The long term effects and sustainability of supervised exercise therapy in the treatment of intermittent claudication

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Abstract

Background:
Peripheral arterial disease (PAD), affects 10-20% of people over the age of 70. The causal risk factors include cigarette smoking and diabetes. It is responsible for significant morbidity and mortality and its social and economic implications are staggering. Exercise therapy has been proven to be an effective first line therapy for treating the primary symptom of PAD, Intermittent Claudication (IC). The addition of supervision to this therapy has resulted in superior clinical improvement in the short term. However, the long term clinical and behavioural impact of supervised exercise therapy remains unevaluated.

Methodology:
A systematic review, in accordance with the Cochrane Guidelines, was performed to examine the evidence on the sustained clinical and behavioural effects of supervised exercise therapy (SET) in the treatment of intermittent claudication.

Results:
The review was limited by the quality and the number of studies that met the criteria. Only three small-scaled studies were identified. The evidence suggests that the superior short-term improvements in claudication markers induced by SET are sustained for as long as six months post-trial. There was a paucity of evidence on the long term behavioural as well as the quality of life impact of SET. As a result of the findings of the systematic review, a protocol for a randomized controlled clinical trial "The Get SET Go Study!" was designed to more effectively evaluate the short and long term clinical and behavioural impact SET on patients with IC. A cost effectiveness analysis was integrated within the trial protocol to ensure that SET sustainability was more completely addressed.

Conclusion:
The conclusions of the review were limited by the number and quality of the trials reviewed. The evidence available does suggest that the superior clinical effects of SET appear to be sustained in the long term up until six months following rehabilitation. There was insufficient evidence to conclude on behavioural modifications and improvements, if any in the Quality of Life. The by-product of the review-"The Get SET Go Study!" randomized controlled trial protocol should be implemented to determine the long term value and cost effectiveness of SET in the management of patients with intermittent claudication.

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… for " Grandma Buddha"

Glossary of terms

CVD: Cardiovascular disease

IC: Intermittent claudication

PAD: Peripheral arterial disease

CHD: Coronary heart disease (also commonly referred to as coronary artery disease)

NCD: Non-communicable disease

DALY: Disability-adjusted life years

QALY: Quality-adjusted life years

HRQOL: Health-related quality of life

NICE: National Institute for Health Excellence

WHO: World Health Organization

ACD: Absolute claudication distance

PFWD: Pain-free walking distance

MHC: Myosin heavy chain

SET: Supervised exercise therapy

ET: Exercise therapy

RCT: Randomised controlled trial

ICER: Incremental cost-effectiveness ratios

CEAC: Cost effectiveness acceptability curves

Chapter I: The global burden of cardiovascular disease

Preview: In this chapter, I will introduce CVDs by reviewing their: definition, classification, risk factors and aetiology, socio-economic, global burden as well as the fundamentals and levels of prevention.

The Epidemiological burden of CVDs:

More people die globally from cardiovascular diseases (CVDs) than from any other cause (8). CVDs have emerged as a dominant issue of global health concern, placing an enormous economic and resource burden on global health care systems. Despite the fact that these diseases are considered to be largely preventable, they have reached epidemic proportions with an estimated 17.3 million people having died from CVDs in 2008 which accounts for 30% of all global deaths (8, 9). This figure is three times higher than that recorded in 1990 (10). The majority of these deaths were attributed to coronary heart disease (CHD) and stroke with estimates of 7.3 million and 6.2 million respectively (9, 11). In 2009 in the UK, CHD had death rates of 33 per 100,000 in men and 8 per 100,000 in women while stroke claimed 7 male deaths per 100,000 and 5 female deaths per 100,000 (12).

From a socio-anthropological perspective, CVDs, formerly conditions associated with the developed economies, have transcended global economic drivers and have begun to infiltrate low and middle income countries (13). Moreover, low and middle-income countries are now disproportionally affected, with over 80% of CVD deaths occurring in these regions (9). Although CVDs mortality figures have declined in many high-income countries, population ageing maintains them as the leading cause of death. In Europe for instance, CVDs cause 4 million or almost 50% of deaths annually (12). CHD is the leading cause of death for both men and women in the US (14). In 2010, CVDs were the biggest killer in the UK, claiming around 180,000 lives (15). It is the chief cause of death in women across Europe and is also the leading cause of death in men in all but 6 European countries (12, 15). CHD and stroke are the top two single most common causes of death across Europe. CHD occupies the top spot with 1.8 million deaths and Stroke ranks second with 1.1 million deaths (12).

The epidemiological projections for CVD are alarming. By 2015, one in three deaths will be due to CVDs. CVD deaths are projected to climb to 23.3 million by 2030, with CHD and stroke

continuing to lead the way (16). According to these projections, CVDs will remain the single leading cause of death globally (9).

Definition, aetiology and clinical picture of CVDs

Cardiovascular diseases (CVDs) are a group of disorders affecting the heart and blood vessels of the body. CVDs can be classified as atherosclerotic or non-atherosclerotic based on their aetiology. Coronary heart disease (disease affecting the coronary arteries supplying the heart), cerebrovascular disease (disease affecting the cerebral arteries supplying the brain), aortic disease (disease of the aorta) and peripheral arterial disease (PAD, disease affecting arteries supplying the lower limbs) constitute the atherosclerotic disorders (9, 14, 15). On the other hand, congenital heart disease (structural malformations of the heart), cardiomyopathies (disease of the heart musculature) and rheumatic heart disease (post streptococcal damage to the heart muscle and heart valves) are members of the non-atherosclerotic group. This classification is illustrated in Figure I. The main emphasis of this dissertation will be on atherosclerotic CVDs, and by way of disambiguation, the term CVDs will refer exclusively to that disease subgroup.

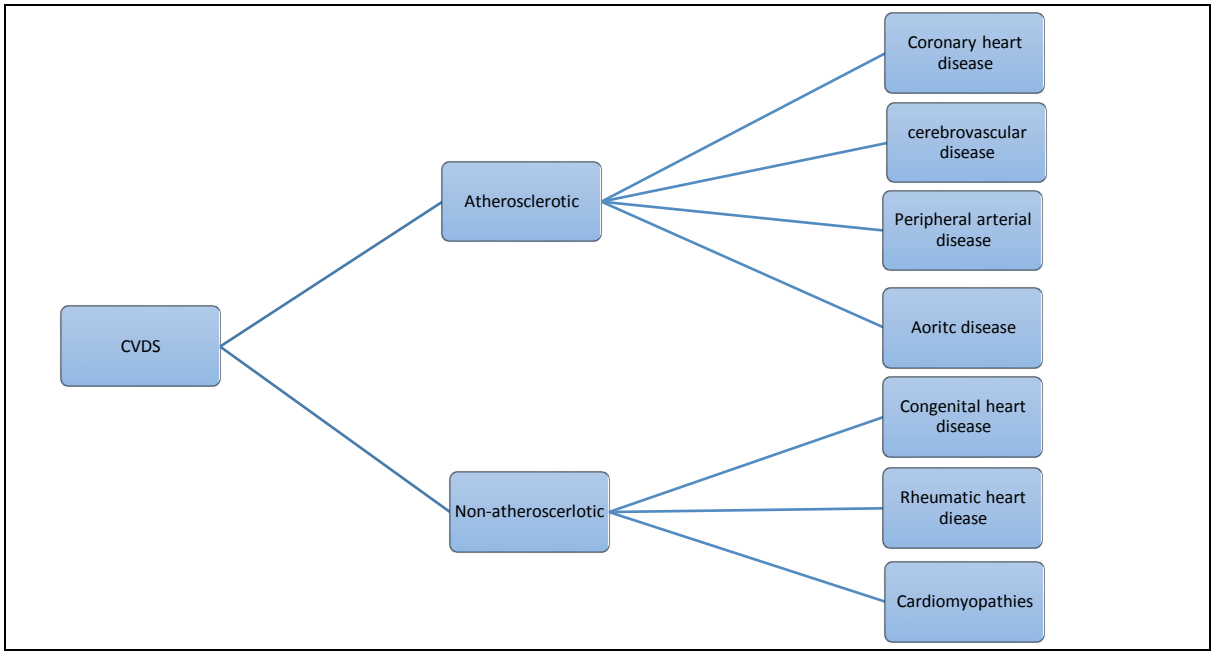


Figure I: Diagram showing the classification of CVDs adapted from WHO Fact Sheet on CVDs (14)

The principal CVDs share the same causal pathway- a process known as atherosclerosis. This refers to a chronic inflammatory process by which fat, cholesterol deposits accumulate within arterial walls forming what are called atheromas (14). A progressive narrowing of the lumen of the vessel occurs as these atheromas grow. Eventually, the vessel lumen becomes so narrowed that blood flow is compromised and threatens the viability of the tissue or organ being perfused by the affected artery. A simplified diagram illustrating the atherosclerotic process is depicted in Figure II. When this process occurs within the coronary arteries, coronary heart disease develops. Alternately, when it occurs within the cerebral arteries, cerebrovascular disease develops and finally, when it occurs within arteries of the lower limb peripheral arterial disease develops.

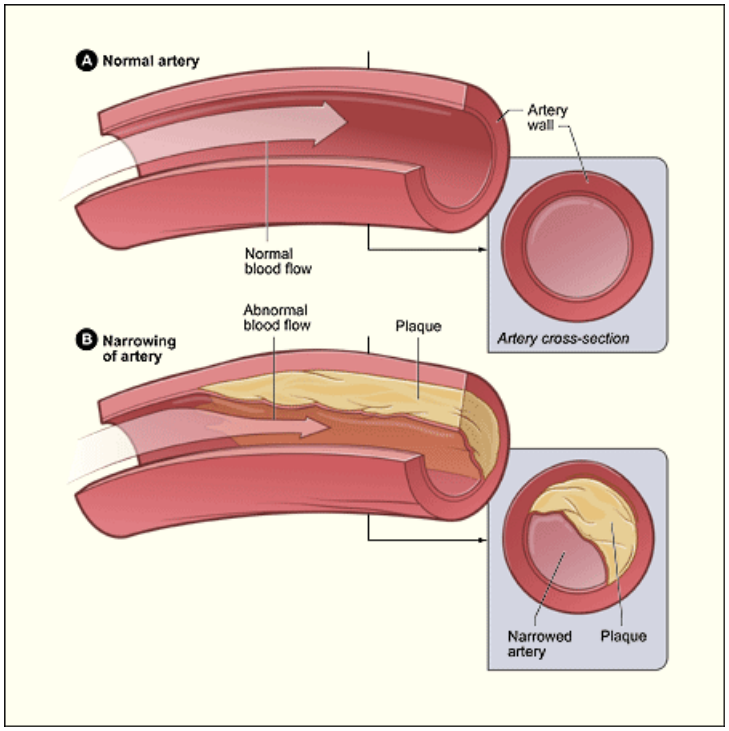


Figure II: A diagrammatic representation of the process of atherosclerosis adapted from National Institutes of Health DoHaHS, US Government What Is Atherosclerosis? USA: National Institutes of Health , Department of Health and Human Services, US Government 2014 [cited 2014 January 10, 2014]. Available from: http://www.nhlbi.nih.gov/health/health-topics/topics/atherosclerosis/ (17)

The clinical picture which emerges, depends on the type and severity of CVD. It is important to note that patients may also be asymptomatic for long periods. Patients with CHD may experience shortness of breath, and chest pain (18). As the disease progresses, these symptoms worsen in terms of severity and frequency until the patient develops a heart attack which can result in severe morbidity and mortality. Patients with cerebrovascular disease may develop a range of neurological symptoms depending on the severity of the disease. Warning symptoms may include short spells of weakness, numbness or tingling in arms or legs on one side of the body lasting less than 24 hours. Persistence of these symptoms beyond that time point combined with onset of seizures, vomiting, inability to speak, swallow among other neurological symptoms are suggestive of a stroke which can result in sudden death or lead to significant morbidity (19).

The risk factors for CVDs

A risk factor can be defined as any environmental, behavioural or biological exposure or attribute of an individual that directly increases the likelihood of developing a disease or injury (9, 20). The "Bradford Hill criteria" published by esteemed epidemiologist Sir Austin Bradford Hill almost 5 decades ago, have been widely accepted as the gold standard framework for assessing causation (21). According to Hill, risk factors should demonstrate a number of characteristics in order to be classified as causal. These features include strength (the greater the strength of the association the greater the probability of causation), specificity (the probability of causation is strengthened in cases where an association is limited to specific groups located in specific environments and which are exposed to a particular risk factor), temporality (the exposure must precede the onset of the outcome), biological gradient (the dose of the exposure is typically proportional to the incidence of the disease but there can be cases of inverse proportionality), plausibility (the biological plausibility of the underlying causal mechanism increases the credibility of the causal hypothesis) , coherence (the cause-effect relationship being evaluated should align with the known facts of the natural history and biology of the disease), experiment (it may be useful to rely on experimental or semi experimental evidence), analogy (the effect of factors similar to established casual factors may be considered). Inherent limitations of some of Hill's criteria means that fulfilment of all the criteria is not a perquisite to confirming causality. This framework serves merely as an aid to judgment.

Longitudinal studies have been useful in evaluating causation. The classic Framingham Heart Study was a ground-breaking cohort study that helped to delineate the risk factors for CHD and by extension CVDs (22). Figure III, which follows on page 11, illustrates the causal pathway

and the relationship between the various groups of risk factors implicated in CVD development. The social determinants of health such as education and poverty represent the most distal risk factors for the development of CVDs. These social determinants increase the exposure to a number of behavioural risk factors such as tobacco use and poor diet. These behavioural risk factors in combination with a group of genetic factors in turn drive the development of a number of health conditions such as diabetes and hypertension which form the intermediate risk factors. These intermediate risk factors ultimately drive the onset of CVDs.

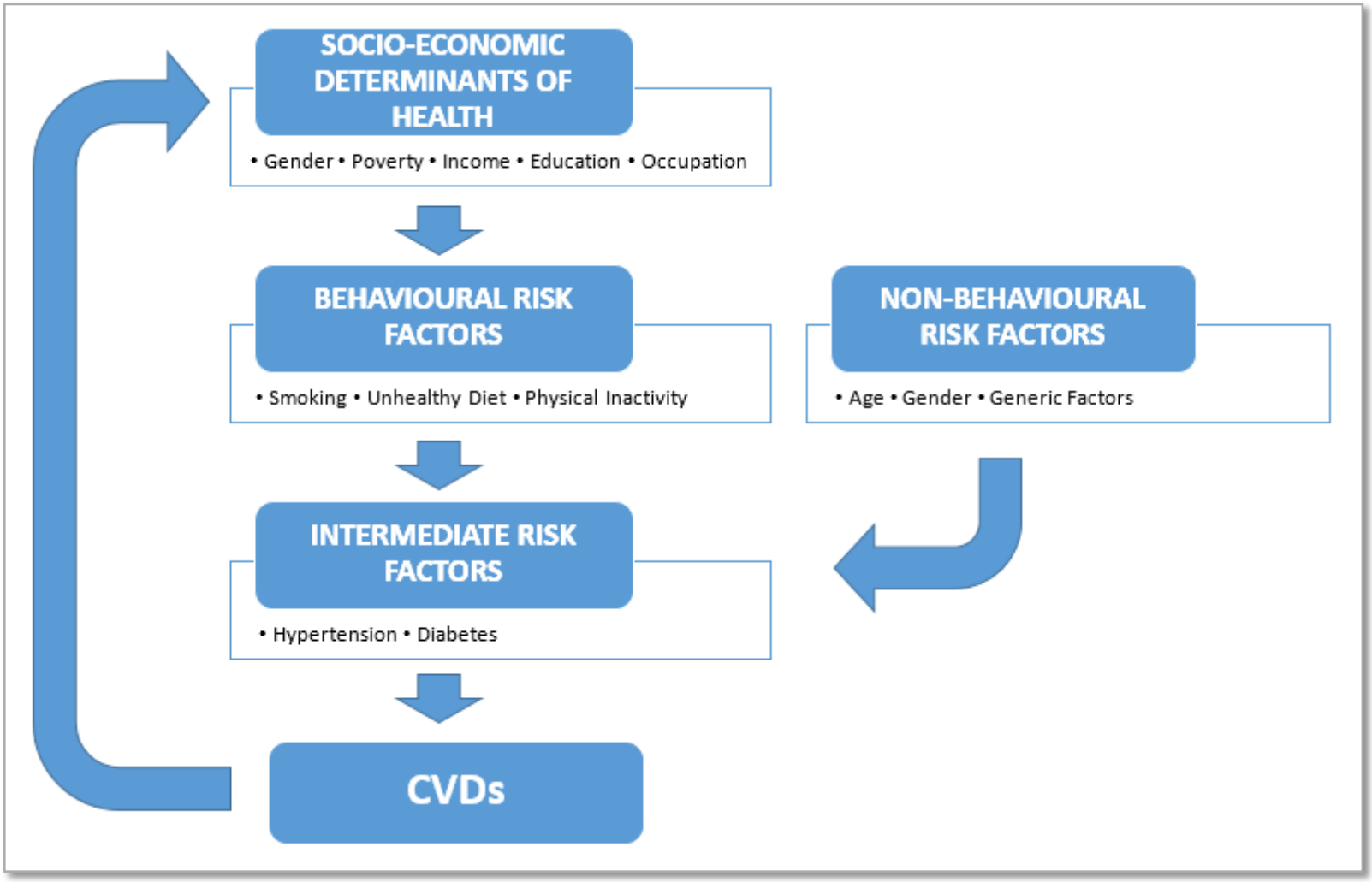


Figure III: The causal pathway for CVDs illustrating the relationship between the risk factors. Adapted from Dahlgren and Whitehead's Determinants of Health Model (23)

The relationship between the social and behavioural drivers of CVDs

CVDs are caused, to a large extent, by four main modifiable behavioural risk factors. These are tobacco use, poor diet, harmful use of alcohol and physical inactivity (19). These behavioural risk factors are estimated to account for nearly 80% of cases of coronary heart disease and cerebrovascular disease (9) These behavioural risk factors are strongly associated with the social determinants of health including education and poverty. It is theorised that within vulnerable populations, a viscous cycle perpetuates: poverty exposes people to behavioural risk factors for CVDs and, in turn, the resultant CVDs propel families towards poverty.

