Study title:	**Feasibility study to evaluate non invasive cycloidal vibration therapy for the symptomatic treatment of intermittent claudication due to peripheral arterial disease.**
REC reference:	**14/YH/0080**
IRAS project ID:	**146195**

Thank you for your letter of 08 April 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Joan Brown, nrescommittee.yorkandhumber-southyorks@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

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

Conditions of the favourable opinion

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

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

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

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

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

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

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

Registration of Clinical Trials

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

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

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

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.
It is the responsibility of the sponsor to ensure that all the conditions are complied with

before the start of the study or its initiation at a particular site (as applicable).

Approved documents

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

Document	*Version*	*Date*
Evidence of insurance or indemnity	NHC Technology Ltd / Policy No: 12ME238916FA329	23 December 2013
GP/Consultant Information Sheets	GP Notification Letter / Version 1	03 February 2014
Investigator CV	CV for Karen Ousey	
Investigator CV	CV for Leanne Atkin	
Letter of invitation to participant	Version 1	03 April 2014
Other: Patient Instructions		
Other: Long Term Product Return		07 April 2014
Participant Consent Form	Version 2	03 April 2014
Participant Information Sheet	Version 3	03 April 2014
Protocol	Version 1	27 February 2014
Questionnaire: SF - 36		
REC application	IRAS Version 3.5	27 February 2014
Response to Request for Further Information		

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

14/YH/0080	**Please quote this number on all correspondence**

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

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

Yours sincerely

pp

Dr Ian Woollands
Chair

Email: nrescommittee.yorkandhumber-southyorks@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mrs Jane Shewan, Mid Yorkshire NHS Trust*

7.2 Appendix - Insurance certificate

QBE Syndicate 1886 at Lloyd's

CERTIFICATE OF INSURANCE

This is to certify that a Policy of Insurance as described below has been issued to the Insured

Policy Number:	12ME238916FA329
The Insured:	NHC Technology Ltd
Business:	All activities of the Insured as advised to and agreed by the Company
Period of Insurance:	30th December 2013 to 17th February 2015 Both days inclusive at Greenwich Mean Time
Cover:	Primary No Fault Compensation for Clinical Trials
Limits of Indemnity:	GBP 5,000,000 any one event and in all for the period
Policy Territory:	United Kingdom as per policy
Protocol Number:	CVTPAD1
Study Title:	Pilot study to evaluate non-invasive cycloidal vibration therapy to increase arterial circulation to provide symptomatic treatment of intermittent claudication due to peripheral arterial disease, resulting in improved quality of life
Subject Numbers:	40
Conditions:	Extended Incident Reporting Period: 12 months Legal Liability Extension
Deductible:	GBP 2,500 any one claim, including costs and expenses

This Certificate is only a summary of the Policy. Nothing contained in this Certificate shall in any way be held or construed to vary alter or waive any of the terms conditions or provisions of the policy Reference should be made to the Policy for the full terms conditions and exceptions

Date: 23rd December 2013 **Signed**

Authorised Coverholders on behalf of the Underwriters

QBE Syndicate 1886 at Lloyd's is managed by QBE Underwriting Limited (no. 01035198), registered office Plantation Place, 30 Fenchurch Street, London, EC3M 3BD, a Lloyd's managing agent authorised and regulated by the Financial Services Authority.

7.3 Appendix - NIHR CRN portfolio acceptance letter

NHS
National Institute for Health Research
Clinical Research Network

Date: 23rd May 2014

NIHR CRN reference: CARD 3410

Title of study/Sponsor reference: Feasibility study to evaluate non-invasive cycloidal vibration therapy for the symptomatic treatment of intermittent claudication due to peripheral arterial disease (PAD).

Protocol version: 27/2/14 – Version 1

Dear Philip,

This study can now be included in the NIHR CRN Portfolio. I would like to draw your attention to the following important points:

- This study has been considered based on the information provided in the protocol version above and the online submission form completed. Should any of the details included in these documents change, please ensure that we are notified as soon as possible in order that we can assess whether the changes are likely to affect study delivery through the network.

- In order to ensure the Networks are able to provide you with the greatest possible benefit, we ask that you ensure that we are kept up to date with study milestones, developments and progress:

Next steps are as follows:

1) You have now been provided with feedback on sites along with Local Clinical Research Network delivery teams. Please involve them in any correspondence with the sites.

2) As soon as a final site list with site recruitment targets is available, please share this with us.
   a. For those sites that have not been selected, please provide us with reasons why, so that this information can be fed back to those PIs who have expressed an interest in your study.

3) Following final site selection, a study milestone schedule (see link below) should be completed in order to outline the key study deliverables that the Network and

Company are jointly working to achieve. We will be in touch to discuss this further once sites have been confirmed.
   a. The Study Milestone Schedule can be downloaded from this link.