There is robust evidence on the connection between poverty and reduced life expectancy, and on the associations between the several social determinants of health and prevalent levels of CVDs. People of lower social and economic positions fare far worse in all countries irrespective of the level of development (24). They tend to be characterised by poor educational attainments, low income, high incidence of unemployment, poor housing conditions and limited access to health care and services (25). All of these factors promote poor health and contribute to the escalating burden of CVDs by exposing these people to tobacco use and poor diets and the other behavioural risk factors.

These behavioural risk factors are the product of not only population ageing; but are also the products of globalization, for instance, unfair trade and irresponsible marketing, rapid and unplanned urbanization and increasingly sedentary lives (24). People in these regions are becoming more exposed to behavioural risk factors common in urban areas. In vulnerable low and middle-income regions, unhealthy diets rich in salt and fat are becoming more prevalent, tobacco use and availability are unregulated, harmful use of alcohol is common and a shift towards more sedentary lifestyles has been observed (24). The Governments of low-income countries are overwhelmed by competing priorities and lack the capacity to adequately

intervene to provide the infrastructure, services and legislation to address these changes (25). Within developed states, there is a distinct difference in the prevalence of harmful behavioural risk factors in poor versus the rich in society (26). The reality that exists is that the higher ones social position the better one's health is likely to be. This consistent finding underscores the point that health inequalities is driven by the underlying social inequities and the attendant effects on behavioural factors. The overall consequence, vulnerable and socially disadvantaged people are more prone to illness and die sooner than people of higher social positions and live their shortened lives with longer periods of health related disabilities (26).

While poverty and other social determinants drive CVDs, the serious socioeconomic consequences of CVDs including increasing individual and household impoverishment is well established. In low-resource settings, the costs related to treatment for cardiovascular diseases and other non-communicable diseases can rapidly drain household resources, driving families into poverty (25). Most of the health care costs are private and out-of-pocket and thus weigh more heavily on those least able to economically cope, driving impoverishment and exacerbating social inequity. In a World Bank qualitative survey of 60 000 poor women and men in 60 countries, sickness and injury were the most frequent triggers for downward mobility (27). According to The World Health Report 2010, each year, 100 million people are pushed into poverty because they have to pay directly for health services; in some countries, this may represent 5% of the population forced into poverty each year (28). Essentially, vulnerable people become trapped in vicious cycle where poverty and NCDs persistently reinforce each other.

The epidemiology of the behavioural risk factors

Tobacco Use: It is reported that each year, almost 6 million people die from direct and second-hand consumption of tobacco (29). By 2020, this estimate is projected to rise to 7.5 million, at which point smoking will account for 10% of all deaths (30). It is currently is reported to cause

nearly 10% of cardiovascular diseases. Global consumption of cigarettes has been climbing steadily since 1970s and this increase is driven mainly by global population growth (29). Smoking prevalence is highest among upper-middle-income nations but among men it is most common in lower-middle-income states (9). In Europe, it still remains a major health concern. Despite downward trends in smoking rates in this region, the rate of decline has slowed, remained stable and the rate has risen in some countries, notably among women (12). In Great Britain, 20% of adults smoke cigarettes (30, 31).

Insufficient physical activity: It is estimated that physical inactivity causes 6% of the global burden of CHD and 7% of that of type II diabetes. It is responsible for 9% of premature mortality, or more than 5.3 million of the 57 million deaths that occurred worldwide in 2008. This figure equates to as many global deaths as tobacco causes, which is traditionally regarded as a major CVD risk factor (32). The prevalence of physical inactivity is highest in high-income countries (9, 33). It is however noted that levels are rapidly rising in some middle-income countries especially among women. Only a small proportion of European adults maintain adequate levels of physical activity, with inactivity more common among women (12). People who are insufficiently physically active have a 20% to 30% increased risk of all-cause mortality (34). Physical inactivity is the main cause for approximately 30% of cases of CHD and is causally implicated in its precursors (35). Notably, it accounts for 27% of diabetes cases and is independently associated with metabolic syndrome (36). As a modifiable risk factor, regular physical activity has been proven to reduce the risk of hypertension and other cardiovascular diseases among other non-communicable diseases (34).

Unhealthy diet: Approximately 1.7 million deaths are attributable to low fruit and vegetable diets globally (36). Within this global frame**,** unhealthy diets are becoming acutely more

prevalent in lower-resource settings. High salt consumption is an established determinant of hypertension and cardiovascular risk. The dietary salt intake in most populations exceeds that recommended by the WHO for disease prevention (9). Diets rich in saturated fats and trans-fats are associated with an increased risk of heart disease (36). Data have indicated a rapid rise in fat consumption in lower-middle-income countries since the 1980s. An overall increase in the fruit and vegetable consumption and a stabilisation of the fat intake has been observed across Europe in recent decades (12, 31). In the UK, less than one-third of men and women consume the recommended five or more portions of fruit and vegetables a day (31).

Harmful use of alcohol: Approximately 2.3 million or 3.8% of global deaths are attributed to the harmful use of alcohol (9). More than half of these deaths occur due to cardiovascular disease and cancers among other non-communicable diseases. The highest per capita consumption has been found in high and upper-middle-income countries (9). In 2010, greater than a third of UK men (36%) and over a quarter of UK women (28%) regularly exceeded the UK Government's recommended alcohol intake (31).

The epidemiology of the intermediate risks factors

These four main behavioural risk factors may lead to the development of hypertension, diabetes mellitus, dyslipidaemias, overweight or obesity. Collectively, they constitute "intermediate risks factors" and signify an increased risk of developing cardiovascular complications such as heart attack or stroke (9).

Hypertension: Elevated blood pressure is estimated to account for 9.4 million or 16.5% of all deaths annually (14) . It is a principal risk factor for cardiovascular disease. Around one in three adults in England and Scotland are hypertensive and nearly half of them are untreated (18). No significant difference in prevalence of hypertension exists across income groups, though it is typically lowest in the high-income bracket (9).

Overweight and Obesity: According to the World Health Organisation (WHO) more than 2.8 million people die each year as result of being overweight or obese (36) The risk of CHD, strokes and diabetes increases with increasing body mass index (BMI). Overweight is most prevalent in upper-middle-income countries but is also quite prevalent in lower-middle-income counties. Under-nutrition has been a characteristic feature of lower-middle income countries in Africa, Latin America and South-East Asia, but a transition towards overweight and obesity has occurred. In fact, the fastest growth in overweight occurs in lower-middle-income countries (36). Child overweight and obesity rates are highest in upper-middle-income populations. Child and adult obesity rates are high across Europe, where over 50% of women are overweight (12). More than a quarter of adults in England are obese (18).

Elevated cholesterol: High cholesterol levels have been proven to increase the risks of heart disease and stroke (14). It is responsible for an estimated 2.6 million deaths each year (9, 33). Approximately, six in ten adults in England have high blood cholesterol levels (≥ 5mmol/l) (15).

Diabetes: Approximately 65% of diabetics die from CVDs (33, 37). Mortality from stroke is increased almost 3-fold in diabetics compared with non-diabetics (14). European prevalence of diabetes is high and has risen rapidly over the last decade, increasing by over 50% in several countries (31). In the UK, the prevalence of diabetes is around 5% among women and 6% among men (18)

The epidemiology of non-behavioural risk factors

Although the behavioural risk factors and their socio-economic determinants are the main drivers of CVDs, non-behavioural factors such as age, gender, ethnicity and genetics factors are also important (18). They interact with the behavioural risk factors to bring about the development of hypertension and diabetes and all the other intermediate risk factor conditions. These factors are non-modifiable and therefore not the focus of preventative interventions. The influence of the risk factors on the global CVD burden is described below.

Age: Age is the most important factor in this category, as the risk of cardiovascular disease increases notably with age. The risk of developing CVD triples with each decade of life (15). Approximately, 82 percent of people who die of from CHD are 65 years or older and the risk of stroke doubles with each decade above 55 (38).

Gender: Men are more predisposed to developing CHD and stroke than pre-menopausal women (9). They manifest the disease earlier in life than their female counterparts. Even after menopause, the prevalence of the disease in female populate is not as high as it is in the male demographic. However, women who suffer cardiac events are more likely to die from them in a few weeks (15).

Race and Family history: UK data has shown that CHD rates are highest in South Asian communities. Strokes are most common in people of Afro-Caribbean descent (15). Hypertension and diabetes, intermediate CVD risk factors, occur most commonly in people of Afro-Caribbean and South Asian populations. A positive family's history of CVD, especially premature strokes or cardiac events in first-degree male relatives under 55 or female relatives under 65 increases an individual's risk (18).

The socio-economic burden of CVDs

CVDs represent a significant source of morbidity and thus reduction in quality of life. In 2010 in the UK, 4045 years of life lost (YLL) per 100,000 men between the ages of 0-69 due to all causes were reported. CVDs accounted for 19% of this figure (784 YLL per 100,000 men). In that same year and age category, 2500 YLL per 100,000 women were reported of which CVDs accounted for 12% (309 YLL per 100,000 women) (12). Disability adjusted life years (DALYs) for a disease is defined as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the disease or its consequences (39). CVDs are the second largest single cause of lost DALYs behind neuropsychiatric disorders in developed European countries (12). Cardiovascular disease is responsible for 10% of DALYs lost in low- and middle-income countries, and 18% in high-income countries (40). However, in less developed European countries it surpasses neuropsychiatric disorders. The costs of CVDs as well as their behavioural and intermediate risk factors to individuals, families, communities, businesses and government are high, and still escalating with significant concomitant macroeconomic implications. Heart disease, stroke and diabetes result in billions of dollars in losses of national income each year in the world's most populated countries. Rough estimates from economic analyses suggest that a 10% rise in NCDs is associated with a 0.5% annual reduction in economic growth (9).

The overall estimated cost of CVDs in the EU is €196 billion a year (12). Of the total cost of CVDs in the EU, about 54% is due to health care costs, 24% due to productivity losses and 22% due to the informal care of people with CVDs. In 2009, CVDs cost the UK health care system £8.7 billion and the UK economy £19 billion in total (15). As a result of the substantial personal (out-of-pocket) absorption of health-care costs in poorer countries, the cost of health care imposes a substantial burden on household budgets, especially for low-income families.

CVDs are chronic diseases and so are cumulatively expensive. Financial investment in healthcare costs for CVD frequently creates a situation where fewer funds are available for basic necessities such as food and shelter fuelling the poverty cycle described earlier.

Prevention of CVDs

Considering the epidemiological, health, and socio-economic burden of CVDs, in both the economically developed and developing world, and the future projections, there is an ever-pressing need for robust multifaceted and all-encompassing interventions to combat CVDs. Since 80% of CVDs cases are caused by preventable behavioural risk factors it is a natural corollary that preventative strategies have been the main thrust of global efforts to combat CVDs. There are three levels of prevention: primary, secondary and tertiary, which target the CVDs at different point in their disease cycle (41). Primary prevention is geared at reducing the impact of the socio-economic drivers and behavioural risk factors to prevent the biological onset of CVDs. Alternately, secondary prevention strives for detection of CVD early in the disease process before it has caused suffering or disability. Finally, tertiary prevention involves rehabilitation efforts to prevent further deterioration once the disease has induced morbidity. Primary prevention, aimed at risk factor reduction, targets the entire group of CVDs but secondary and tertiary preventative strategies vary from one CVD to another. In many settings especially in low and middle-income populations, there is inadequate tertiary preventative care for people with CVDs as a result of limited access to required technologies and drugs.

The primary prevention of CVDs generally as well as the secondary and tertiary prevention of specific CVDs, namely CHD and cerebrovascular disease, have been the centre of extensive research and global health control efforts. This dissertation aims instead to shift focus to a relatively overlooked member of the CVD family of disease, peripheral arterial disease. It will specifically seek to look at various aspects of the tertiary prevention of the disease.

Chapter II: A case for peripheral arterial disease and exercise rehabilitation

Preview: In this chapter, I will review the relevant clinical and epidemiological features of peripheral arterial disease. I will then take a closer look at exercise rehabilitation exploring the evidence supporting its effectiveness as well as the gaps in the evidence.

What is PAD?

Intermittent claudication (IC) is defined as muscular pain or discomfort elicited by physical exertion and rapidly relieved by rest. It typically occurs in the calf but can be experienced in the foot, thigh or buttock. It is the primary and first recognizable symptom of peripheral arterial disease (PAD), which by definition refers to atherosclerotic disease of non-cerebral and non-coronary arteries. PAD is generally used to describe atherosclerotic disease of the lower limb arteries and is an important cause of mortality and morbidity for people in many Western countries (42).

Epidemiology and risk factors

The epidemiology and aetiology of the underlying PAD is well established. The worldwide prevalence of PAD is estimated to be 10% and this figure rises to 15-20% in people over 70 years (38). There are over 27 million people affected in North America and Europe alone (43). Data on annual incidence rates for PAD were lacking. The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) explained that the paucity of evidence was due to the difficulty in measuring the incidence of PAD considering that a significant fraction of the PAD population are asymptomatic of IC (see page 23).As described previously, atherosclerosis is at the core of the causal pathway for PAD and other CVDs and so they all share the same risk factors. These can be divided into modifiable and non-modifiable. The non-modifiable risk factors include age, ethnicity and gender. The incidence of PAD increases with age. There is a slight male preponderance as the male to female ratio commonly reported, is 2:1. It is most common in the black ethnic group with an odds ratio of 2.83 (43).

The modifiable risk factors include cigarette smoking, diabetes mellitus, hypertension, hyperlipidaemia, obesity, physical inactivity and poor dietary intake.

The relationship between smoking and PAD is well established. Data have suggested that cigarette smoking is the strongest single individual risk factor in the development of PAD. There are currently 1 billion smokers globally and they have been found to demonstrate a 4 times greater risk of developing intermittent claudication than non-smokers (43). The diagnosis of PAD is made about a decade earlier in smokers than in non-smokers and the severity of the disease tends to increase with increased numbers of cigarettes smoked (44) Additionally, of patients with PAD, those who smoke are more likely to require intervention or amputation than non-smokers (38).

Diabetes mellitus is also strongly associated with PAD. Globally, 347 million people suffer from diabetes and they are twice as likely to develop PAD as non-diabetics (44). According to a meta-analysis of 13 studies a 1% rise in glycosylated haemoglobin level (a reliable indicator of blood glucose control) was associated with a 26% increased risk for developing PAD (43). Further, diabetics undergo a more rapid clinical deterioration.

Hypertension and hyperlipidaemia have been established as independent risk factors. A blood pressure reading exceeding 160/95 mmHg is associated with a two and half-fold and four-fold increase in risk of developing intermittent claudication for men and women respectively (44). A fasting blood cholesterol level greater than 7mmol/L is associated with a two-fold greater risk of intermittent claudication. Other factors have been associated with an increased risk of PAD but these have not been proven to be causal. These include elevated blood haematocrit level, a condition known as hyperhomocysteinemia or elevated plasma levels of fibrinogen (43).