4) The NIHR CRN works closely with companies to monitor site set up and recruitment into NIHR CRN Portfolio studies. A specific and crucial condition of inclusion in the NIHR CRN Portfolio is that the NIHR CRN receives recruitment updates on a monthly basis. Site recruitment updates must be provided in the appropriately specified format using the NIHR CRN recruitment template (see link below). Patient recruitment will be collected for all UK study sites (Network and non-Network) once the study is open to recruitment. Please note that minimum ICMJE details on your study will be shown on the NIHR CRN portfolio.
   a. The recruitment template spreadsheet can be downloaded from this link

5) If during the course of the study you wish to add additional sites to your study (not agreed in the study milestone schedule), please contact the NIHR CRN at the earliest opportunity, as these sites will not be automatically eligible for Network support. Following notification we will liaise with the Local Clinical Research Networks to confirm whether they are able to support the sites.

6) Free NIHR CRN training is available to all staff (company/NHS/academic) associated with NIHR CRN Portfolio studies. For details please see http://www.crn.nihr.ac.uk/workforce_development

We would like to remind you that we are happy to assist in the identification of additional sites.

Please could you complete a short survey about our processes? Your feedback plays a vital role in improving the effectiveness of the Clinical Research Network. The survey is available at the following link: https://www.surveymonkey.com/s/NewCommercialEligibilityFeasibilityProcess

We very much look forward to working with you on this study and I hope that you find the involvement of the Networks to be of considerable benefit.

If you have any further questions or concerns, please do not hesitate to contact me.

Yours sincerely

Lyndsey Donbavand

NIHR Clinical Research Network
16 Clarendon Place, Leeds, LS2 9JY
Tel: 0113 3430160
Email: industry.crnH@nihr.ac.uk
Web site: www.supportmystudy.nihr.ac.uk

7.4 Appendix - Patient information sheet

Cycloidal Vibration Therapy study: Patient Information sheet

The Mid Yorkshire Hospitals NHS
NHS Trust

Please read this document carefully.

We would like to invite you to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Feel free to discuss this with anyone else you wish, for example, a friend / nurse / doctor or relative. Ask us if there is anything that is not clear. We are happy to provide more information. Take as much time as you need to decide whether you want to take part. If you are unsure and want to discuss with this anyone else we can arrange a research nurse to phone you in a couple of days.

Thank you for reading this.

What is the purpose of this study?
Peripheral Arterial Disease can reduce day to day activities due to pain when walking or resting. This is due to reduced blood flow in the lower legs causing intermittent claudication. Reduced blood flow occurs due to narrowing of the arteries and this can be as a result of a number of factors including smoking and diabetes. This study is to test a new potential treatment option for Peripheral Arterial Disease. It will determine if this device will help to improve blood flow and circulation as a result improving your walking and reducing lower limb pain.

What is the treatment being studied?

The medical device you are being asked to use applies a specific form of vibration therapy to the legs either above or below the knees, the machine that delivers the vibration therapy is called Vibropulse.

The above picture shows the Vibropulse machine in place on the lower leg. The Vibropulse machine has been shown in clinical trials to improve blood flow and circulation. However we want to determine in greater detail if it will help with the treatment of Peripheral Arterial Disease. The device is simple to use at home. Patients have found the treatment comfortable and very relaxing.

Why have I been chosen? Your nurse and / or doctor think that the Peripheral Arterial Disease you have means that you could take part in this study.

Do I have to take part? Participation in this study is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and you will be asked to sign a consent form. If you do agree to take part in this study and decide at a later

time that you would like to withdraw from the study, then you are free to do so at any time. Your decision will not influence your future care or treatment. Direct costs of taking part in this study such as parking charges will be reimbursed by the hospital.

What will happen to me if I agree to take part? We are interested in how this treatment will potentially affect your lower limb circulation and as a result you're walking without pain. If you agree to take part in this study you will be asked to carry out a number of simple tests within the clinic and then you will be shown how to use the machine. You will receive a Vibropulse machine which you need to apply to your leg for 30 minutes twice a day every day. A research nurse will be available for you to access throughout the study if you have any questions or need support with any of the aspects of the study or the machine.

What do I have to do? You will continue receiving best practice standard care for your Peripheral Arterial Disease.

At the start of the study, you will be asked to carry out a walking distance test and the circulation at your ankle's will be measured using a similar method as measuring your blood pressure, plus you will be asked a range of questions about your general quality of life. You will then be shown how to use the Vibropulse machine. You will be asked to use the machine for 30 minutes 2 times a day at home. Leaving at least 2 hours between treatments, the machine can be applied at any time during the day that is suitable for you. The device will record number of times it is used.

We will contact you by phone on day 7 to see how you are getting on and to address any questions you have.

At 4, 8 and 12 weeks you will be asked to return to clinic so that we can repeat the walking test, measure your circulation and complete some simple questions relating to your quality of life.