The pathophysiology and prognosis of PAD

PAD occurs consequent on atherosclerotic narrowing of the arteries of the lower limb. When narrowing begins to compromise the blood flow to the musculature of the lower limb, ischemia occurs on exertion which manifests causing pain in the affected muscle group. This pain is

what is referred to as IC. One third of patients with PAD experience intermittent claudication, the remainder are asymptomatic. Of the asymptomatic patients 7-15% of them develop IC within 5 years. IC is associated with reduced exercise capacity, functional limitations and ultimately overall reduction in quality of life.

Approximately 20-25% of patients with IC will worsen and develop critical limb ischemia (the most severe stage of the disease in which the viability of the limb is threatened and intervention is required) (43). Major amputation is common in diabetic patients but is otherwise a rare outcome with only 1-3% of patients with intermittent claudication requiring major amputation in a 5 year time span (44). In spite of this, there are still 500-1000 new cases of critical limb ischemia per million of the population in the UK (43). The prognosis for patients with critical limb ischemia is unfavourable. Approximately 12% of affected patients require amputation within 3 months of presentation and 20-25% will die within a year (44). Only about 50-60% of patients with critical limb ischemia will survive 5 years. This 5-year mortality rate is lower than for most cancers.

PAD is a manifestation of generalized atherosclerotic disease and it therefore follows that 65% of patients with PAD also have clinically significant coronary artery and cerebrovascular disease and 25% have renal artery stenosis (38, 43). One fifth of patients with intermittent claudication have non-fatal cardiovascular events. The results of a large UK cohort study showed that patients with PAD have a six fold higher risk of cardiovascular disease related death than those without PAD (43).

The socio-economic burden of the PAD

In the US the total annual cost of PAD is estimated to exceed 21 billion USD, with the costs related to treatment of PAD further increasing this estimate (45). Critical limb ischemia costs the NHS in the UK government greater than £200 million (43). The burden is not purely an

economic one and there are a number of personal and social implications of PAD, which include disability-related functional limitations, reduction in quality of life, implications on the family infrastructure, and loss of wages.

Aims of therapy and description of the intervention

The main aims of therapy for IC are to reduce the symptoms burden, prevent clinical deterioration and decrease the incidence of cardiovascular events. The forms of therapy include risk factor reduction (cessation of smoking, control of diabetes etc.), pharmacotherapy (antiplatelet agents, vasoactive drugs) and exercise therapy (ET). This paper will isolate and focus exclusively on exercise therapy in PAD management.

ET is reported to be the primary and most effective treatment for intermittent claudication (46). The benefits of exercise therapy in the treatment of PAD were identified from as early as 1966 when the first randomised controlled trial investigating its effect on PAD, was conducted. Leng et al, conducted a Cochrane review of randomised controlled trials in 2000 which was updated in 2008 by Watson, which showed that exercise therapy was responsible for a roughly 150% increase (50%-200%) in overall maximal walking ability when compared with no exercise, medical therapy or surgical therapy (42). It has also been found to reduce the incidence of cardiovascular events in patients with IC (43).

How might an exercise the intervention work in PAD?

The physiological mechanism(s) by which ET induces symptomatic improvement in intermittent claudication has not yet been established. The existing hypotheses include an increased and more effective blood perfusion throughout the legs, a shift from anaerobic to more aerobic metabolism and increased rheological properties of the blood (42) .

It has been hypothesized that the changes are due to the development of collateral blood vessels, which facilitates enhanced blood flow throughout the entire limb (47). The collaterals are thought to facilitate the redistribution of blood flow from inactive to active muscle groups. This increased blood flow is then thought to increase the oxygenation of active muscles. Though plausible and demonstrated in a study, there exists no reproducible evidence to support this hypothesis.

Subsequent review of the evidence has revealed that the resultant functional improvement is not proportional to the extent of revascularisation, which suggests that there is another mechanism contributing to the functional improvement. It has been theorised that PAD produces not only a reduction in blood flow but also a metabolic defect or "metabolic myopathy" at the level of the muscle cells (48). ET is thought to reverse this metabolic change by altering the relative proportions of the isoforms of the three myosin heavy chains (MHC I, IIa and IIb) found in mature skeletal muscle. The relative proportion of the MHC influences the metabolic behaviour of the myocytes. MHC I one fibres promote efficient oxidative metabolism whereas MCH IIb fibres are linked to anaerobic metabolism leading to the accumulation of lactate. A recent study demonstrated that SET had increased the proportion of MHC I which promoted more oxidative metabolism and less anaerobic metabolic activity. This finding has not yet been corroborated by other studies and as such definitive conclusions cannot be drawn about the mechanism by which ET is mediated (48).

It has been postulated that exercise induces changes in the blood rheological properties, which facilitates increased flow across foci of atherosclerotic narrowing within blood vessels. This hypothesis is thought to be the least robust of the existing theories and like the others it remains unproven (47).

The additional benefit of supervision

The exercise programmes included in Watson's meta-analysis varied in their degree of supervision, format, intensity, and composition among other elements. The degree of supervision has emerged as one of the key elements of SET programmes. The traditional exercise prescription consisted of "go home and walk" advice with or without accompanying brochures containing written guidance. This exercise regime has the advantage of being relatively cheap and low risk compared with more invasive treatment options. Despite this, evidence revealed that only half of the patients adhere to exercise advice regimes; the lack of supervision was found to account for the poor compliance rates (49). A Cochrane review of systematic trials comparing supervised with unsupervised exercise therapies found that supervised exercise therapy (SET) is a more effective exercise prescription than non-supervised exercise therapy for patients with IC (50). The beneficial clinical results of supervision over advice could be explained by a few reasonable theories. The treadmill walking is of a higher workload than ground walking at regular speed, which is the usual mandate for the advice group (51). Exercise intensity is difficult to measure, but it is considered safe to assume that SET is of greater intensity than home regimes. Further, the greater the exercise workload the better the overall physical condition of the patient leads to better cardiovascular conditioning and more marked exercise induced adaptations (52). This theory was given credence by a study that demonstrated the positive impact that improved general physical condition had on walking distance (53). Additionally, supervised regimes provide added external motivation and positive reinforcement to boost the patient morale and improve adherence to the programmes (54). Based on this evidence, The National Institute for Health and Clinical Excellence (NICE) in its PAD guidance entitled "Lower limb peripheral arterial disease: diagnosis and management" recommended that a supervised exercise programme should be offered to all people with intermittent claudication. This programme should involve "2 hours of supervised exercise a

week for a 3-month period" and "encouraging people to exercise to the point of maximal pain" (55).

IC versus PAD

It is essential to note that many studies have used both the terms IC and PAD to refer to the same disease process at the level of the study title. From a technical standpoint these two terms are distinctly different, IC refers to a symptom whereas PAD represents the underlying disease process. This has incited some confusion as to whether a disease or a symptom is being treated and thus must be disambiguated. As described previously, ET, which is the intervention of focus in this study, targets the symptom (improving claudication pain) as well as the underlying disease process (reducing atherosclerosis, reducing cardiovascular events). PAD patients are either asymptomatic, symptomatic of IC, or have severe disease (critical limb ischemia). Asymptomatic patients are often undiagnosed and patients with severe disease require more invasive interventions (vascular surgery). The author has postulated that IC has often been used in preference to PAD (at the level of the title) in research investigating exercise in PAD because ET is the treatment of choice for PAD patients who suffer IC. This thinking justified the use of IC as the title focus for this research.

Chapter III: The rationale for research methods

Preview: In this chapter, I will outline the advantages and appropriateness of carrying out a systematic review to evaluate the existing evidence on the long term value of SET. I have also built a case for a randomized controlled trial should the evidence be lacking.

The gaps in the evidence on supervised exercise therapy for intermittent claudication

Although the evidence shows that SET confers the greatest benefits to patients with IC, there are a few areas of uncertainty surrounding this intervention. There is a paucity of data on the long-term clinical and behavioural effects, which are critical in evaluating sustainability of SET. A Cochrane review which was carried out in 2009 and which compared centre-based supervised with non-supervised home based therapy in the treatment of a range of chronic diseases found that while supervised programmes were superior in the short term but home based programmes were superior in terms of adherence (56). Importantly, it was noted that no long term data were available for PAD which has left the question of longevity unanswered. Long-term adherence is thought to translate into more sustained benefits but the absence of evidence has precluded a reliable confirmation of this hypothesis.

My review of the existing literature has also revealed that to a large extent, the studies have focused on clinical outcomes while neglecting behavioural outcomes. It is paramount that SET interventions induce behavioural changes where physical activity patterns and compliance levels are concerned, in order for sustained clinical benefits to be realised. It is also particularly important to determine the behavioural changes post receipt of intervention and not just during the course the intervention (57).

The rationale for a systematic review

For these reasons, these relatively unevaluated areas must be examined more closely. Fortunately, a number of recent studies exploring aspects of supervised exercise therapy have emerged which could potentially provide more comprehensive data on long-term effects. I propose that a systematic review of the evidence would be the most effective research method to evaluate the evidence to determine if the question of sustainability can be answered more comprehensively.

A systematic review strives to compile all the empirical evidence that has met pre-set eligibility criteria to answer the desired research questions (58). It is characterised by a number of features which include: a clearly defined set of research objectives with pre-defined eligibility criteria for studies, a replicable and transparent methodology, a systematic search for studies geared at identifying studies meeting the inclusion criteria, an assessment of the validity of the included studies, a systematic description and combination synthesis of the characteristics and findings of the studies. These features collectively help to reduce the risk of bias in so far as to provide reliable findings from which more concrete conclusions can be drawn (58)

Once the existing evidence is adequate, a review would allow me to produce recommendations on the long-term value and sustainability of SET. These recommendations stand to optimise the therapeutic benefit of SET as a first line therapy for patients with IC.

The ideal alternative to a systematic review: a randomised controlled trial

Carrying out primary data collection would have been a possible alternative to the performing a systematic review. Of the types of primary research methods, a randomised controlled clinical trial would have been the most ideal option to answer the research question. It is defined as a prospective study comparing the effect and value of intervention(s) against a control group (59). Study participants are randomly assigned to two or more treatment groups to test a particular intervention. One group (the experimental group) receives the intervention being assessed; the other group (the control or comparison group) receives an alternative intervention, a placebo intervention or no intervention at all. The groups are followed up over time to determine the relative effectiveness of the experimental intervention (59). Outcomes are typically measured at defined points and differences in response between the experimental and control group are assessed statistically.

They are characterised by the following features:

(I) Random assignment of participants to intervention groups. Randomisation ensures that there are no systematic differences between the intervention groups where confounding factors are concerned.

(II) The researchers and the participants are unaware of which intervention administered during the course of the study. This helps to minimise the impact of bias.

(III) All factors are kept constant between the intervention groups with the exception of the experimental intervention. This ensures that any observed difference between the groups can be attributed to the experimental intervention

(IV) Participants are analysed within the group to which they were originally allocated (intention to treat analysis). This statistical approach preserves randomisation.

(V) The analysis is geared at estimating the size of the difference in the response of each intervention group to the intervention each received.

Based on the above features and their stated advantages RCTs are considered to be the gold standard for assessing treatment effects. In this case, I would seek to compare the long term clinical and behavioural outcomes of SET compared to usual care (exercise or walking advice) among patients with IC. Despite the enormity of the benefits of conducting an RCT, the realization of such a study would prove to be logistically and financially infeasible. Firstly, the various phases involved including RCT design, obtaining ethics approval, implementation, data collection and analysis could not realistically be executed in a single academic year. Secondly, the aim of the trial would be to examine long-term effects which would certainly be in excess of one year. Thirdly, as an independent researcher, I would not have access to the size research team required for the successful implementation of a RCT. Undoubtedly, the

delivery of SET would be highly cost intensive and thus would be financially prohibitive based on the limited financial resources.

In the event that the systematic review reveals that evidence on sustainability is in fact lacking and determinative conclusions cannot be drawn, I propose to design a full protocol for the ideal RCT to answer the question of sustainability of SET programmes. This course of action would be both financially and logistically feasible. Having identified the study design and methodological deficiencies of the existing studies, the protocol would grant me the opportunity to practically apply the solutions to the identified weaknesses into designing an improved study. Indeed, well-designed studies have profound impact on clinical practice. A well thought-out and optimally designed RCT usually facilitates effective implementation of RCT, which in turn provides high quality evidence to shape clinical practice and health policy.

Chapter IV: The long-term effects and sustainability of supervised exercise therapy in the treatment of intermittent claudication: a systematic review

Preview: In this chapter I will present the specific objectives, the methodology, the results, discussion and conclusions of the systematic review investigating the long term value of SET.

Objectives:

This review aims to explore the gaps in the evidence by addressing the following research questions:

1. What are the sustained effects of supervised exercise therapy (SET) on the behavioural outcomes of patients with intermittent claudication?
2. What are the sustained effects of supervised exercise therapy (SET) on the clinical outcomes of patients with intermittent claudication?

Methods

Search Conducted: April 2013

Criteria for selection of studies for this review

Types of studies

All relevant randomised-controlled trials (RCT) published in peer-reviewed journals were considered for this review. Non-English studies and those produced before 1990 were not considered for the purpose of this review.

Types of Participants

Studies considered for this review comprised of patients who had established IC and at least one documented baseline claudication measure: initial claudication distance, absolute claudication distance, pain free/maximal walking distance or maximum walking time. All studies that included patients with severe PAD or other debilitating co-morbidities such as osteoarthritis or severe CVD that preclude or restrict exercise therapy were excluded from consideration.

Types of Interventions and Comparison

RCTs considered for this review compared SET with a control group receiving usual care (advice) or home based structured programmes as alternatives to SEP. All trials where the control group did not receive exercise instruction (home based or otherwise) were excluded. The inclusion of studies was not limited by features of the SET regimes namely the intensity, duration, frequency.

Types of outcome measures:

RCTs included post-trial follow up outcome evaluations at least 3 months after cessation of the trial dose of supervised exercise therapy. The primary behavioural outcomes of interest are as follows: Post-trial physical activity levels assessed by self-report or objective measures. The primary clinical outcomes included objective measures of claudication severity including: Absolute/maximum claudication distance (ACD) or maximum walking time (MWT). Secondary outcomes include quality of life and adverse effects.

Search Method for identification of studies

A search strategy including set search terms for the main concepts such as "intermittent claudication" and "exercise therapy" etc. was designed. The following electronic health databases were then searched: PubMed, EMBASE, The Cochrane Library and CINAHL. The same research strategy was used against all databases. The reference lists of relevant studies were carefully perused for any additional papers.

Study Selection:

The results obtained from the database searches were examined to remove duplicates, screened by title and abstract and subsequently placed into inclusion, exclusion or undecided categories

based on the selection criteria in the protocol. A full text screening of all included papers as well as the undecided ones was conducted. A final decision on inclusion or exclusion of the undecided pool was made. A seconder researcher (my supervisor) confirmed the suitability of selected trials for inclusion in the review and also reviewed a 20% sample of the rejected trials.

Data Extraction

Data was extracted from the papers selected and entered into a standardised data extraction form. The data extracted entailed description of and characteristics of the studies in addition to the effects of the interventions.

Quality of evidence and the risk of bias assessments:

The quality of evidence and the risk of bias assessments were conducted according to the Cochrane guidelines for reviews of interventions. The quality of trials included was determined by assessing the following parameters: the adequacy of allocation concealment, how incomplete data was addressed, the comparability of the treatment groups at baseline, whether or not intention to treat analysis was employed, blinding of the outcome assessors, validity of the tools used for outcome measurement, whether measures were taken to protect the trial against contamination and evidence of selective outcome reporting.

Statistical Analysis

Heterogeneity between studies was subjectively assessed by clinical judgements of differences in intervention (intensity, duration, content, and frequency), the outcome measures and timings. A quantitative synthesis by way of a meta-analysis to determine the effect size of SET on ACD was determined to be the ideal statistical method to analyse the extracted data. An analysis of the studies against the research questions and a narrative combination of the effects were

deemed to be the most suitable alternative statistical approaches should extensive heterogeneity preclude the meta-analysis.

Results

Each database was explored using the same search strategy. The results were then de-duplicated using EndNote X7 software and screening was conducted to produce the following PRISMA flow chart displayed in Figure VI.

Note: The review protocol as well as the search strategy employed are presented in Appendix I and II respectively.