At week 12 you will stop using the product.

We will ask you to return to clinic at week 16, week 24 and finally week 36 for a follow up assessment and we will repeat the walking test, circulation measurements and complete questions relating to your quality of life.

Overall the study will require 6 clinic visits, one per month for first 3 months then every other month for the next 3 visits, each visit should take at most one hour.

There are no restrictions on your activity when you are in this study. You will continue with any other medical care or treatments, such as taking regular medication, as you would normally do. There are no limitations on you seeking other medical advice, if you need to, whilst you are taking part in this study.

Why are we doing the study? Cycloidal vibration therapy may or may not be effective at improving walking and reducing walking pain caused by Peripheral Arterial Disease we do not know if this is the case. It is therefore important to carry out this study so patients with Peripheral Arterial Disease can be provided with the most appropriate and effective care.

Are there any alternatives to the treatments being studied? There are alternative treatments available for Peripheral Arterial Disease and your nurse will be happy

to discuss other options with you, if you wish. These are likely to include medication and stopping smoking. But also additionally involve exercise programmes or surgical operations.

Are there any side effects from the treatment being investigated? Side effects for the therapy being trialled are uncommon, there are no known reported side effects. Whilst we do not anticipate any side effects please contact us straight away if you experience any unpleasant side effects.

Are there possible disadvantages to taking part? We do not anticipate that being in this trial will harm you. Should this occur, however, normal NHS negligence procedures apply. If you have any medical queries or in an emergency you should contact your doctor or nurse as you would normally do. The name of a contact research nurse responsible for this research study in your area and the telephone number where they can be reached is provided below. We can not guarantee that the research nurse or person running the trial will always be available to take your call but we will always return your call as quickly as we can.

What are the possible advantages of taking part? We hope that your lower limb circulation will improve as a consequence improving walking and reducing pain. Although we are unable to guarantee this, the information we get from this study may help us to better treat people with Peripheral Arterial Disease in future.

What if new information becomes available? Sometimes during a research project, new information becomes available. If this happens, your nurse / doctor will tell you about it. They will discuss with you whether you want to continue in the study. If you decide to withdraw from the study your care will continue as it would normally. If you decide to continue, then you will be asked to sign an updated consent form. If new information means that your nurse / doctor decides to take you out of the study, then she / he will discuss this with you. He/she will explain the reasons for this and your care will continue as it normally would outside of the study.

What happens when the research study stops? The outcome of the study may determine if the therapy being evaluated becomes available to every nurse / doctor in the UK.

What if something goes wrong? If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential? All information that is collected about you during the course of the research will be kept strictly confidential. At the beginning of the trial we will record your name and address and ask you to sign a consent form. This information will be stored securely. We will also let your GP know that you are taking part in the trial. All further information about you that leaves

hospital/surgery/home will not contain your name or address, so you cannot be recognised from it. If you consent to take part in the research, the NHS Trust (for purposes of checking data collection) may inspect your medical and nursing records. People from regulatory authorities may also look at your records to check that the study is being carried out correctly.

What will happen to the results of the study? The results of the study will be published in medical and nursing journals. You will be able to obtain a copy of the results upon request, when these become available. You will not be identified in any publication arising from this study.

Who is organising and funding the research? The study is being funded by the medical device company. Your nurse or doctor is not personally receiving any money for including you in the trial.

Who has reviewed the study? Your Local Research Ethics Committee has approved this study.

What do I do now? If you are interested in taking part please sign the consent form, returning it to your study nurse.

Where can I get more information about the study? If you do not understand anything on this information sheet or would like further information, please contact your nurse on the telephone number below.

Principal Investigator:
Leanne Atkin
Telephone: (01924) 542473
Email: leanne.atkin@midyorks.nhs.uk

7.5 Appendix - Participant consent form

The Mid Yorkshire Hospitals NHS
NHS Trust

Cycloidal Vibration Therapy Peripheral Arterial Disease Study: Patient Consent Form

Patients Initials ☐☐☐ Patients Date of Birth ☐☐/☐☐/☐☐☐☐
Day month year

Name of reasearcher._____

Please read the following ten statements and, if you agree and would like to participate in this study, add your initials inside each box. Ask the nurse with you if you have any questions or would like the statements to be read to you. Finally, if you agree with all the statements, please sign your name at the bottom of the page. By doing this you will have consented to take part in the Cycloidal Vibration Therapy PAD study.

	Please initial each box
1. I agree to take part in the Cycloidal Therapy PAD study.	☐
2. I confirm that I have read and understood the information sheet dated …/…/2013 for the above study and have had the opportunity to ask questions.	☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐
4. I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports of this study.	☐
5. I understand the compensation provisions for this study.	☐
6. I understand that data collected as part of this trial will be stored for 5 years.	☐

Consent Form – 03/02/14 - Version 1

7. I understand that anonymised data may be used in the future for further analysis strictly in connection with this study. ☐

8. I agree that responsible individuals nominated by the funders of this study or Mid Yorkshire NHS Trust may access my medical and nursing records in relation to my taking part in this study. ☐

9. I agree that any identifiable study data collected can be retained in the event of loss of capacity to consent to further participation. ☐

10. I agree to my GP being informed of my participation in this study. ☐

Patient name (please print)

_____

Signature_____

Date _____

Name of researcher taking consent (please print)_____

Signature_____

Date ☐☐/☐☐/☐☐☐☐

7.6 Appendix - General Practitioner information sheet

The Mid Yorkshire Hospitals NHS
NHS Trust

Vascular Department
Mid Yorkshire NHS Trust
Pinderfields General Hospital
Aberford Road
Wakefield
WF1 4DG

Tel: 01924 542473
Leanne.atkin@midyorks.nhs.uk

Cycloidal Vibration Therapy – A feasibility study of the non-invasive application of cycloidal vibration therapy for the symptomatic treatment of peripheral arterial disease.

GP Information sheet

Name of Participant: ……

Date of Birth: ……/……../19……..

The patient named above has agreed to take part in the non-invasive application of Cycloidal Vibration Therapy PAD research study.

Background to the study
Peripheral Arterial Disease is a growing problem (PAD).

Recent NICE guidelines for the treatment and management of PAD included treatments for aiding symptomatic relief. This advised on referral for smoking cessation, undertaking a supervised exercise program and if appropriate angioplasty to improve peripheral blood flow.

Supervised exercise has been shown to provide symptomatic relief for PAD, improved mobility may also help to reduce associated cardiovascular risk factors. However supervised exercise is expensive, only 30% of PAD patients agree to attend exercise programs and not all patients fully comply in completing the programme or attend as scheduled. This is believed to be due to the physical and pain tolerances required to undertake exercise.

The purpose of this research is to investigate the use of a home use passive applied medical device to stimulate lower limb circulation. This device applies a specific form of vibration to the lower limbs that has been shown to increase circulation by stimulating vascular endothelial cell synthase (eNOS). This device is already available to the NHS and has been shown in case evaluations to stimulate lower limb blood flow in critical ischemic patients providing symptomatic relief such as increased walking distance before pain. The medical device is simple to use at home and will be self-applied by the patient 2 x a day for 30 minutes over a period of 12 weeks and will confirm patient compliance. At 4 weekly intervals we will assess the patients for both vascular and symptomatic changes. Therapy will be stopped after 12 weeks, the patients will attend for review at 16, 24 and 36 weeks to assess whether there are any sustained benefits of the therapy.

All other treatments will be carried out, as normal, and standardised where possible. The patient has been informed that in the case of an emergency they should contact their usual nurse of doctor. Please contact the local investigator should you require any further information.

Local nurse investigator: Leanne Atkin
Telephone: (01924) 542473
Email: leanne.atkin@midyorks.nhs.uk

7.7 Appendix - Instructions relating to positioning of the Vibropulse machine

Vibrant MEDICAL LTD

Using the Cycloidal Vibration Therapy.

Contents

1. Cycloidal Vibration Therapy Pad and Hand Control Unit
2. Instructions and diary.

The Cycloidal Vibration Therapy Pad is plugged directly into a mains socket. When not in use the product should be disconnected from the mains supply.

How to use.

Treatment of upper legs if instructed.

Position the therapy pad on a seat or bed with the grey housing facing towards your knees as illustrated.

Treatment of lower legs if instructed.

Position the therapy pad on a sofa, footstool or bed with the grey housing under your knees as illustrated.

NOTE: **NEVER** use the CVT Pad under a blanket, or obstruct, in any way, the ventilation holes in the motor housing. **NEVER** pick up the CVT Pad by the electrical cable.

- To start the therapy press the on/off button, a number in the LCD display screen will indicate number of treatments applied to date.
- Press the Start / Stop button.
- 30 minutes will appear on the LCD display and the therapy will start.
- The timer will count down in one-minute increments, thus showing what time is left, when time reaches 0, the therapy will slowly decrease until it switches off.

Disclaimer: The product MUST be used following the stated protocol for optimum patient safety and effectiveness. Vibrant Medical Ltd accepts no responsibility for any clinical complication or incident due to the protocol not being followed accurately and any misuse of the product. Adverse events should be reported to Vibrant Medical Ltd information on +44 (0)114 2242249

Cleaning (recommended once per week minimum) - First disconnect the product from the power supply. Clean all the product using a cloth dampened with a mild detergent and water solution. **DO NOT USE** solvent-based cleaners, dry cleaning products, bleach and abrasive compounds. **DO NOT** immerse the product as this may damage the electronics.