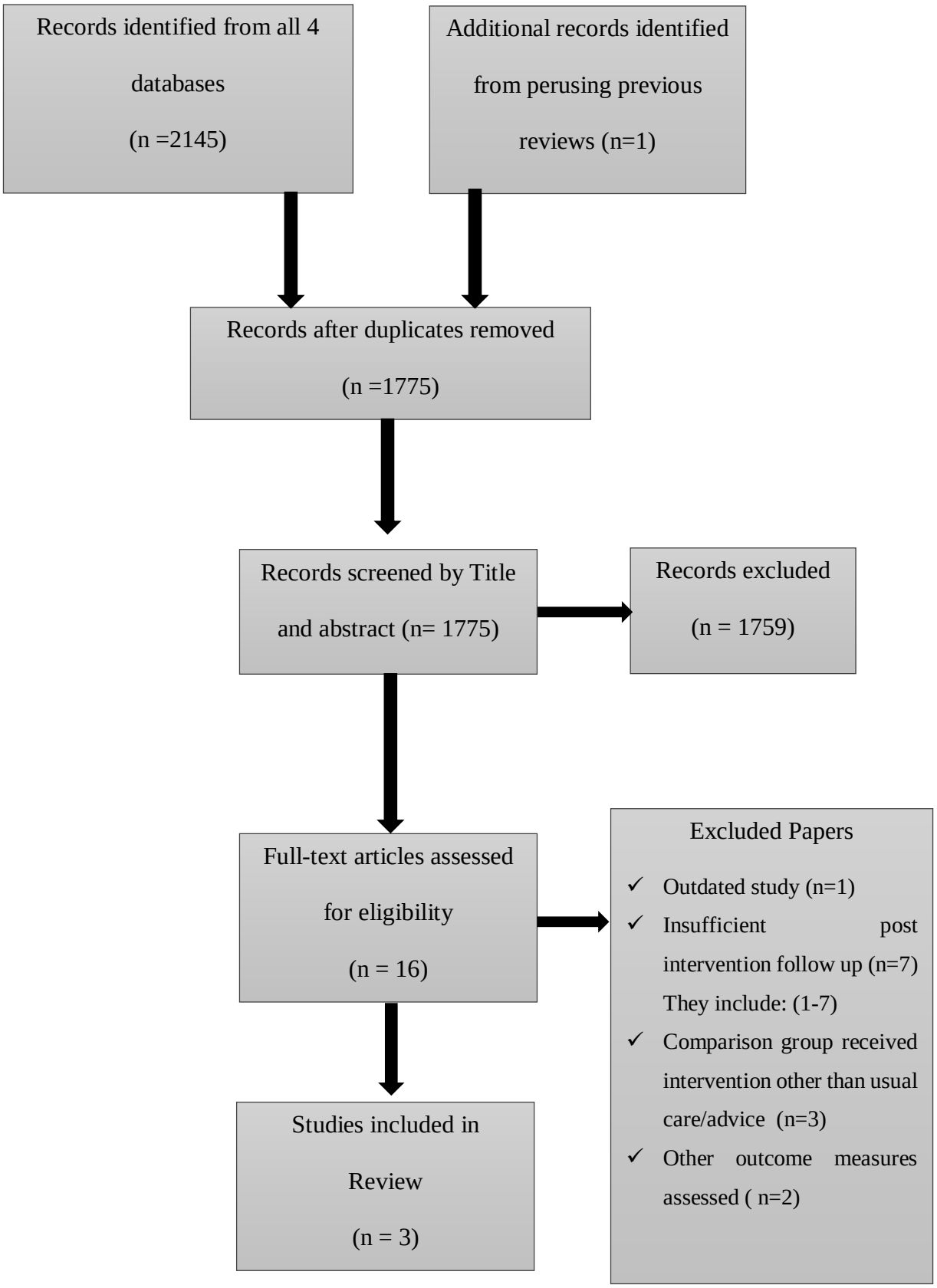


Figure IV: Prisma flow chart depicting the study identification process

Description of studies

After removing duplicates, performing title and abstract screening, 16 randomised controlled trials were deemed eligible for the review. We were able to the source the full texts for all the eligible trials. Thirteen of these were rejected on full text screening for a variety of reasons. Seven were excluded due to the absence of post-trial follow up of participants, one was excluded as it was deemed out-dated, and three studies were excluded because the control group received advice or exercise therapy at all. This screening and selection process is summarised in Figure VI.

The three included trials (60-62) comprised a total of 159 randomised participants, 96 received SET and 63 received non-supervised regimes. Two of the trials were conducted in the USA and the other in the United Kingdom. The trials were carried out between 1997 and 2009. The mean age of participants ranged from 64 to 69 yrs. There was a male preponderance in each study, with each study reporting between 53 to 73% male participants. Only one study reported on the ethnicity of the participants (61) with 85.4% of participants being Caucasian. Diabetics accounted for between 19 and 36.6% of study participants in each of the studies. Two studies reported on the proportion of participants with coronary heart disease, one described 66% of participants (61) and the other described 9.1% (62). The proportion of past smokers was high across all three studies. Two quoted past or current smokers as 92.7% and 100% (60, 61) and the other reported 82.6% of participants as past smokers (10). The characteristics of the three studies are presented in Table 1 and III.

Inclusion criteria

For the two studies that stipulated age restrictions, patients were required to be over 18 years (61) and between 50 and 75 years (62) In all three trials, the diagnosis of intermittent

claudication was made by an Ankle Brachial Index (ABI) measurement of less than 0.9 or a defined fall in the ABI after an exercise stress test (which varied between the trials). In one study, duplex ultrasound scans and positive responses to the Edinburgh Claudication Questionnaire were used to confirm the diagnosis.

Exclusion Criteria

All three studies excluded participants with severe IC symptoms of critical limb ischemia (rest pain, evidence of impending or actual tissue loss). All three studies also excluded patients with comorbidities such as severe coronary heart disease, osteoarthritis or chronic obstructive pulmonary disease etc. which limited exercise participation. In one study diabetic and hypertensive patients were excluded if their blood glucose levels and blood pressure levels were uncontrolled (61) Participants being treated medically for intermittent claudication were excluded if the medical therapy was commenced within 3 months (61) or 6 months (60) prior to the start of the trial. These criteria along with the inclusion set are presented in Table II.

Title	First Author (Publication year), Location	Ethical approval & Informed consent	Eligible	Randomised	Completed	Intervention Group	Control group
Efficacy of arm-ergometry versus treadmill exercise to improve walking distance in patients with claudication	Diane Treat-Jacobson (2009), USA	Yes	62	45	31	(I) Arm-ergometry (II) Treadmill Walking (III) Combination of I & II	Walking instructions
Does supervised exercise offer adjuvant benefit over advice alone for the treatment of IC? A randomised Trial	D.R. Cheetham (2003), USA	Yes	59	59	55	Supervised exercise (plus advice and motivational talk)	Walking advice
Value of supervised exercise program for the therapy of arterial claudication	Robert Patterson (1997), USA	Yes	Not stated	55	33	Supervised exercise plus lecture	Home based instructions

Table I showing the characteristics of the included studies

Trial by Author Last name & Publication Year	Inclusion Criteria	Exclusion Criteria
Diane Treat-Jacobson (2009)	≥ 18 & lifestyle limiting claudication, ABI ≤ 0.90 or decrement in ABI ≥ 10% after a symptom-limited treadmill exercise test, able to walk @ 2mph on a treadmill, willingness to participate in a 12wk exercise programme, DM with controlled blood glucose levels according to standard guidelines	Uncontrolled HTN (> 200 SBP or > 100 DBP), Rest pain or tissue loss, comorbid illness reducing exercise capacity (CHD including severe angina, recent MI, severe arthritis, marked exertional dyspnea, revascularisation procedure (coronary or otherwise) within 3 months
D.R. Cheetham (2003)	Resting ABI < 0.9 or a positive response to a validated stress test (a drop in ankle pressure of > 30 mmHg following 1 min of treadmill walking @ 10% slope & 4km/h measured 40s post exercise), PAD confirmed by duplex scans of affected limb, A positive response to the Edinburgh Claudication Questionnaire, a minimum of a 6 month period of stable symptoms of mild to moderate IC (able to walk > 300m on the flat in 6 mins)	Not fulfilling all inclusion criteria, Severe IC deemed to warrant radiological or surgical intervention, CLL, significant co-morbidity preventing participation in an exercise programme, vascular endovascular intervention within the last 2 years, having received pharmacological agents aimed at improving symptoms within the previous 6 months
Robert Patterson (1997)	Patients between the ages of 50 & 75 with symptoms, ABI < 0.9 and decrease in ankle pressure by ≥ 15 mm Hg after a standard exercise protocol (10° incline, 1.5 mph, 10 minutes of exercise), no evidence of myocardial ischemia at exercise capacity on a submaximal exercise cardiac stress test, by bicycle ergometry.	Not fulfilling all inclusion criteria, rest pain or tissue loss, comorbid illness precluding exercise programme (arthritis, COPD)

Table II showing the Inclusion and exclusion criteria of the included studies

Descriptive Characteristics	Intervention Group	Diane Treat-Jacobson (2009)	D.R. Cheetham (2003)	Robert Patterson (1997)
Age (Mean, SD)	T	64 (8.6)	67 (*)	69.3 (8.1)
	TI	64 (11.7)	*	67.9 (7.5)
	TII	71.9 (11.3)	-	-
	TIII	70 (7.8)	-	-
	WA	67.7 (10.5)	*	70.3(8.6)
Gender (% Male)	T	70.7	73	52.7
	TI	80	*	59.3
	TII	64	-	-
	TIII	58	-	-
	WA	88	*	46.4
Ethnicity (Mean % Caucasian)	T	85.4	*	*
	TI	100	*	*
	TII	75	*	*
	TIII	-	*	*
	WA	75	*	*

Table III showing characteristics of included studies (continues on page 42 with legend)

Demographic Factor	Intervention Group	Diane Treat-Jacobson (2009)	D.R. Cheetham (2003)	Robert Patterson (1997)
Smoking status (% of population)	T	P/C: 92	100	C: 23.6, P: 82.6
	TI	P/C: 100	*	C: 25.9, P: 0.9
	TII	P/C: 100	-	-
	TIII	P/C: 83	-	-
	WA	P/C: 88	*	C: 21.4, P:75.0
% Diabetes	T	36.6	19	34.5
	TI	60	*	29.6
	TII	9	-	-
	TIII	42	-	-
	WA	37.5	*	39.3
% CHD	T	65.9	*	9.1
	TI	70	*	7.4
	TII	63.6	*	-
	TIII	53.8	*	-
	WA	50	*	10.7

Table III continued

Table III Legend						
Symbol/abbreviation	C	P	-	*	T	WA
Meaning	Current smoker	Past smoker	Not applicable	Not reported	SET treatment arm	Walking advice

Exercise Regimes

The active ingredients of the supervised exercise regimes varied widely between studies. The SET was administered in a standard hospital gym in one study (60), in an exercise science laboratory in another study (61) and the setting was not explicitly stated in the other. Physiotherapists and medical personnel delivered the intervention (provided the exercise supervision) in one study (60) while it was not clearly stated in the other two studies. The supervised exercise sessions were implemented three times weekly in two trials (61, 62) and once weekly in the other (60). The two trials with more frequent sessions also had longer sessions lasting 1 hour per session, while the sessions in the other study lasted just thirty minutes. The trials varied the most in terms of the protocol content of the SET regimes. Treadmill walking was common to the regimes in all three trials. However the regimes in each trial comprised other forms of exercise. In one study arm-ergometry protocol as well a special protocol involving a combination of arm-ergometry and treadmill walking were also implemented (61). Another study included arm-ergometry in addition to leg-ergometry and cycling. The final study included the lower limb strengthening exercises in addition to the treadmill walking. Co-interventions were incorporated into the regimes of two studies. In one study SET was delivered in addition to motivational talks and walking advice and in the other it was accompanied by lectures on PAD and risk factor modification. These SET characteristics by study are displayed in Table IV and the walking advice regimes are described in Table V.

Outcome Measures

Each trial used a treadmill walking test to measure the claudication parameter being assessed-maximum claudication distance or time. These assessment protocols varied significantly and are described in Table VII. Two trials assessed maximum or absolute walking distance while one assessed maximum walking time. Trials included did not investigate the primary

behavioural outcomes of this review and so no post-intervention (long term) data on physical activity levels were available. This is an important finding as this essentially answers our research question on the long-term behaviour impact of SET. However, some in-trial data was collected. One study examined the adherence of the participants to the SET during the trial (61) and another trial invested the frequency of (unsupervised) walking outside of the intervention prescription by means of self-report tools (60). Two trials evaluated the quality of life using a generic health related quality of life questionnaire, the Short Form-36 (SF-36).

Study	Intervention name (s)	Setting	Content / Type	Who delivered Intervention	Duration (per session, length of programme)	Frequency (Sessions/week)	Co intervention
Treat-Jacobs (2009)	Arm-ergometry (T1)	Laboratory of physical hygiene and exercise science (Exercise laboratory) at the University of Minnesota	Arm--ergometry exercises began at one work level or 10 watts below the maximal level achieved during the baseline arm-ergometry test, a rate of 50 cycles per minute was maintained. Participants worked intermittently against this load for period of 2 mins followed by 2 mins of rest for a total of 60 mins. After 3 weeks of training the intensity was increased to the work level in watts achieved during the baseline test. Exercise periods were progressively increased by 1 mins q 2-3weekly and rest periods were reduced to 1 minute for maximum volume of 5 mins of exercise and 1 minute of rest for 60 minutes.	Not stated	60 Min 12 weeks	3	None
	Treadmill walking (TII)	Laboratory of physical hygiene and exercise science (Exercise laboratory) at the University of Minnesota	Walking at 2mph at 0 grade until moderately severe claudication pain developed. Patients were rested while seated until pain resolved. The exercise-pain-rest cycle was repeated through the session. When participant achieved 8 mins of uninterrupted walking at initial work load the treadmill grade was increased by increments of 0.5% until an 8-10% grade was achieved. The exercise intensity was increased by increasing treadmill speed by increments of 0.1-0.2 mph as tolerated.	Not stated	60 Min 12 weeks	3	None
	Combination The,rapy (T3)	Laboratory of physical hygiene and exercise science at the University of Minnesota	Both Upper and lower body training each session.After warm up 20 mins of arm-ergometry following a similar protocol to arm-ergometry alone group→40 mins of intermittent treadmill walking using a similar protocol to the treadmill group.	Not stated	60 Min 12 weeks	3	Not Stated

Table IV showing the SET protocols used in each study

Study	Intervention name (s)	Setting	Content / Type	Who delivered Intervention	Duration (per session, length of programme)	Frequency (Sessions/week)	Co intervention
Cheetham	Supervised exercise (T1)	Standard Hospital gym	• Completing a walking circuit in addition to a 7 two minutes exercise stations aimed at lower limb strengthening. • These stations included stair climbing, low-step climbing, high step climbing, tip toe walking, standing on tip toe from flat, standing on tip toe from ankle dorsiflexion, power-jogger walking • Each exercise was interspersed by circuit walking for 2 minutes Rate at which they exercised was determined by the participant.	Physiotherapists and medical personnel	30 min 24 weeks	1	• Motivational talk Walking advice as per control group
Patterson	Supervised exercise (T1)	Not stated	• Each programme is specific to the participant and based on the guidelines of the Amercan College of Sports medicine for cardiac and elderly patients. Customised for each patient. • Aerobic component consisting of arm and leg ergometry and Air-Dyne cycling designed for cardiovascular training • Claudication specific exercise periods performed on the treadmill after the method of Feinberg et al. (graduated programme, redesigned two weekly based on performance)	? Nurse specialist, not clearly stated	60 Min 12 weeks	3	Lecture • (educational sessions on Atherosclerosis risk factors as well risk factor modification, potential complications of cardiovascular disease including warning signs and symptoms)

Table IV continued

Study	Group	Content	Setting	Providers	Co interventions
Treat-Jacobs (2009)	Walking advice	Provided with specific standardized written walking instructions for claudication patients and a daily exercise record and asked to record the type and amount of daily exercise.	Home Exercise laboratory	Participant directed.	Medical therapy: Instructed to continue the usual prescribed medical care Review: The subjects' exercise records were reviewed weekly at the exercise laboratory.
Cheetham (2007)	Exercise advice	Advised to walk at least 3 times weekly to near maximum pain for at least 30 minutes per session. Additional leg exercises such as stair climbing and tip toe walking were recommended	Home	Participant - directed	None
Patterson (1997)	Home exercise	Instructed to walk a minimum of 3 times weekly at home to tolerance, for a period of 20-40 minutes.	Home	Participant-directed Nurse specialist	Lectures: 12 week programme of educational lectures on Atherosclerosis risk factors as well risk factor modification, potential complications of cardiovascular disease including warning signs and symptoms Review and counselling: Subjects asked to keep weekly logs which were reviewed by nurses at lecture sessions. Individual counselling and review of home protocol was provided by study nurse at each lecture.