Transformer Plug - This appliance should be fitted with a suitably approved plug for use in the country of destination. U.K. plugs may be of moulded construction or of the fitted type and, if so, should be to BS1363. In any event a 3A fuse should be fitted to the plug or circuit in either the adapter or at the distribution board.

Important- The wires in the mains lead are coloured in accordance with the following code:

Brown - Live Blue -Neutral The blue wire must be connected to the terminal marked "N" or coloured "black". The brown wire must be connected to the terminal marked "L" or coloured red. Any replacement plug you fit must be protected by a 3amp fuse.

Warning - Should it be necessary to replace a moulded or fitted plug for any reason, the supplied plug must be removed from the wall socket. The plug should then be cut from the cable and a suitable replacement, as described above, fitted. Once removed from the flexible cable, the supplied plug should be disposed of immediately.

Manufacturing Standards products are independently tested to ensure they comply with the latest Harmonised European Standards with respect to EMC Directive (89/336/EEC) and the Low Voltage Directive (73/23/EEC). Our products also comply with The Medical Devices Regulation 1994, SI No 3017 1994.

Customer Service: Vibrant Medical Ltd, The Innovation Centre 217 Portobello, SHEFFIELD,UK, S1 4DP Tel: +44 (0) 114 2242249 Fax: +44 (0) 114 2232300 Email: enquiries@vibrant-medical.co.uk

Made by NHC Technology Ltd, Colomendy Industrial Estate, Rhyl Road, Denbigh, Denbighshire. UK, LL16 5TS Tel: +44 (0) 1745 811200 Fax: +44 (0) 1745 816106

7.8 Appendix - Clinical research file

CONFIDENTIAL

Evaluation of non-invasive application of cycloidal vibration for the symptomatic treatment of PAD.

Clinical Research File

Site: Mid Yorks NHS Trust

Patient Initials:

Patient number:

Eligibility check list

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Details

1. Has the patient been diagnosed with PAD as per NICE guidelines. YES ☐ NO ☐

2. Please provide details of PAD diagnosis. (Claudication / critical lower limb ischemia)

_____

_____

_____

3. Duration of symptoms_____

Eligibility Criteria

4. Is the patient able to understand the aims and objectives of the trial YES ☐ NO ☐

5. Is the patient willing to participate in the trial YES ☐ NO ☐

6. Has the patient read the patient information sheet and signed the consent form YES ☐ NO ☐

7. Has the patient participated in this trial previously YES ☐ NO ☐

8. Does the patient have any condition(s) which seriously compromises the patient's ability to complete this study, or have a known history of poor compliance with medical treatment YES ☐ NO ☐

9. Has the patient been diagnosed with or has any of the following clinical conditions a DVT within the last 6 months. Pregnancy. Unstable lower limb bone and joint structures. Active cancer., Pulmonary embolism Lower limb soft tissue or bone infection not being treated with antibiotics.
YES ☐ NO ☐

If any of the shaded boxes have been ticked, the patient is <u>not</u> eligible to enter the study

....

Study personnel signature Print Name

Date ☐☐ ☐☐ ☐☐

Initial Assessment

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Patient Details

1. Date of assessment ☐☐ ☐☐ ☐☐
2. Patient Date of Birth ☐☐ ☐☐ ☐☐
3. Age ☐☐
4. Patient sex ☐ Male ☐ Female
5. Leg affected with pain ☐ Right ☐ Left ☐ Both
6. Location of pain ☐ Thigh ☐ Calf ☐ Both
7. Lowest palpable pulse ☐ Femoral ☐ Popliteal ☐ Foot
8. Suspected level of disease ☐ Inflow ☐ SFA ☐ Crural

Medical History

9. History of the following:

Angina ☐ Diabetes ☐ CVA/TIA ☐

MI ☐ DVT ☐ IHD ☐

Rheumatoid arthritis ☐ Hypertension ☐

....

Study personnel signature Print Name

Date ☐☐ ☐☐ ☐☐

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Past medical history

10. History of peripheral arterial disease ☐ Yes ☐ No

If yes please give details of which leg/legs have previously been affected and any interventions received including angioplasty, medication or bypass surgery:

_____

_____

_____

_____

_____

_____

11. Medication History

Currently prescribed any of the following (pls tick all that apply)

Antiplatelet	☐	Betablockers	☐
Warfarin	☐	Ace inhibitors	☐
Statin	☐	Cilostazol	☐
Naftidrofuryl	☐		

12. Smoking status

Does the patient currently smoke? ☐ Yes ☐ No

If Yes how many per day? _____ For how many years? _____

Does the patient intent to stop smoking in the next 12 weeks? ☐ Yes ☐ No ☐ Maybe

If No When did patient stop smoking?_____

How many did they smoke?_____ How long did they smoke for?_____

.....
Study personnel signature

.....
Print Name

Date ☐☐ ☐☐ ☐☐

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Initial Assessment

11. ABPI Assessment

Left Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Right Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Highest Brachial reading: ☐☐☐ mmHg

ABPI Right leg: ☐.☐☐

ABPI Left leg: ☐.☐☐

12. Shuttle test

Time of onset of pain (pain free walking distance): ☐☐ mins ☐☐ secs

Time of stopping (maximum walking distance): ☐☐ mins ☐☐ secs

Location of pain that forced rest: Right ☐ Left ☐

Buttock ☐ Thigh ☐ Calf ☐

13. Quality of Life

SF36 completed: Yes ☐ No ☐ if no why?_____

.....
Study personnel signature

.....
Print Name

Date ☐☐ ☐☐ ☐☐

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Initial Assessment

14. Device

Device Number: _____

Verbal instruction of how to use device: Yes ☐ No ☐

Written device information provided: Yes ☐ No ☐

Location of devices use: Thigh ☐ Calf ☐ Both ☐

Device counter reading: _____

15. Demonstrate to the patient device application and apply therapy for 30 minutes then immediately repeat shuttle test.

Shuttle test

Time of onset of pain (pain free walking distance): ☐☐ mins ☐☐ secs

Time of stopping (maximum walking distance): ☐☐ mins ☐☐ secs

Location of pain that forced rest: Right ☐ Left ☐

Buttock ☐ Thigh ☐ Calf ☐

....

Study personnel signature Print Name

Date ☐☐ ☐☐ ☐☐

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

7 day follow up

16. 7 day follow up:

Patient contacted Yes ☐ No ☐ if no reason for no contact_____

_____

Date of contact ☐☐.☐☐.☐☐

Is the patient comfortable applying the product? Yes ☐ No ☐

Does the patient require further instruction on how to use? Yes ☐ No ☐

Is the patient keeping to the regime of 2 x a day? Yes ☐ No ☐

Is there any change in patients medication status? Yes ☐ No ☐

If yes please provide details:_____
_____

Has there been any contact with any other health care professionals in relation to peripheral arterial disease including investigations, interventions and hospitalisation?
Yes ☐ No ☐

If yes please provide details:_____
_____
_____

Have you found the product to use? _____
(0–Very difficult, 1-difficult, 2-neutral, 3-easy, 4-very easy)

Have you been satisfied with the results of using the product?_____
(0- Very Dissatisfied, 1-Not satisfied,2-Neutral,3-Satisfied,4-Very satisfied)

Have you found using the product?_____
(0-Painful,1-Mild discomfort,2-Neutral,3-Comfortable,4-Very Comfortable).

Any other comments from the patient? _____
_____
_____

....
Study personnel signature Print Name

Date ☐☐ ☐☐ ☐☐

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Four week review

Four week review completed? Yes ☐ Date of review: ☐☐ . ☐☐ . ☐☐

No ☐ if no reason for no contact:

_____

_____

_____

17. ABPI Assessment

Left Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Right Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Highest Brachial reading: ☐ ☐ mmHg

ABPI Right leg: ☐.☐☐

ABPI Left leg: ☐.☐☐

18. Shuttle test

Time of onset of pain (pain free walking distance): ☐☐ mins ☐☐ secs

Time of stopping (maximum walking distance): ☐☐ mins ☐☐ secs

Location of pain that forced rest: Right ☐ Left ☐

Buttock ☐ Thigh ☐ Calf ☐

19. Review

Is there any change in patients medication status? Yes No

If yes please provide details:_____

_____

Has there been any contact with any other health care professionals in relation to peripheral arterial disease including investigations, interventions and hospitalisation?

Yes ☐ No ☐

If yes please provide details:_____

_____

_____

Has there been any change to the patients smoking status? Yes ☐ No ☐

If yes please provide details:_____

_____

_____

20. Follow up

8 week follow date :_____

....

Study personnel signature Print Name

Date ☐☐ ☐☐ ☐☐

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Eight week review

Eight week review completed? Yes ☐ Date of review: ☐☐.☐☐.☐☐

No ☐ if no reason for no contact:

21. ABPI Assessment

Left Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Right Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Highest Brachial reading: ☐ ☐ mmHg

ABPI Right leg: ☐.☐☐

ABPI Left leg: ☐.☐☐

22. Shuttle test

Time of onset of pain (pain free walking distance): ☐☐ mins ☐☐ secs

Time of stopping (maximum walking distance): ☐☐ mins ☐☐ secs

Location of pain that forced rest: Right ☐ Left ☐

Buttock ☐ Thigh ☐ Calf ☐

23. Review

Is there any change in patients medication status? Yes No

If yes please provide details:_____

_____

Has there been any contact with any other health care professionals in relation to peripheral arterial disease including investigations, interventions and hospitalisation?