Table V depicting the walking advice/usual care instructions

Risk of bias of included Studies

Allocation sequences were adequately generated in all three trials. However, it was unclear if allocation was adequately concealed in all three trials. The control and intervention group were comparable at baseline in two trials (61, 62). There was a statistically significant difference in mean age between the control and intervention group in Cheetham's trial. The two treatment groups were otherwise comparable at baseline. Incomplete data was adequately addressed in each trial. In Cheetham's trial attrition was minimal with 2 participants from each of the two groups failing to complete the trial. There was significant attrition in Patterson's trial with 10 patients lost due to medical reasons, 7 due to refusal to continue, 2 due to death and 3 due to transportation and job factors. Attrition was evenly divided between control and intervention group in this trial. In Treat Jacobson's trial 31 (76%) participants completed trial and all assessments. Attrition was attributed to study-unrelated health problems in 8 cases, family crises in 3 cases, and lost to follow up in 3 cases. There was no evidence of selective outcome reporting in any study. It was unclear whether Cheetham and Treat-Jacobson had employed strategies against contamination while Patterson described taking steps to prevent mixing of groups in his trial. Measurement tools were applied as intended and in their entirety in all 3 trials. It was uncertain whether the treadmill tests carried out were validated claudication measurement tools. The final results were adjusted for baseline physical activity level in all 3 trials. The personnel conducting the primary outcome assessments were not described in any of the 3 studies and so it was unclear as to whether the assessments was independent and blind. Intention-to-treat analysis was not applied in any of the studies. This assessment is displayed in Table VI.

Quality assessment	Treat-Jacobs (2009)	Cheetham (2007)	Patterson (1997)
Allocation sequence generated adequately?	+	+	+
Allocation concealment adequately carried out?	?	?	?
Incomplete data adequately addressed?	+	+	+
Selective outcome reporting?	-	-	-
Control and intervention comparable at baseline?	+	-	+
Validated Outcome measurement tools used?	?	?	?
Measurement tools applied as intended and in their entirety?	+	+	+
Final analysis adjusted for baseline physical activity levels?	+	+	+
Outcome assessment independent and blind?	?	?	?
Was an intention-to- treat analysis applied?	-	-	-

Table VI showing the risk of bias assessment for the included trials

Legend for Table VI	
+	Yes
-	No
?	Not stated or ambiguous

Commentary on the quality assessment

Both the quality of reporting and the quality of the methods applied in the study have to be considered in the overall assessment of the quality of the studies. All studies were characterised by poor reporting of study methods. I have assumed that the failure to report on these methodological steps implies that they were not applied in the studies. These methodical

deficiencies compromised the quality of the studies by rendering them prone to the effects of bias.

All three studies failed to report on whether allocation concealment was applied or not, which rendered the studies prone to selection bias. This could have been associated lack of baseline comparability in Cheetham's trial which suggested that randomisation was disrupted. The studies also failed to describe whether the outcome assessors were independent and blind or whether the tools used to evaluate outcome measures were validated. These inadequacies rendered the studies prone to detection bias and raises questions about the validity of the findings presented. Importantly, all studies failed to apply a true intention-treat-analysis. This statistical approach is necessary to preserve the effect of randomisation through the study. All studies adequately addressed incomplete data which protected the studies against attrition bias.

Based on the above inferences, it is safe to conclude that all the studies were of equally low quality and therefore prone to the impact of bias.

Effects of intervention

Primary behavioural effects:

In-trial adherence to SET was reported only in Treat Jacobs' trial. In this trial 61% of participants completed the full SET regime in 14 weeks, 12% completed the regime, taking longer than 14 weeks, and 97% completed more than 75% of the regime. The in-trial adherence to WA was reported in two of the three trials. Treat Jacobs' trial reported that 75% of patients assigned to walking advice reported participating in outside exercise ≥ 3 times a week. In Cheetham's trial, 31% of participants in the walking advice group reported walking more than three times weekly, 38% reported walking exactly 3 times weekly and 31% reported walking

less than three times weekly. Importantly, none of the three trials examined the impact that SET had on the post-trial physical activity levels. These results are displayed in Table X

Primary clinical outcomes by trial:

Treat-Jacobs' Trial

The change in maximum walking distance from baseline was the primary outcome in this trial. There were no baseline differences between the four treatment groups. At 12 weeks follow-up, the marked change in the MWD in all intervention groups compared to the control group was noted. The differences between intervention groups were not statistically significant. At 24 weeks, the increase in MWD was sustained in the arm-ergometry and treadmill groups. The MWD declined in the combination group and was no longer statistically different from the control group. These results are presented in Table VIII

Cheetham's trial

Median ACD was the main claudication parameter for this trial. There was no significant difference between the control and intervention groups' median treadmill distance at baseline. At 3 months the SET group demonstrated a 67% improvement while the control group demonstrated a 19% improvement. The intergroup difference was statistically significant. At 6 months, the SET group recorded a 129% increase while the control group recorded a 69% increase at this stage. This intergroup difference was again statistically significant. This effect was sustained 12 months the SET group recording a 130% increase compared to the 70% increase reported in the control group. The intergroup differences remained statistically significant. These figures are displayed in Table IX

Patterson's Trial

Maximum walking time was the claudication parameter of interest in this trial. Data were presented only in the form of a bar-chart and commentary, and relevant figures were not presented. There was no statistical difference between groups at baseline. Improvement was observed in both groups at 3 months, with the SET demonstrating a greater improvement. These improvements from baseline and the intergroup differences were determined to be statistically significant. These improvements were sustained at the final follow up point (6 months), with the SET group recording a 207% improvement compared to the 70% improvement in the control group.

Secondary Clinical Outcomes:

Quality of life

Treat-Jacobson's trial did not investigate the quality of life effects of the SET intervention. In Cheetham's study the SET group reported marginal improvement in physical functioning compared to the WA group. It is not clear whether there was any change from baseline in the other domains. This difference was statistically significant (p=0.02). Patterson also described no baseline differences in SF 36 scores between groups. Improvements were noted for both groups in a number of the domains including physical function, bodily pain, physical composite, walking 1+ miles, many blocks and 1 block. There were no statistically significant differences between groups.

Adverse Events:

Of the three trials, a total of 4 deaths were reported. In Patterson's trial, the causes of death of the two participants who died during the course of the follow up period were not mentioned.

Cheetham's Trial accounted for remaining two deaths. One was registered from each group and both were not attributed to vascular events or to the intervention. No other adverse events were reported.

Study	Outcome	Definition	Unit of measurement	Measurement Protocol
Treat-Jacobs (2009)	Maximum Walking Time (MWD)	The distance that the patients can walk before pain forces them to stop	Meters	All subjects were required to walk on the treadmill at a speed of 2mph starting at a 0% grade (flat), The treadmill grade was increased 3.5% every 3 minutes until a 10.5% grade was obtained, at which point the speed was increased by 0.5 mph every 3 minutes while maintaining 10.5%.
Cheetham (2007)	Absolute Claudication Distance (ACD)	The maximum distance walked until the subject is forced to stop due to pain on a fixed treadmill load	Meters	All subjects underwent a graded progressive maximal treadmill exercise treadmill exercise test initiated at 1mph with a grade of 5%, increasing in speed and grade at 5-min intervals through four stages to 2.5 mph at 10% grade
Patterson	Maximum Walking Time (MWT)	Maximum walking time to limiting claudication	Minutes	All subjects underwent a fixed load treadmill at 3.5 km/h with a 12% gradient

Table VII showing the primary outcomes and treadmill assessment protocols

Intervention Group	Baseline (SD)	Mean Change in MWD Baseline to 12 weeks (SD)	Mean Change in MWD Baseline to 24 weeks (SD)
Arm-ergometry (TI)	423.6 (188.7)	182.1 (126.7)	240.3 (164.1)
Treadmill walking (TII)	483.3 (290.9)	294.7(163.5)	294.4 (162.2)
Combination (TIII)	441.3(184.1)	217.2 (72.7)	109.7 (159.6)
WA/Home based therapy	360.8(185.2)	45.3 (92.7)	73.3 (65.6)
Statistical significance	No statistical difference between groups	Statistical significant difference between intervention groups and control, but no diff between the intervention groups (p=0.1)	Statistically significant difference between T1 and T2 and control, none between T3 and control

Table VIII showing the mean change in Meters in MWD from Baseline to final follow up in Treat-Jacob's trial

Intervention group	Baseline(n=56)	3 Months	6 Months	9 Months	12 Months
SET	132	220 (67% ↑)	302 (129%↑)	305 (131%↑)	304 (130%↑)
WA/Home based	103	119 (18% ↑)	174 (69% ↑)	164 (59% ↑)	175 (70% ↑)
Statistical significance	none	P = 0.001	P= 0.001	P=0.001	P=0.001

Table IX showing mean change in ACD over time in Cheetham's Trial

Study	In trial-adherence		Post-trial Physical activity levels	
Trial	SET	WA	SET	WA
Treat-Jacobs (2009)	61% of participants completed the full SET in 14 weeks, 12% completed the regime taking longer than 14 weeks and 97% completed ≥ 75% of the regime. Out of trial physical activity levels were reported. 45% of TW group reported exercising ≥ 2 days outside of days of supervision versus 25% in the combined group and 20% in the arm-ergometry group.	75% of control group members reported participating in outside exercise ≥ 3 times a week.	NR	NR
Cheetham (2007)	No data provided for adherence to SET. But at the trial termination point self-report frequency of walking to near maximum pain was reported with 65.5% reporting walking > 3 times/week, 27.6% reporting walking 3 times/week and 6.9% reporting walking < 3 times/week. There were no baseline out of trial physical activity levels.	31% reported walking >3 times/ week, 38% reported walking 3 times/week and 31% reported walking < 3 times/week	NR	NR
Patterson (1997)	NR	NR	NR	NR

***NR = Not reported**

Table X showing the behavioural outcomes for each trial.

Discussion

Despite the small number and size of studies, the difference between the effects of the SET and walking advice on the claudication measures was clear, statistically significant and consistently demonstrated as the SET outperformed the WA or home based groups. These superior benefits were likely achieved due to increased adherence and all the benefits of SET programmes outlined in Chapter II (increased work load, improved cardiovascular conditioning, positive reinforcement etc). The behavioural impact of the exercise regimes was not thoroughly assessed in any of these studies, and so it not possible to draw any conclusions on long-term adherence. This was a key limitation of the studies analysed.

Patients with severe co-morbid conditions were excluded from the selection consideration for three main reasons. Firstly, the exclusion was to reduce impact of confounding factors (co-morbid illnesses) on the outcomes. Secondly, to ensure that patients had the functional capacity to receive the full dose of the intervention. Finally, the ethical considerations about the exercise stress worsening severe pre-existing health status. The latter was perhaps the most important consideration. While the rationale for these exclusions is sound, a limitation on the generalizability of the results and conclusions of this study is imposed. The reality is that prevalence of comorbidities among patients with IC is high (diabetes mellitus is the most significant risk factor and approximately 65% of patients with IC have clinically significant coronary heart disease and or cerebrovascular disease) and so the study population would therefore not be a true reflection of the PAD population.

The extensive heterogeneity precluded combination statistical analysis leaving narrative commentary of the results as the only option. The significant sources of heterogeneity identified fell under the following headings: the content, duration, frequency of supervised sessions, the co-interventions offered alongside supervised exercise, the main clinical outcome (Claudication distance versus time), the assessment method for primary claudication

parameters and the time points at which the outcomes were measured. I did investigate the possibility of creating a standard outcome metrics across all studies based on converting time to distance estimates, but I felt this would be too assumptive due to the lack of raw data. Furthermore, the claudication distance measures reported in the other two trials employed and reported different measures of central tendency, the median in Cheetham's trial and mean in Treat-Jacobson's. The cumulative impact of these sources of heterogeneity prevented a combination analysis. The lack of a combination analysis and the small number of studies prevented us from conducting further stratified analysis to identify differences between demographic groups. It also precluded the determination of the more successful components of the SET regime. The quality of all the studies was assessed to be low which justifiably raises questions about the internal validity of the studies. Additionally, the overall statistical power of the evidence compromised by high attrition rate in two of the three studies.

Evidence on effect on quality of life was not sufficient to make reasonable inferences on how the improved claudication markers influence quality of life of the participants. Only two of the three studies examined this outcome. Patterson's reported improvement in QOL in both groups but no significant difference between groups across domains. Cheetham reported a significant improvement in the physical functioning domain for the SET group but did not comment on the change from baseline in the other studies. Inferences on QOL cannot therefore be based solely on the results of Patterson's trial and so more research is required to assess the effect of SET on QOL. I was not able to determine from the review what was the clinically important difference between groups, despite results being presented as statistically significant. I am therefore unable to comment on the practical translation of an observed improvement in walking distance.

A reflection on the definition of sustainability revealed that the question of sustainability was not thoroughly investigated in the systematic review. This element would provide information on the value for money and whether the intervention was a worthwhile and economically sustainable one.

Conclusions:

Despite the small number and partially reduced quality of studies, SET induces clinically significant improvement in the walking capacity of patients in IC when compared with walking advice. This effect appears to be sustained in the long-term. There is insufficient evidence to make conclusions on the impact of SET on the both the quality of life and the physical activity related behavioural habits of patients with IC. Cost-effectiveness of SET needs to be assessed to more thoroughly address the question of sustainability of the intervention. I believe that a randomised controlled trial with a built-in cost effectiveness analysis is the ideal research methods to fill these gaps in the evidence.

Chapter V: “The Get SET Go! Study”- A randomised controlled trial

Preview: In this chapter, I present the protocol for RCT investigating the long term effects and cost effectiveness of supervised exercise therapy in the treatment of intermittent claudication. The protocol follows a standard trial design. The protocol for the cost effectiveness will be presented in the subsequent chapter.

Background, rationale and objectives:

Considering the findings of the critical appraisal of the existing studies on the longterm value of SET described in the previous chapter, the two most important research implications emerging were (I) the necessity for more high quality (studies which employ more robust strategies against bias and larger sample size estimates to withstand attrition and maintain statistical power, and which investigate behavioural as well as clinical outcomes) research to thoroughly answer the question of sustainability of the SET and (II) the necessity for an expanded definition of sustainability to more comprehensively address the topic. The first implication is supported by the fact that arriving at a number of important conclusions was precluded due to a paucity of evidence. These included conclusions on the long-term behavioural outcomes and the relationship between the long term improvement in clinical markers of claudication and quality of life of the patient. Although evidence for the long-term clinical outcomes of SET was available, they were sourced from a few small studies.

A randomised controlled trial would be the ideal primary research method to fill the gaps in evidence on the long-term value of SET. RCTs are the gold standard study design for assessing the effects of an intervention. The strong rationale for and advantages of designing an RCT, if the systematic review had proved inadequate in answering our questions, were well laid out in Chapter 3 where the research methodology was justified. The implementation phase of the RCT was deemed infeasible and a protocol assessed to be the practical option in view of existent limitations.

My proposed recommendation for a RCT to assess the long-term value of SET (clinical, behavioural and value for money) aligns with the research recommendations stipulated by the NICE guide for the diagnosis and management of PAD. NICE recommended, "A community-based randomised controlled trial is required to compare the long-term clinical and cost effectiveness of a supervised exercise programme and unsupervised exercise. The trial should

enrol people with peripheral arterial disease-related claudication, but exclude those with previous endovascular or surgical interventions. The primary outcome measure should be maximal walking distance, with secondary outcome measures including quality of life, function, levels of uptake of exercise programmes and long-term engagement in physical activity" (55).

A reflection on the findings of the review cemented the idea that in order to completely assess the sustainability of SET in IC treatment, the cost effectiveness of SET implementation needs to be addressed. The short and long-term behavioural and clinical effect and the impact of induced clinical effects on the quality of life of patients were collectively insufficient to completely assess sustainability. The term cost effectiveness also described as a health economic evaluation, is essentially the extent to which an intervention represents good value for money. NICE defines the cost effectiveness analysis as an economic study design in which the impact of an intervention(s) is measured using a single outcome, typically a natural unit (life years gains, deaths avoided, cases identified) (63). The interventions are then compared in terms of cost per unit effectiveness. NICE requires that the health outcome be measured in quality adjusted life year (QALY). QALY is a measure of the state of health of a person or group taking into consideration the both the quality and quantity of life generated by a health care intervention. Costs per QALYs can then be used to compare interventions. The cost effectiveness of an intervention is a critical factor to consider from a policy and investment standpoint. Governmental health care organisations such as NICE place considerable weight on the results of high quality cost effectiveness analyses in making recommendations and policies on interventions. The cumulative costs involved with the implementation of an intervention can also be obtained from these analyses; this may be useful for budgeting purposes.

In this context it is important to determine whether SET offers better value for money than walking advice. Delivering SET is likely to be the more expensive option but it has been shown to induce superior clinical effects. The critical question is whether the cost for the added benefits is a good return on investment. A limited number of studies have been conducted in The Netherlands. In one study, van Asselt concluded that it is likely that SET is more cost effective than WA (64). In the other, Spronk et al. compared the cost-effectiveness of a vascular surgery versus hospital-based exercise therapy and concluded that exercise was more cost effective as there was not a significant difference in effectiveness but revascularisation was much more costly (65). There have been no UK based studies evaluating the cost effectiveness of SET implementation.