Yes ☐ No ☐

If yes please provide details:_____

_____

_____

Has there been any change to the patients smoking status? Yes ☐ No ☐

If yes please provide details:_____

_____

_____

24. Follow up

12 week follow date :_____

Patient to be advised to bring Vibropulse machine back with them to next follow up appointment at 12 week.

....

Study personnel signature Print Name

Date ☐☐ ☐☐ ☐☐

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Twelve week review

Twelve week review completed? Yes ☐ Date of review: ☐☐.☐☐.☐☐

No ☐ if no reason for no contact:

_____

_____

_____

Vibration therapy now to be stopped.

25. ABPI Assessment

Left Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Right Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Highest Brachial reading: ☐ ☐ mmHg

ABPI Right leg: ☐.☐☐

ABPI Left leg: ☐.☐☐

26. Shuttle test

Time of onset of pain (pain free walking distance): ☐☐ mins ☐☐ secs

Time of stopping (maximum walking distance): ☐☐ mins ☐☐ secs

Location of pain that forced rest: Right ☐ Left ☐

Buttock ☐ Thigh ☐ Calf ☐

27. Quality of Life

SF36 completed: Yes ☐ No ☐ if no why?_____

28. Device Questionnaire

Have you found the product to use? _____
(0–Very difficult, 1-difficult, 2-neutral, 3-easy, 4-very easy)

Have you been satisfied with the results of using the product?_____
(0- Very Dissatisfied, 1-Not satisfied,2-Neutral,3-Satisfied,4-Very satisfied)

Have you found using the product?_____
(0-Painful,1-Mild discomfort,2-Neutral,3-Comfortable,4-Very Comfortable).Device

29. Review

Is there any change in patients medication status? Yes No

If yes please provide details:_____
_____

Has there been any contact with any other health care professionals in relation to peripheral arterial disease including investigations, interventions and hospitalisation?
Yes ☐ No ☐

If yes please provide details:_____
_____
_____

Has there been any change to the patients smoking status? Yes ☐ No ☐

If yes please provide details:_____
_____
_____

30. Device compliance

Device counter reading:_____

Difference from original reading:_____
(This should have increased by 168 if fully compliant).

31. Follow up:

16 week follow date :_____

....

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Sixteen week review

Sixteen week review completed? Yes ☐ Date of review: ☐☐.☐☐.☐☐

No ☐ if no reason for no contact:

32. ABPI Assessment

Left Limb: PT ☐☐☐mmHg DP ☐☐☐mmHg

Right Limb: PT ☐☐☐mmHg DP ☐☐☐mmHg

Highest Brachial reading: ☐ ☐ mmHg

ABPI Right leg: ☐.☐☐

ABPI Left leg: ☐.☐☐

33. Shuttle test

Time of onset of pain (pain free walking distance): ☐☐ mins ☐☐ secs

Time of stopping (maximum walking distance): ☐☐ mins ☐☐ secs

Location of pain that forced rest: Right ☐ Left ☐

Buttock ☐ Thigh ☐ Calf ☐

34. Quality of Life

SF36 completed: Yes ☐ No ☐ if no why?_____

35. Review

Is there any change in patients medication status? Yes No

If yes please provide details:_____

_____

Has there been any contact with any other health care professionals in relation to peripheral arterial disease including investigations, interventions and hospitalisation?

Yes ☐ No ☐

If yes please provide details:_____

_____

_____

Has there been any change to the patients smoking status? Yes ☐ No ☐

If yes please provide details:_____

_____

_____

36. Follow up:

24 week follow date :_____

....

Study personnel signature Print Name

Date ☐☐ ☐☐ ☐☐

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Twenty four week review

24 week review completed? Yes ☐ Date of review: ☐☐.☐☐.☐☐

No ☐ if no reason for no contact:

37. ABPI Assessment

Left Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Right Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Highest Brachial reading: ☐ ☐ mmHg

ABPI Right leg: ☐.☐☐

ABPI Left leg: ☐.☐☐

38. Shuttle test

Time of onset of pain (pain free walking distance): ☐☐ mins ☐☐ secs

Time of stopping (maximum walking distance): ☐☐ mins ☐☐ secs

Location of pain that forced rest: Right ☐ Left ☐

Buttock ☐ Thigh ☐ Calf ☐

39. Quality of Life

SF36 completed: Yes ☐ No ☐ if no why?_____

40. Review

Is there any change in patients medication status? Yes No

If yes please provide details:_____
_____

Has there been any contact with any other health care professionals in relation to peripheral arterial disease including investigations, interventions and hospitalisation?
Yes ☐ No ☐

If yes please provide details:_____
_____
_____

Has there been any change to the patients smoking status? Yes ☐ No ☐

If yes please provide details:_____
_____
_____

41. Follow up:

36 week follow date :_____

....
Study personnel signature Print Name

Date ☐☐ ☐☐ ☐☐

Patient Initials ☐☐☐ **Patient No** ☐☐ ☐☐

Thirty Six week review

36 week review completed? Yes ☐ Date of review: ☐☐.☐☐.☐☐

No ☐ if no reason for no contact:

42. ABPI Assessment

Left Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Right Limb: PT ☐☐☐ mmHg DP ☐☐☐ mmHg

Highest Brachial reading: ☐ ☐ mmHg

ABPI Right leg: ☐.☐☐

ABPI Left leg: ☐.☐☐

43. Shuttle test

Time of onset of pain (pain free walking distance): ☐☐ mins ☐☐ secs

Time of stopping (maximum walking distance): ☐☐ mins ☐☐ secs

Location of pain that forced rest: Right ☐ Left ☐

Buttock ☐ Thigh ☐ Calf ☐

44. Quality of Life

SF36 completed: Yes ☐ No ☐ if no why?_____

45. Review

Is there any change in patients medication status? Yes No

If yes please provide details:_____
_____

Has there been any contact with any other health care professionals in relation to peripheral arterial disease including investigations, interventions and hospitalisation?
Yes ☐ No ☐

If yes please provide details:_____
_____
_____

Has there been any change to the patients smoking status? Yes ☐ No ☐

If yes please provide details:_____
_____
_____

46. End of study

Thank patient for involvement and offer extended loan of Vibropulse for a further 6 months free of charge

....
Study personnel signature Print Name

Date ☐☐ ☐☐ ☐☐

7.9 Appendix - SF-36 example

The SF-36v2™ Health Survey

Instructions for Completing the Questionnaire

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

EXAMPLE

This is for your review. Do not answer this question. The questionnaire begins with the section ***Your Health in General*** below.

For each question you will be asked to fill in a bubble in each line:

1. **How strongly do you agree or disagree with each of the following statements?**

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
a) I enjoy listening to music.	○	●	○	○	○
b) I enjoy reading magazines.	●	○	○	○	○

Please begin answering the questions now.

Your Health in General

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor	
○1	○2	○3	○4	○5	GH01

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago	
○1	○2	○3	○4	○5	HT

Please turn the page and continue.

3. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all	
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	O1	O2	O3	PF01
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	O1	O2	O3	PF02
c) Lifting or carrying groceries	O1	O2	O3	PF03
d) Climbing **several** flights of stairs	O1	O2	O3	PF04
e) Climbing **one** flight of stairs	O1	O2	O3	PF05
f) Bending, kneeling, or stooping	O1	O2	O3	PF06
g) Walking **more than a mile**	O1	O2	O3	PF07
h) Walking **several hundred yards**	O1	O2	O3	PF08
i) Walking **one hundred yards**	O1	O2	O3	PF09
j) Bathing or dressing yourself	O1	O2	O3	PF10

4. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) Cut down on the **amount of time** you spent on work or other activities	O1	O2	O3	O4	O5	RP01
b) **Accomplished less** than you would like	O1	O2	O3	O4	O5	RP02
c) Were limited in the **kind** of work or other activities	O1	O2	O3	O4	O5	RP03
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	O1	O2	O3	O4	O5	RP04

5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) Cut down on the **amount of time** you spent on work or other activities	O1	O2	O3	O4	O5	RE01
b) **Accomplished less** than you would like	O1	O2	O3	O4	O5	RE02
c) Did work or other activities **less carefully than usual**	O1	O2	O3	O4	O5	RE03

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely	
O1	O2	O3	O4	O5	SF01

7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very severe	
O1	O2	O3	O4	O5	O6	BP01

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely	
O1	O2	O3	O4	O5	BP02

9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) did you feel full of life?	O1	O2	O3	O4	O5	VT01
b) have you been very nervous?	O1	O2	O3	O4	O5	MH01
c) have you felt so down in the dumps that nothing could cheer you up?	O1	O2	O3	O4	O5	MH02
d) have you felt calm and peaceful?	O1	O2	O3	O4	O5	MH03
e) did you have a lot of energy?	O1	O2	O3	O4	O5	VT02
f) have you felt downhearted and depressed?	O1	O2	O3	O4	O5	MH04
g) did you feel worn out?	O1	O2	O3	O4	O5	VT03
h) have you been happy?	O1	O2	O3	O4	O5	MH05
i) did you feel tired?	O1	O2	O3	O4	O5	VT04

10. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time	
O_1	O_2	O_3	O_4	O_5	SF02

11. **How TRUE or FALSE is <u>each</u> of the following statements for you?**

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
a) I seem to get sick a little easier than other people	O_1	O_2	O_3	O_4	O_5	GH02
b) I am as healthy as anybody I know	O_1	O_2	O_3	O_4	O_5	GH03
c) I expect my health to get worse	O_1	O_2	O_3	O_4	O_5	GH04
d) My health is excellent	O_1	O_2	O_3	O_4	O_5	GH05

7.10 Appendix - Permission letter for reproduction of images

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Director

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