In the UK, SET cost effectiveness data is therefore needed and as such, I propose that the protocol for an economic analysis should be incorporated in into the design of the RCT. The trial has been entitled: "The Get SET Go Study!" The protocol for the trial will be presented over two chapters. The long-term effects elements of the trial protocol is presented in this chapter and the economic analysis arm of the trial protocol will be presented in the following chapter.

The objectives for long-term effects element of the trial are the determination of the following questions:

1. What are the sustained effects of supervised exercise therapy versus walking advice on the clinical outcomes of patients with intermittent claudication?
2. What is the impact of the improvement in clinical outcomes produced by supervised exercise therapy versus walking advice on the quality of life patients with IC?

Trial design

The sustainability of supervised exercise therapy (SET) for the intermittent claudication trial will be a multi-centre, randomised controlled pilot-study based in London, England. Participating clinics could potentially include the Kings College Hospital Vascular and Endovascular Clinic, The vascular clinics at the NHS North-West London hospitals: Northwick Park and Central Middlesex Hospital and Endovascular clinic as well as the London and Surrey Vascular clinic.

The study population

Eligibility:

Patients will be recruited from vascular surgery or cardiovascular disease clinics at the centres included in the study. All adult patients, symptomatic of intermittent claudication, will be considered eligible for the study and subjected to screening.

The following inclusion and exclusion criteria will then be used to screen all eligible participants to determine the final set of patients who will be enrolled in the trial.

Inclusion criteria:

1. PAD must be confirmed by means of a resting ABI measure of less than 0.9 in most cases (60-62), but some symptomatic patients may produce borderline or normal ABI measurements (0.91-1.30) and must be subjected to a post-exercise ABI measurement or duplex ultrasonography to confirm the diagnosis (60, 66).
2. A stable six month period of mild to moderate symptoms Fontaine Stage II (60)
3. Capacity to walk at least 500 M on a standardised treadmill assessment (67)

Exclusion criteria:

1. Patients who have previously received SET (67)
2. Patients with critical limb ischemia (characterised by rest pain, evidence of tissue loss or ABI below 0.3) which warrants surgical intervention (60, 61).
3. Patients who previously received any surgical interventions- vascular, endovascular, amputation as treatment for IC (67)
4. Patients who had commenced medical therapy for claudication within the previous 6 months (61).
5. Patients with ischaemic heart disease or congestive cardiac failure who either have established severe disease status or passed unfit by a validated cardiac exercise stress test (62).
6. Patients with severe (I) osteoarthritis (IV) Severe COPD (V) or any other co-morbidities that either restricts physical activity or is likely to be negatively impacted by physical activity (60-62).

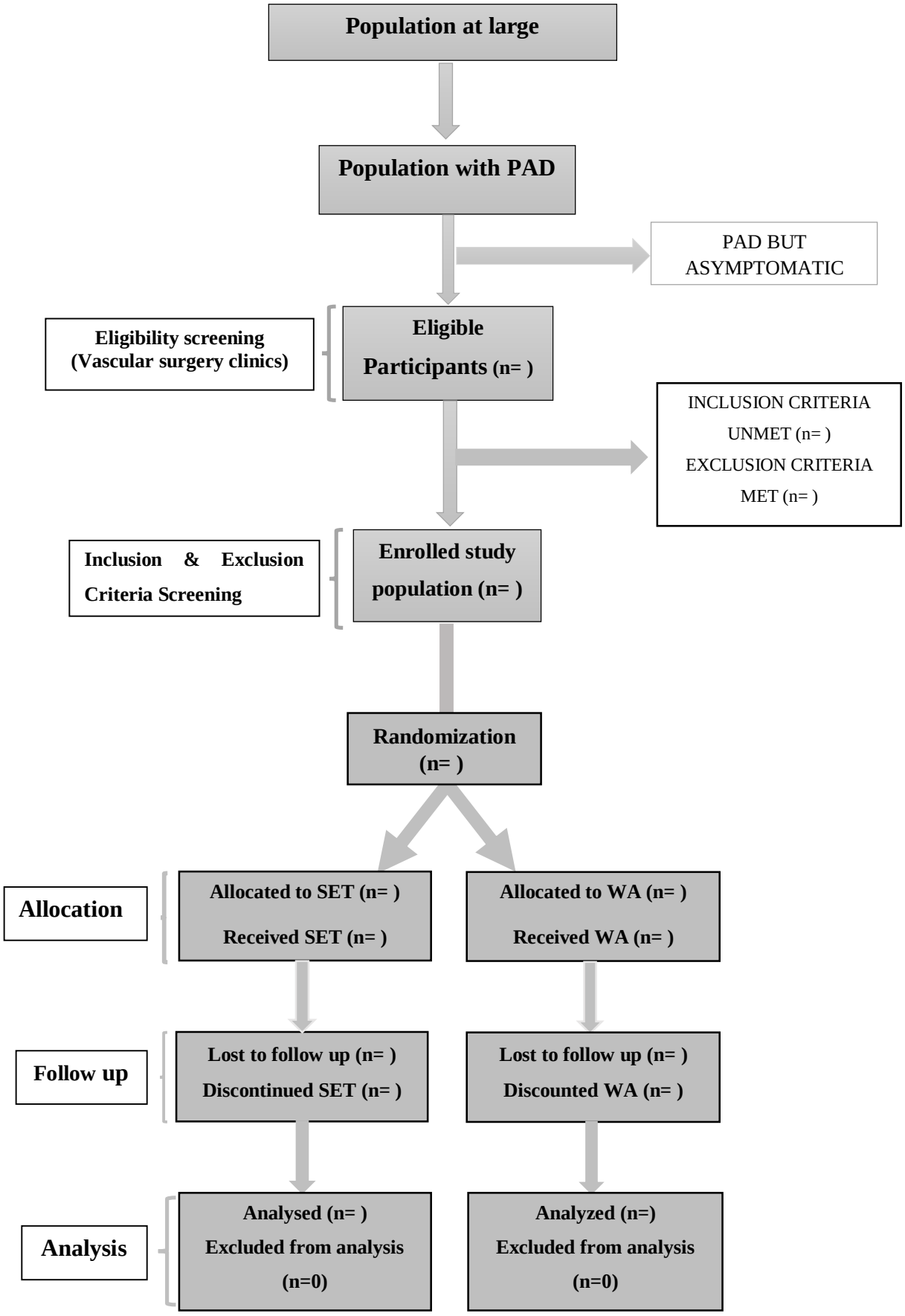


Figure IV: "Get SET Go study!" consort diagram

Sample size estimation

The sample size equation for calculating the appropriate sample sizes for groups where the difference between the means is of interest is as follows:

N = [2*(standard deviation of the sample) ^ 2 *(Z_beta + alpha) ^ 2] /Delta^2 (68)

Where:

N= the number randomised to each group

Delta = the desired difference

Z_beta = the normalised z-score for the power level

Z_alpha = the normalised z-score for the significance level and the standard deviation of the change in walking distance of sample is decided a priori.

Participants will be randomly allocated to one of two arms, the study will be powered at 90%. For power of 90%, Z_beta = 1.28. A 5% significance level will be used which corresponds to a Z_alpha = 1.96. Delta will be approximated at 35% (50). A conservative estimate of the standard deviation of 163.5 m was obtained from Treat-Jacobs' trial. The sample size produced is 20. To adjust for an anticipated loss to follow-up 30% we will aim to enrol 30 participants.

Ethical approval and informed consent

The research investigators and sponsors of the trial have ethical obligations to trial participants as well as to the scientific and medical fields. An application of ethics should be made and successfully approved by the Central University Research Ethics committee prior to the implementation of the trial. This application will address all ethical considerations throughout the trial. It will include a strong rationale for the clinical trial outlining the likely benefits and

justifying these benefits against potential adverse events and threats to the safety or health of the participants. Steps to mitigate or eliminate these adverse outcomes will also be proposed. It will also describe the process of informed consent (which will be described in subsequent paragraphs) as well as how privacy and confidentiality of patient information will be handled. Potential conflicts of interest and how they will be managed will also be discussed.

Appropriate informed consent is essential. Informed consent will be obtained from participants deemed eligible for the study during enrolment and selected by the trial nurses or investigators. The informed consent form will include a statement that the study involves research, it will describe the purpose of the research, the expected duration of the subject's participation, the procedures to be followed, all the potential benefits as well as all the risks to the participant. It will also include a statement reassuring the participants about privacy and confidentiality of their records. The participants will be made aware of whom to contact for answers to pertinent questions about the research or for research related injuries and also their rights. They will be made aware that participation is voluntary, refusal to participate will involve no penalties. It will be explicitly stated that they have the option of discontinuing at any time without a penalty. The patients will be informed that they can request a copy of the final study report detailing the findings and outcomes.

The process of obtaining informed consent essentially gives participants the opportunity to understand the concepts of the research and what is being requested of them. They will have the time to consider the implications of joining the trial, to ask questions, review and discuss the material with their family and medical contacts.

Method of randomisation and blinding

Patients will be randomised to exercise therapy in the form of walking advice only or SET sessions conducted by physiotherapists. Randomisation will be operated centrally by

telephone. Patients will be randomised by means of a block randomisation strategy with a block size of 10. Participant details will be provided by phone and the allocation sequences will be concealed to staff at the randomisation office until a participant is irreversibly registered. However, the patients, enrolling vascular surgeons, the physiotherapists will be not be blinded to the allocation assignments after the official assignment. The study personnel, who will perform the treadmill assessments, collect the questionnaires and exercise diaries will be independent and blinded from the allocations. Patients will be instructed to refrain from commenting on treatment assignment and therapy progress during the assessments.

Intervention

Prior to randomisation, all patients will receive cardiovascular risk management from the enrolling vascular surgeon. The guidelines will be in accordance with the NICE recommendations. The management will vary from patient to patient depending on the risk factor profile of each patient. This will include medical control of diabetes or hypertension control, advice to stop of smoking, and the provision of lipid lowering agents where appropriate.

Walking advice group:

Patients randomised to the WA group will receive verbal walking advice and written instructions to walk at least 3 times a week to maximum or sub-maximal pain for no less than 30 minutes.

SET group:

Patients randomised will be referred to participating physiotherapists who will be trained on the SET regime protocol. Three one-hour sessions will be conducted weekly for duration of 4

months or 16 weeks. The sessions will be conducted in a standard hospital gym. The main objectives of the SET programme are to improve maximal walking distance, aerobic endurance, pain tolerance, gait pattern, walking efficiency and patient-specific activity limitations such as stair climbing. The protocol has been built to combine the elements of each of the three studies previously reviewed. The session will involve mainly treadmill walking regime but will also involve aerobic endurance exercises on a bicycle, leg strengthening, exercises geared specifically at walking technique, stair climbing and other specific functions. The treadmill protocol will be adapted from the one used in Treat-Jacobson's trial. Participants will begin walking at 2 mph (3.3 km/h) at 0 % grade. They will walk until the point of submaximal or maximal pain is achieved at which point they will rest until the pain resolves. This exercise/rest cycle will be replicated at least 5 times during the session. When a participant was able to walk for 8 minutes without pain limitation the treadmill grade was increased incrementally by 0.5-1% until a maximum of 10% was achieved. The intensity of the exercise treadmill speed will also adjusted incrementally with 0.2-0.3 km/h increases as tolerated.

The SET programme will also include weekly educational and motivational sessions concentrating on cardiovascular diseases including PAD, their common risk factors and approaches to risk-reduction behaviour. These sessions will also strive to provide the patients with recommendations on how to improve consistency where exercise programmes are concerned and to address the variety of challenges that patients describe.

Outcome measurements and follow up description and schedule

The clinical and behavioural outcomes that will be measured to assess change from baseline to follow up are listed and then described in text and also in Table XI:

Primary clinical outcomes:

Absolute claudication distance (ACD)

Primary behavioural outcomes:

In-trial regime (SET & walking advice) adherence, Post-trial physical activity levels

Secondary clinical outcomes:

Pain free walking distance (PFWD)

Health related quality of life (HRQL)

Adverse events (including musculoskeletal injuries, cardiovascular events)

Outcome: ACD, PFWD Assessment: Treadmill test

The two claudication specific outcome measures being assessed in this trial are ACD and PFWD. Both will be evaluated at: Baseline, 8 weeks, 16 weeks, 32 weeks, 52 weeks, 76 weeks, 104 weeks. ACD is defined as the maximum distance walked when the participant is forced to stop due to pain. PFWD is defined as the distance walked by the participant at the initial onset of claudication pain. They will be assessed by means of a treadmill test.

A familiarisation test will be administered at least 3 days before the baseline assessment to minimise the training effect and the learning (62). Patients will perform a graded treadmill test at a speed of 3.2 km/h starting at 0% incline and increasing incrementally by 2% every 2 minutes. For practical purposes, the incline and test duration will be limited to 10% and 30 minutes (1600 m) respectively.

Outcome: QoL, Assessment: HRQOL tool

Health related Quality of Life (HRQOL) defined as the degree to which health impacts an individual's capacity to function, and his or her perceived well-being in physical, mental, and social domains of life. It will be evaluated at Baseline, 8 weeks, 16 weeks, One year, 78 weeks, 2 years.

The EQ-5D-5L, a self-report tool, will be used to measure patients' HRQOL across five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The raw scores will presented but will also be converted to utility score for the purpose of the economic analysis described in the following chapter.

Outcome: In trial-Regime adherence, Assessment: Attendance logs

Trial nurses will keep records of the attendance of each participant throughout the 16-week programme. Participants assigned to the walking advice group will be asked to maintain weekly logs of their walking sessions in a special walking advice exercise recall diary. They will be required to record the weekly frequency and duration of their walking sessions. These logs will be collected by trial nurses at assessment points and entered into the trial database. Supervising physiotherapists will be asked to keep a log of the frequency, duration and content of the SET sessions. These records will be completed monthly for the 16 weeks of the trial. So records will be kept for each intervention group from baseline to 16 weeks.

Outcome: Post-trial physical activity levels, Tools: Accelerometer & Physical activity recall diary

The post-trial physical activity levels of all the participants randomised will be assessed over the 20-month period following the end of the trial (16 – 104 weeks). This outcome will be assessed both subjectively and objectively. A personal activity monitor (PAM) accelerometer will be used as the objective tool while a self-report physical activity recall diary will be used as the subjective tool. A subjective baseline assessment of the physical activity level of all participants will be taken

The 43 ActiGraph GT1M accelerometer will be used to evaluate physical activity levels during normal life. It is worn on the hip and specifically measures the acceleration force

generated by the body during movement. It will generate a count/score for each movement proportional to the intensity/force of the action and is assessed depending on device settings. The cumulative scores of all the movement counts will be downloaded for each participant at the end of the assessment week (69).

Physical activity recall diary: All participants will be given a retrospective self-report tool to record the type of physical activity, the weekly frequency, the duration of the physical activity to be filled out weekly and logs collected by trial nurses at regular intervals in the post-trial period. Please see Appendix IV for the draft recall diary.

Outcome: Adverse events:

All adverse events such as hospitalisations, cardiac events or musculoskeletal injuries sustained by participants thought to be related to the intervention will be recorded (70)

	Assessment Timings						
Outcome	Baseline	8 weeks	16 weeks	32 weeks	52 weeks	76 weeks	2 years
ACD	●	●	●	●	●	●	●
PFWD	●	●	●	●	●	●	●
In-trial Adherence		●	●				
Post-trial physical activity Levels	●			●	●	●	●
QoL	●	●	●	●	●	●	●
Adverse events		●	●				

Table XI showing the data collection time points for each outcome variable

Statistical analysis

The Shapiro-Wilk test will be used to assess the batches of data for normality. Chi squared tests will be used to assess the baseline differences (demographic and risk factors) between the WA and SET groups following randomisation. The non-parametric Mann-Whitney test will be used to analyse the absolute claudication distance and pain free claudication distance data, both for group differences from baseline and intergroup differences. Descriptive statistics will be employed to describe (I) the in-trial adherence rates for the SET and WA groups, (II) the post-trial physical activity data obtained from the physical activity recall diary and (III) HRQL data from the EQ 5D 5L questionnaire. An intention-to treat analysis will be applied throughout the analysis. The accelerometer data will be analysed using the standard accelerometry cut-point approaches (69).

Organisational structure and flow

Generating a solid and comprehensive organisational structure and flow is integral to the successful implementation of the trial protocol. The principles, series of critical steps and roles and responsibilities in the organisational framework from the design to the execution phase of the trial are outlined below. Each phase is highlighted and the key principles and features of the phases are described.

I. Establishment of a planning committee.

Responsible for organising and overseeing the various phases of the trial (planning, recruitment, participant follow up, data analysis and write up). The committee will be a multidisciplinary team consisting of a team of researchers including me, consultant vascular surgeons, statisticians and expert trial managers.

II. Assessment of trial feasibility

The feasibility of this proposed trial must be assessed critically by the planning committee. They will consider a number of factors including but extending beyond the study design presented in this protocol. The objectives will include:

(I) re-exploring and building on this protocol, for instance, reassessing study size estimations or the timelines stated,

(II) ascertaining confirmation of participation of the potential participating centres and determining the availability of participants at each of the participating centres,

(III) The procurement of competent trial staff,

(IV) Establishing a cost structure to finalise the capital investment required,

(V) Ruling out the existence of a competing trial right up until the planning phase has concluded and just before the point of implementation.

After considering these various factors a final decision on the trial feasibility will be made.

III. Establishment of a clinical coordinating centre

This centre will manage research project to completion. Its roles will include implementation of the randomisation process, overseeing day-to-day trial activities, conducting site visits and controlling data collection and monitoring.

This centre will be based in London. The staff will include small teams of statisticians, epidemiologists, vascular surgeons and trial managers. The staff will maintain strong communication with each of the participating centres.

A separate data analysis centre will be established at the University of Oxford's Department of Population Health. This centre will comprise statisticians who will be responsible for data analysis phase of the project. This team of analysts will confirm the statistical methods proposed in this protocol and modify them if necessary.

IV. Early collaboration between the planning committee and the participating institutions.

It is important that the planning committee engages with the trial investigators at each of the participating institutions before the final protocol is produced. This will not only allow the researchers at the participating institutions to make early estimates of the staff size and capital requirements but also to provide input on protocol design and make cases for changes in light of any potential limitations at the institutions.

V. Defining roles and responsibilities within the organisational structure

At the coordinating centre a steering committee should be created. Once the planning phase is complete, the members of the planning committee will form the Steering committee for the implementation phase of the trial. This group will provide scientific direction for the trial at an operational level.

A scientific group, which is independent of the trialists and sponsors, appropriately referred to as the monitoring committee must be established. This committee's role is to monitor the safety and integrity of the trial. It executes this role by reviewing and approving the protocol, periodically monitoring the trial outcome data especially adverse events. As an independent body this committee provides very reliable assessments on the trial integrity.

VI. Ensuring consistency across all participating centres.

Some variation in the delivery of the project protocol by the participating centres is to be expected. Emphasis should be placed on minimising this discordance in order to achieve adequate consistency. There will be a heavy investment in the training and development of the research staff at each institution. This process will be standardised to ensure that staff across all the centres are properly educated and trained to the same degree. The steering committee

must assess the capabilities of the research team at each centre, before giving each centre the approval to begin the enrolment process.

VII. Monitoring of the participating centres.

The team at the coordinating centre must monitor the performance of all the included centres. These centres will be assessing the recruitment process, quality of data collection, the quality of the delivery of the SET, adherence to protocol stipulations, and the rate at which the centres submit data to the coordinating centre. Monitoring will identify under-performing centres, which need support and will ultimately improve the quality of execution of the trial across the participating centres.

Chapter VI: The cost effectiveness of delivering SET for intermittent claudication (IC)

Preview: In this chapter, I will present the protocol for a health economic analysis of SET using the standard format objectives and methodology for data collection and analysis.

Objectives:

The health economic analysis will be incorporated into the RCT and will consider the following questions:

1. What are the costs associated with the delivery and utilisation of SET in the management of patients with intermittent claudication?
2. How cost-effective are SET programmes in terms of cost per metre improvement in absolute claudication distance?
3. How cost-effective are SET programmes in terms of cost per QALY gained?

Methods:

The proposed economic evaluation will adhere to guidelines for good economic evaluation practice as outlined in the reference case by the National Institute for Health and Clinical Excellence (71). For the purpose of this health economic analysis the SET treatment group will be compared with the walking advice group.

Data collection:

(I) Outcome measurements

There will be two outcomes of interest for the purpose of the economic evaluation: the absolute claudication distance (ACD) and the Quality of Life (QoL). The ACD will be measured in metres by means of the treadmill assessment described in the trial protocol in the previous chapter. The same assessment points of baseline, 8 weeks, 16 weeks will be used. For QoL, NICE recommends the use of a preference-based health-related quality of life (HRQL) measure. This HRQL will be used to determine Quality Adjusted Life Years (QALY) for subsequent economic evaluation. The use of QALYs strives to capture the impact of disease progression and non-fatal events on quality of life in addition to any impact on survival. The

EQ-5D-5L, a self-report tool, is used to measure patients' HRQL across its five dimensions, which are, mobility, self-care, usual activities, pain/discomfort and anxiety/depression (72). A sample of this form is displayed in Appendix III. It will be completed by patients at the fixed assessment point at 8 weeks, 16 weeks. These assessment points are aligned with the claudication assessment time points and so the patients will be required to complete the forms at each of those visits to the assessment gym or lab. The EQ-5D-5L scores at each time point will be converted into utility score on a 0 to 1 scale where 0 is equivalent death and 1, to prefect health. This conversion will be carried out using an algorithm based on the UK value set currently being built by the EuroQol Group, if available at the time of analysis. If this algorithm is not available, the current crosswalk algorithm provided by the EuroQol group, which is based on the EQ-5D 3 level value set estimated by Dolan et al., will be used. This crosswalk algorithm was derived from data obtained from a survey of the UK population (n=3337). The utility values in the tariff set range from no problems on any of the five dimensions descriptive system (Value=1) to severe or extreme problems across all five dimensions (value=-0.594) (73, 74). The utility score will be combined with survival data to estimate the QALY's required for the cost-utility analysis. This utility data will be used for the purpose of modelling the costs per QALY gained by SET.

(II) Costs

The analysis will take a societal perspective, which indicates that the relevant costs, within and outside the health-care sector, will be taken in account. A retrospective resource-utilisation questionnaire will be developed and administered to the patients at: 8 weeks and 16 weeks to capture the costs incurred in the interval between that point and the last assessment. For the purpose of the cost effectiveness analysis, only costs after baseline will be taken into consideration. The questionnaire will include items on general practitioner (GP) contracts, out-

patient specialist visits, visits to the emergency room, hospital admissions, out and in-patient procedures, supervised therapy sessions, hospital gym/exercise physiology lab fees, home and informal care, prescribed and over-the-counter (OTC) medications, miscellaneous items such special walking shoes or a treadmill and lost productivity time due to absence from paid or unpaid work (75). Patient-time costs will be calculated as (hourly wage rate) x (number of hours in-hospital) (76). Additionally, costs incurred for travel to and from health care providers were included. These transportation costs will include parking costs and mean estimated gasoline costs.

Where possible, the value of items of health care resource utilisation will be estimated using appropriate unit costs (staff, equipment, drugs etc.) obtained from published sources, including the most recent version of Unit costs of Health and Social Care and NHS Reference Costs (77). The unit costs, which are not available from secondary sources, will be estimated using a micro-costing approach. Under this approach, the SET programmes will be subjected to a time and motion bottom-up costing structure to reflect all staff, equipment, consumables etc.

Data analysis

Missing data:

The resource-use/cost and the EQ-5D-5L data will be examined to determine the extent of missing data and whether data is missing at random or censoring is responsible. Standard methods will be used to address missing data (78, 79).

Cost analysis:

The health care resource utilisation evaluation serves to establish how the delivery of SET affects the costs of treating and managing the disease. The aim of the cost analysis is to explore the costs in terms of the average total cost per patient of delivering and implementing the SET

programme and the subsequent patient pathway. Analysis will be used to determine the proportion of costs which is attributable to primary care, secondary care, informal care, out-of pocket expenses and lost employment. Additionally, it will determine the costs on a national basis.

Cost per meter improvement in claudication disease and QALY:

The incremental cost-effectiveness of receiving SET compared to receiving advice will be determined using the cost-analysis data previously described. The cost of delivering SET plus its cost impact on treating and managing IC in the intervention group will be compared with the costs associated with IC in the routine advice group. This incremental cost will be weighed up against the incremental benefit, that is, the incremental increase in ACD in the SET group compared to the routine advice group over the 16 week follow up period. Discounting, at a rate of 3.5%, will be applied and the incremental cost-effectiveness ratios (ICER's) will be reported and one-way and probabilistic sensitivity analysis will be undertaken (64). Non-parametric bootstrapping and probabilistic sensitivity analysis will be undertaken to explore uncertainty in the confidence to be placed on the results of the economic analysis and the cost effectiveness acceptability curves (CEAC) will be presented. The CEAC illustrates the probability that, provided a certain threshold for the willingness to pay for a QALY or for an extra meter on the treadmill test, SET is cost-effective at that threshold (64). The curve will be constructed through the utilization of an arbitrary threshold and calculating the proportion of bootstrapped ICER falling below that threshold, and therefore demonstrating cost effectiveness. This is repeated for various threshold levels, where a curve is generated with the threshold values on the X axis and the probability of the intervention being cost effective on the Y axis. The probability that SET would be cost effective given the NICE recommendation for the acceptable costs per QALY of £ 20-30,000 (80) will be determined from the graph.

Chapter VII: Final conclusions

Preview: In this chapter, I will present a summary of the results and methodological steps. I will then discuss the strengths and limitations of each of the methodologies and finally I will reflect on the implications for research, practice and policy.

Summary of methods & results

CVDs are the leading cause of death globally and are the dominant focus of global health agenda. This body of work has highlighted the significant global burden of CVDs, their key drivers and causal mechanisms, socio-economic implications and the principles of prevention. It has reviewed peripheral arterial disease, an overlooked member of the CVD family of diseases and built a case for exercise rehabilitation as a form of tertiary prevention. It highlighted the evidence confirming the effectiveness of exercise therapy in improving claudication symptomology and reducing the incidence of cardiovascular events. It then goes on to describe the emergence of SET therapy as the most effective form of ET. The main thrust of the paper was utilisation of the appropriate methodologies including a systematic review and protocols for a health economic analysis and a randomised clinical trial, to assess the long-term value and cost effectiveness of SET in the treatment of PAD.

Comparing the systematic review with previous reviews to highlight its strengths and limitations

There have been a few reviews in the last decade on investigating exercise therapy in the management of IC - Watson et al (2008), Cassar (2010) and Bendermacher (2006). Of these three reviews only Bendermacher's isolated and explored SET specifically, the others treated all exercise programmes as a group irrespective of supervision. Bendermacher's review therefore provides the only benchmark comparison to highlight the relative strengths and limitations of my review. Whereas Bendermacher's review was essentially a short term efficacy evaluation of SET, mine attempted to evaluate the sustained impact of SET. As such, adequate post-trial follow up was a critical in inclusion criteria but not required in Bendermacher's review. Both reviews included only trials that excluded participants with severe comorbidities for ethical reasons. This exclusion limits the generalizability of the

findings because a large proportion of the true population of the patients with PAD have comorbid illnesses. The inclusion and exclusion criteria were otherwise similar and unremarkable. My review sought to investigate the short and long term behavioural outcomes such as adherence and physical activity levels in my review while Bendermacher's review explored only evidence in-trial compliance. My review therefore represents the first review emphasizing the need to explore the behavioural impact of SET as a crucial determinant of sustained clinical benefits.

The results of the reviews are limited by the number and the methodological quality of studies included. Both reviewed were limited by low numbers of small-scale studies - Bendermacher's included eight trials (seven randomised controlled and one controlled trial) while mine included even fewer trials, three. The disparity in the number of trials was largely attributed to the narrow focus on long term value of SET in my review. The degree of heterogeneity among the trials was significant in both but more pronounced in my review to the extent that it precluded combination statistical analysis. However, Bendermacher's review enabled analysis to estimate the effect sizes of SET. Both reviews confirmed that SET induced clinically superior to walking advice irrespective of any differences in the characteristics and delivery of the SET programmes.. Quality of life data was limited in both reviews and so, the extent to which the clinical benefits translate into practical benefits is not a conclusion which can safely be drawn. Although I attempted to investigate behavioural outcomes, the existing trials had no data on behavioural outcomes, which rendered the issue unanswered and therefore a necessary area of further study.

Strengths and limitations of the RCT protocol

A randomised controlled trial was deemed the ideal methodology to evaluate the gaps in evidence emerging from the systematic review. Logistic and financial feasibility challenges

restricted the scope of the project to the design phase only. The protocol presented was able to improve upon the methodological quality of studies included in the systematic review in a number of key areas.

Strengths of trial design

The statistical power of the trial should be increased due to a better estimate of the drop-out rate. A more realistic drop-out rate was determined by taking the average percentage of the three studies. Two of the three studies had under estimated the dropout rate which ultimately compromised the statistical power of those trials. This step should ensure that the statistical power is preserved at 90%.

A more comprehensive list of outcomes were now included to sufficiently evaluate the behavioural and clinical impact of the SET. In-trial adherence and post-trial physical activity levels were included as behavioural outcomes. PFWD was included as clinical claudication measure to more objectively assess the onset of symptoms and how it is influenced by SET. Unlike previous trials, a longer follow up period of 1 year 8 months post-trial was scheduled. The extended follow up period was applied to ensure that outcomes were monitored for a sufficient period to assess sustained effects (57).

Advantages of the multi-centred structure

The multi-centred organisation of the trial will confer a number of advantages. Emanating from the multiplicity of participating centres, the recruitment of sufficient numbers of participants within a reasonable time will be better facilitated by virtue of the broader reach made possible by these participating centres. While it is impossible to create a completely representable trial population where all the demographic, risk, geographic, socioeconomic factors are concerned, a multi-centre trial will potentially create a more generalizable study population. The

conclusions and inferences derived may therefore be more reliable. The research team will comprise researchers and clinicians from the various participating institutions. This could enable collaboration and fusion of ideas where the development of the project is concerned, potentially improving its quality.

Strategies minimising the risk of bias

A number of steps were built into the methodology to optimise the validity of the findings. Unlike previous trials, allocation concealment will be ensured in the central independent randomisation process. This was implemented to safeguard against selection bias in intervention allocation. Importantly, an intention to-treat-analysis will be employed for statistical analysis. All previous trials applied a modified intention-to-treat analysis, which negatively affected their quality by increasing the risk of bias. The hallmarks of intention-to-treat analysis are that (I) participants in the treatment groups are kept in the groups to which they were randomised, regardless of the intervention they received, (II) the outcome data is measured as far as possible on all participants and (III) all randomised participants are included in the final analysis. This helps to prevent bias due to the participant attrition which possibly disrupts the intergroup baseline equivalence established by the process of randomisation.

For the behavioural outcomes, validated tools will be used for measurement; the accelerometer for objective assessment and the physical activity recall diary for subjective assessments. Accelerometers have been shown to be a valid and reliable objective measure of physical activity intensity (69). The physical activity recall diary has also been validated. The validity of the measurement tools help to increase the validity of the results and by extension, the trial. The inclusion of an independent body to assess the integrity of the trial will also ensure

transparency and the rule out any conflicts of interests which would otherwise decrease the quality of the trial.

Study design limitations

The study size estimates may have to be adjusted based on the availability of patients at the participating centres. A number of patients with PAD will be excluded on the basis of comorbidity. It is established that 65% of patients with PAD also have clinically significant CHD or cerebrovascular disease and so it is highly probable that the availability of eligible population for enrolment may be affected. The exclusion of patients with comorbidities as explained throughout this paper also limits the generalizability of this study. However, ethical considerations (protection of these patients who are prone to exercise related adverse events) must prevail in this instance.

Limitations of the outcome measures

The protocols for the treadmill walking assessments vary significantly in structure. None have actually been officially validated as reliable measures for claudication. Although the quality of the results of the trial from which the protocol was adapted was satisfactory, there is no guarantee that the protocol is a precise and reliable measure.

Hip worn accelerometers actually underestimate several types of activities that do not include central body movements. Additionally, accelerometers cannot confirm the context of the physical activity. That is, it is impossible to distinguish a number of features of activity using accelerometer data alone. For instance it will be impossible to tell if the physical activity was supervised or group or alone, indoors on a treadmill or outdoor walking. It is also important to note that the extent to which participants are compliant with wearing the device will directly influence the quantity of data received. This will undoubtedly introduce the issue of

missing data and how that will be addressed in the analysis. Possible strategies that could be employed to dealing with the missing data would include over-recruiting, adopt an imputation strategy or to bring forward baseline data.

There is the potential for use of the device to influence the behaviour of the participants usually positively. The act of measurement could in this context become a potential confounding factor. This phenomenon is known as the Hawthorne effect (81).

Social desirability bias is likely to impact self-report data. This bias refers to the tendency of study participants to provide socially desirable responses in preference to true historical accounts of questions posed. I postulate that this form of bias will affect the SET participants to a greater extent than the WA group because the former would have been exposed to a formal exercise regime accompanied by educational sessions which would have increased their awareness of the ideal level of participation. The physical activity recall diaries will also be prone to recall bias and limited by participant compliance and its attendant complication of missing data.

Statistical limitations

The calculation of the sample size estimate were limited by lack of studies to provide a reliable estimate of the variability of the mean ACD. Only one trial Treat-Jacobs presented estimates of the standard deviation of the mean ACD. The other studies either used another measure of central tendency (median) or investigated another claudication measure which precluded their utility leaving one set of values to be used. Although Treat-Jacobs' study does provide us with standard deviation estimates, it does not provide whole group estimates which the formula demands. Instead, it provides estimates for each intervention group. The more conservative value was used for the calculations. This value was therefore not a true reflection of the true variability of the study population. If logistically and financially feasible, a pilot version of this

study could be could be implemented to obtain another set of reference values which could help to provide a more robust estimate of the standard deviation.

Potential ethical and practical limitations

Although RCTs are inherently powerful tools, their use is limited by ethical and practical concerns. Exposing patients to an intervention believed to be inferior to current treatment is often thought unethical. SET has been established to be the superior treatment when compared to walking advice. It could be argued that it is unethical to use exercise advice, the inferior intervention in a clinical trial. The counter argument to this underscores the value of our study as the long term adherence to SET has not yet been evaluated; it may be that adherence to walking advice is superior in the long term. The long-term benefits of walking advice could therefore be superior to SET in the long run due to compliance or accessibility issues. Furthermore, the lack of and accessibility of centres offering SET, though not officially researched is thought to be limiting factor. Walking advice is clearly unaffected by accessibility issues. These represent strong arguments for its continued use in practical medical scenarios and importantly in this trial.

Another limiting practical factor is that randomised controlled trials are generally more expensive and time consuming than other studies. Full implementation of this protocol could easily be limited by capital available for the study. However, is impossible to know at this stage of the process if capital will be a limiting factor, as funding has not yet been contemplated. The logistics of the organisational structure and flow could not be precisely outlined at this early phase of the project. Only the crucial principles of effective organisational strategies could be outlined.

The strengths and limitations of the protocol for the health economic analysis:

The cost effectiveness analysis will be a ground-breaking study in the UK context. If implemented successfully it could provide reference points on costs per meter improvement and costs per QALY against which future UK based studies as well as international can be compared. While the absence of pre-existing data provides a research opportunity it also confers a limitation. There is no existing reference point that can be used to determine an appropriate threshold for cost effectiveness particularly where cost per QALY is concerned. Statistical analysis will have to be applied to determine an appropriate threshold (75). This will have to be determined by assessing the cost per meter at which the probability of SET being cost effective surpasses 50% and is therefore greater than the probability of WA being more costly.

The fact that cost analysis will be performed from a societal perspective, and not an NHS perspective, the patient level out-of-pocket expenses and lost employment time can also be evaluated in addition to the costs to the NHS. The high quality of the NHS costing data relative to costing data in other health care systems in Europe will also help to provide reliable estimates for items in the cost analysis. Investigating both QALYs and Claudication parameters numerators facilitates more comparisons to existing literature in the area and also comparisons to other PAD interventions.

Implications for practice, research and policy

The systematic review highlighted a major void in the body of existing evidence on the long-term value of SET especially with respect to its impact on behavioural and quality of life outcomes. In light of the paucity of evidence, the RCT "The Get SET Go Study!" was designed and should be implemented to address these deficiencies in the evidence. Subsequent to the

implementation of this trial, research on the extent to which SET is recommended and utilised in practice and the various factors that influence utilisation needs to be conducted. The diversity among the SET regimes suggests that the most effective elements, in terms of content, intensity, duration and frequency of the programmes need to be evaluated.

There was not enough quality evidence to make any sound recommendations on the the use of SET. The review did suggest that the clinical effects appear to be sustained in the long term and so it should still be considered to be the gold standard, first line therapy for patients with IC. The recommendations for SET should be modified to exclude patients with significant comorbidities as ethical factors have precluded the evaluation of impact of SET on these groups of patients.

At the policy level, it is valuable to consider the generation of programmes and guidelines, which facilitate the gentle reintegration of patients, who graduate from SET programmes back into society. The Phase IV Cardiac rehabilitation model could be modified, designed by the NIC, and applied to PAD. This phase is centred on ensuring long term maintenance and based on the position that in order to sustain the effects of the rehabilitation, physical activity and lifestyle changes need to be maintained over the long-term period. A PAD protocol needs to be designed and should include the regular review of patients by the primary health care team and the establishment of community based exercise centres and programmes. Together they will ensure that the patients receive continued support to maintain the changes in the physical activity levels induced by the SET rehabilitation.

Recent updates to the existing body of evidence

There have been two important updates in the body of evidence investigating SET in the treatment of IC released following the completion of the research component of my thesis. Firstly, the Cochrane Collaboration updated its 2006 systematic review comparing the effects

of SET with unsupervised ET in 2013(82). The findings were consistent with the previous review, showing that SET was superior to WA in improving the walking distance up until 6 months. This effect was maintained at up until 6 months post-trial. The practical relevance of this improvement remained unanswered. Short-term improvement of quality of life was reported but this effect was not maintained at the long term follow up assessments. In spite of this, the authors recommended that more research be carried out to focus on the quality of life impact or other disease-specific functional outcomes. They also recommended that more research be undertaken to examine the effects on walking behaviour, patient satisfaction, costs and long term follow up. These recommendations are in line with aims of The Get SET Go! Study and thus gives the focus and rationale added credence.

Bermingham et al conducted the first UK based cost effectiveness study comparing SET to unsupervised ET (83). The study found SET was more cost effective than its unsupervised counterpart and therefore represent good value for money. It was the first cost-utility analysis to account for the impact of exercise on CVD events and mortality. This study will therefore serve as a solid reference against which my cost-effectiveness analysis can be compared.

Final Conclusion:

This thesis has managed to shape the PAD evidence base in three key ways (I) Although the systematic review failed to provide definitive conclusions, it does highlight some of the critical deficiencies in the existing body of evidence on exercise rehabilitation in the management of PAD. It is now clear that the long term clinical and behavioural impact of SET as well as its cost effectiveness in the UK context needs to be further evaluated. (II) It provides a solid rationale for the ideal methodologies to address these gaps in evidence-a randomised controlled

trial and a health economic analysis (III) It presents the protocol for a study “The Get SET Go Study!” which incorporates both methodologies and improves upon the designs of previous studies in the area. The next step requires implementation of this study, a process which fell outside of the scope of project.

Appendix I: Review Protocol

The long-term effects and sustainability of supervised exercise therapy in the treatment of intermittent claudication: a systematic review

Objectives:

1. What are the sustained effects of supervised exercise therapy on the behavioral outcomes of patients with intermittent claudication?
2. What are the sustained effects of supervised exercise therapy on the clinical outcomes of patients with intermittent claudication?

Methods:

Criteria for selection of studies

Types of studies:

1. All relevant Systematic reviews (SR) and Randomised-controlled trials (RCT) published in peer-reviewed journals will be included
2. Studies will not be included if they are non-English
3. Restriction by publication date: *to be determined*

Types of participants:

1. All patients with established IC with at least one documented baseline claudication measure: initial claudication distance, absolute claudication distance, pain free/maximal walking distance or maximum walking time.
2. All studies including patients with severe PAD or other debilitating co-morbidities such as osteoarthritis or severe CVD that preclude or restrict exercise therapy.

Comparison:

1. RCTs must include control group receiving usual care (advice) or home based structured programmes as alternatives to SET

Types of interventions:

1. Supervised exercise therapy
2. Walking advice/instructions

Types of outcome measures:

RCTs must include post-trial follow up outcome evaluations at least 6 months following cessation of trial dose of exercise therapy. The outcomes of interest are as follows:

1° Behavioural Outcomes:

In trial adherence to a SET

Post-trial physical activity levels assessed by self-report or objective measures.

2° Clinical outcomes:

Claudication measures

Initial claudication distance

Absolute claudication distance/maximal walking distance

Maximum walking time

Quality of life (Generic, Disease Specific)

Adverse effects (Mortality, Cardiovascular events)

Search methods for identification of studies and data collection

1. **Search methods for identification of studies**: A search strategy including set search terms for the main concepts such as "intermittent claudication" and "exercise therapy" etc. will be designed. The following health electronic data bases will then be searched: PubMed, EMBASE, The Cochrane Library and CINAHL. The same research strategy will be used against all data bases. The reference lists of relevant studies will be carefully perused for any additional sources (See Appendix II).
2. **Study Selection:** The criteria for selection of studies with respect to the type of studies, comparisons, participants, interventions and outcome measures are outlined above. The results obtained from the data base searches will be examined to remove duplicates, screened by title and abstract and subsequently placed into inclusion, exclusion or undecided categories based on the selection criteria in the protocol. Full text screening of all included papers as well as the undecided ones will be conducted. A final decision on inclusion or exclusion of the undecided pool will be made.
3. **Data Extraction**: Data will be extracted from the papers selected and entered into a standardised data extraction form. The data extracted will pertain to the description of and characteristics of the studies in addition to the effects of the interventions.
4. **Quality of evidence and the risk of bias assessments:** The quality of evidence and the risk of bias assessments will be conducted according to the NICE/ Cochrane guidelines for reviews of interventions.

5. **Data analysis**: It is likely due to the heterogeneity of the studies that a quantitative synthesis of the effects of the studies will be precluded. Studies will be analysed against research questions and effects combined narratively.

Results:

Description of studies, Risk of bias in included studies, Effects of the intervention

Appendix II: Sample Database Search Strategy

Proposed Electronic data bases: PubMed, EMBASE, The Cochrane Library and CINAHL

Search terms for main concepts: Condition: "*intermittent claudication"*, Intervention: *"exercise therapy" &* "walking"

Table showing the search strategy and results from the PubMed Database Search.

Set	Main Concepts	Search Term	Search Strategy	# of search results
1	Intermittent claudication (IC)	"intermittent claudication"	Search for "intermittent claudication" as a MeSH term or in Tittle and abstracts	7995
2	Supervised exercise therapy (SET)	"exercise therapy"	Search for "exercise therapy" as a MeSH or in Title and abstracts	27410
3	SET	"walking"	Search for "walking" as a MeSH or in Title and abstracts	44639
4	SET	-	Combine sets: 2 OR 3	69813
5	IC & SET	-	Combine sets: 1 AND 4	1491
6	IC & SET & Study types	-	Search set 9 in clinical queries for SR& RCT*	**853**

* This step filters the search by study type to include systematic reviews (SR) and randomized controlled trials (RCT) only. This restriction is done by means of the clinical queries filter within the PubMed database. Restriction by study type can alternatively be

conducted on the PubMed database using the guidelines stipulated in the Cochrane Handbook for Systematic Reviews of Interventions.

Appendix III: The EQ-5D-5L

Health Questionnaire

English version for the UK

you can imagine

Please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑ I
have slight problems in walking about ❑ I have
moderate problems in walking about ❑ I have
severe problems in walking about ❑ I am unable
to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑ I
have slight problems washing or dressing myself ❑ I have
moderate problems washing or dressing myself ❑ I have
severe problems washing or dressing myself ❑ I am unable
to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑ I
have slight problems doing my usual activities ❑ I have
moderate problems doing my usual activities ❑ I have
severe problems doing my usual activities ❑ I am unable
to do my usual activities ❑

PAIN / DISCOMFORT

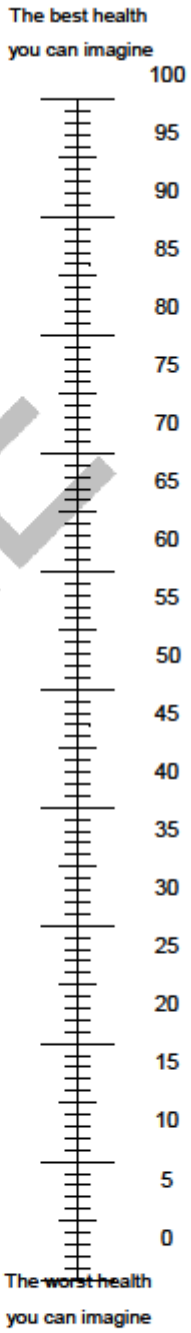
I have no pain or discomfort ❑ I
have slight pain or discomfort ❑ I have
moderate pain or discomfort ❑ I have
severe pain or discomfort ❑ I have
extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑ I am
slightly anxious or depressed ❑ I am
moderately anxious or depressed ❑ I am
severely anxious or depressed ❑ I am
extremely anxious or depressed ❑

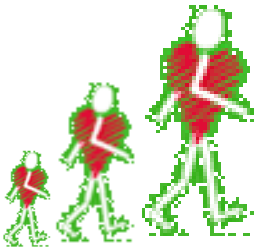
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



Appendix IV: Post trial physical activity recall diary

“Get SET Go Study!”
Physical activity Questionnaire



Surname	**Date**
Forenames (in full)	

Thank you for agreeing to participate in the “Get SET Go! Study”; your contribution is greatly appreciated. We would be very grateful if you would complete this questionnaire which will tell us about the types of activities that you have done during the last week, the number of times you did each activity and the length of time you spent doing each activity at each occasion. The answers to these questions will, of course, be kept strictly confidential. All information on individuals will go into statistics for all subjects in the study and it will not be possible to identify your responses from any reports or scientific publications.

Address
Post Code
Telephone Number
Date of Birth

FOR OFFICE USE ONLY
Project Code

Please turn over…..

General Instructions

Please read this carefully before filling in the rest of this questionnaire

- Please answer ALL the questions that apply to you by ticking a box for occasions and time
- Do NOT tick any activities that you don't do
- Where a question requires you to indicate a number, simply tick the rectangle below the appropriate number. The example below shows 1 hour and 20 minutes.

Example: Average time per occasion Hrs: 1 2 3 4 5 6 or more

☑ ☐ ☐ ☐ ☐ ☐

Mins: Under 10, 10 20 30 40 50

☐ ☐ ☑ ☐ ☐ ☐ ☐

- Where the answer is likely to be a phrase or sentence please write in the space provided.

Example: Other: please specify

∑ BOWLS

Below is a list of different speeds of cycling that you may have done during **last week**. For each of the speeds of cycling please indicate:

(a) The number of times you did each speed of cycling in the last week.
(b) On average, how long you spent cycling at each speed at each occasion.
(c) Whether the cycling made you breathe hard.

ACTIVITY	Number of times in the last week	Average time spent per occasion	Did the cycling make you breathe hard?
Cycling at a slow speed (<10 mph)	0 1 2 3 4 5 6 7 8 or more □ □ □ □ □ □ □ □ □ □	Hrs: 1 2 3 4 5 6 or more □ □ □ □ □ □ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Cycling at a steady average speed (10-15 mph)	0 1 2 3 4 5 6 7 8 or more □ □ □ □ □ □ □ □ □ □	Hrs: 1 2 3 4 5 6 or more □ □ □ □ □ □ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Cycling at a fast speed (>15 mph)	0 1 2 3 4 5 6 7 8 or more □ □ □ □ □ □ □ □ □ □	Hrs: 1 2 3 4 5 6 or more □ □ □ □ □ □ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □

Below is a list of different pace walks that you may have done during **last week**. For each of the types of walk listed please indicate:

(a) The number of times you did each type of walk in the last week.
(b) On average, how long each walk lasted.
(c) Whether or not the walk made you breathe hard.

ACTIVITY	Number of times in last week	Average time spent per occasion	Did the walk make you breathe hard?
Walking at a slow pace	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Walking at a steady average pace	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Walking at a brisk pace	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Walking to maximal pain	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □

Below is a list of sports and recreational activities that you may have done during **last week**. For each of the activities listed please indicate:

(a) The number of times you did the activity in the last week.
(b) On average, how long you spent doing the activity at each occasion.
(c) Whether or not the activity made you breathe hard.

ACTIVITY	Number of times in the last week	Average time spent per occasion	Did the activity make you breathe hard?
Aerobics/keep fit	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Dancing	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Gym workout	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Badminton	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Tennis	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Yoga	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Golf	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Swimming	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Running/jogging	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □
Other: please specify ∑ _____	0 1 2 3 4 5 6 7 8 or more □□□□□□□□□	Hrs: 1 2 3 4 5 6 or more □□□□□□ Mins: 10 20 30 40 50 □ □ □ □ □	Yes □ No □

Thinking about your everyday activities in the past week, would you say that you have been …

Very physically active	□	Fairly physically active	□
Not very physically active	□	Not at all physically active	□

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