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University of Southampton

FACULTY OF HEALTH SCIENCES

Physiotherapy

A feasibility study evaluating if the cardiac model of rehabilitation is more effective than standard care in reducing cerebrovascular risk factors post Transient Ischaemic Attack.

By

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Thesis in part completion for the degree of Doctor in Clinical Practice

November 2012

ABSTRACT

Faculty: HEALTH SCIENCES **Discipline:** Physiotherapy
Degree: Doctorate in Clinical Practice **Author:** Hayden Kirk
Title: A feasibility study evaluating if the cardiac model of rehabilitation is more effective than standard care in reducing cerebrovascular risk factors post Transient Ischaemic Attack.

Background: Atherosclerosis is the leading cause of death in the UK and is the most common cause of stroke, TIA and heart attack. Most of the risk factors for atherosclerosis are shared by both stroke and cardiac patients and are linked to lifestyle factors such as diet, exercise and smoking.

Addressing lifestyle factors plays an important role in secondary prevention, and patients with heart disease who undertake cardiac rehabilitation programs involving exercise and education sessions, can reduce the risk of cardiac mortality by 26% (Joliffe 2001). The widespread availability of cardiac rehabilitation programs contrasts with the limited lifestyle support available for stroke patients, with only 37% of patients receiving verbal advice from their doctor (Rudd 2004).

Aims: To investigate the feasibility of conducting a randomised controlled trial requiring TIA and minor stroke patients to participate in a standard NHS cardiac rehabilitation programme. The trial will also evaluate the suitability of outcome measures for assessing if the intervention will significantly reduce the risk of secondary cardiovascular events more effectively than standard care.

Methods: A single blinded randomized controlled feasibility trial was conducted with patients randomised to standard care or standard care and cardiac rehabilitation. Baseline measurements were taken one month post event with end point data collection six months post event.

Results: Twenty four patients (18 TIA, 6 minor stroke) completed the trial and provide evidence that it is feasible for stroke patients to undertake a programme of cardiac rehabilitation the effect of which can be assessed with a battery of risk factor and quality of life measures. Group analysis showed a significantly greater reduction in the primary outcome measure of Cardiovascular Disease (CVD) risk score for subjects in the intervention group in relation to standard care (intervention 25.7 ± 22.8 to 23.15 ± 18.3 , control 25.03 ± 15.4 to 27.12 ± 16.1 , $t = -1.81$, $P < 0.05$). There were also significant improvements for the intervention group in activity levels and aspects of health related quality of life.

Conclusion: Current secondary prevention strategies for stroke patients are reliant upon pharmacological therapies for managing a lifestyle related disease. This is the first trial to suggest that existing NHS lifestyle modification programmes are an effective and feasible means of reducing the risk of future cardiovascular events.

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DECLARATION OF AUTHORSHIP

I, Hayden Kirk declare that the thesis entitled

A feasibility study evaluating if the cardiac model of rehabilitation is more effective than standard care in reducing cerebrovascular risk factors post Transient Ischaemic Attack.

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- parts of this work have been submitted for publication as: *A qualitative study exploring patients' experiences of standard care or cardiac rehabilitation post minor stroke and Transient Ischaemic Attack*

Signed:

Date: ____/____/____

ACKNOWLEDGEMENTS

This research has only been possible due to the combined efforts of many people and I am very grateful to the help and support of:

Dr Paula Kersten, Supervisor, Auckland University of Technology

Professor Ann Ashburn, Supervisor, University of Southampton

Professor Joy Conway, Supervisor, University of Southampton

Dr Peter Nicholls, Statistician, University of Southampton

Dr Pamela Crawford, Director of Stroke Services

Angie Keens, TIA nurse specialist

Cardiac Rehab Nursing Team, Solent NHS Trust

Fleur Kitsell, Wessex Deanery

Liz Cullen, South Central Stroke Network Project Manager

Louise Johnson, Consultant Physiotherapist

Susan Caddy, Research nurse, Wellcome Trust

Vanessa Pressly, Clinical Trials Coordinator

Peter and Valerie Kirk, proof readers and parents

Stroke survivors, project advisory group

All of the *study participants*

I am especially grateful to my wonderful family, *Marie, Dylan, Louis*, and *Alisha* for giving me the time and support without which this thesis would not have been possible.

CHAPTER 1

Introduction

1.1 Introduction

Strokes and Transient Ischaemic Attacks (TIA's) form two components of what Sacco (2007) refers to as 'Global vascular risk' silos. These include the multiple overlapping disease states of stroke, myocardial infarction, peripheral arterial disease, and vascular death. Strokes are the second most frequent cause of death in England and Wales each year, accounting for 11% of deaths (National Audit Office, 2005). However, the majority of strokes are not fatal and concentrating on mortality figures alone can underestimate the disease burden. In the UK, stroke is the largest cause of adult disability with an estimated 900,000 stroke survivors (Department of Health, 2007) of whom only 65% are likely to be functionally independent one year post event (Wolfe, 2000). The impact of a stroke can be devastating for the patient and their family. From a purely financial perspective alone the cost to society is high, with the NHS spending £2.5 billion per annum, with additional costs to families and social services of a further £2.4 billion each year (National Audit Office, 2005).

The extensive burden of cerebrovascular disease has made primary and secondary prevention a national priority (Boyle, 2006). As a single disease entity stroke incidence is high (Rothwell et al., 2004 a), with 17% of fifty five to seventy five year olds (Seshadri et al., 2006), and 25% of all eighty five year olds being likely to experience a stroke (National Audit Office, 2005). Although 25% of strokes occur in those under sixty five, it is predominantly a disease of the elderly. The association with age and disability is one of the factors that, until recently, created a fatalistic and dismissive approach to stroke medicine, as stroke was regarded as an inevitability of ageing (Department of Health, 2007), with little attention paid to either primary or secondary prevention. In the past decade stroke has increasingly been viewed as both a preventable and treatable disease (RCP, 2008). However, its management in the UK contrasts poorly in comparison with similar industrialised countries (Boyle, 2006), and lags behind similar diseases such as coronary heart disease (National Audit Office, 2005). With an increasing incidence of vascular disease and a high risk of recurrent major vascular events post stroke (Clark et al., 2003, Dhamoon MS et al., 2006) there is an urgent need for further research into secondary stroke prevention (Liao, 2007).

1.2 Research Origins

This research developed from clinical practice. Working as a Trainee Consultant Practitioner in Stroke, involved gaining experience in different settings than those normally encountered as a physiotherapist. One such example was working in TIA clinics where patients are assessed to confirm a diagnosis, and then given treatment (medicines and / or referred to surgery) to reduce the risk of subsequent events (secondary prevention). In these clinics it was apparent that the TIA patients' risk factors were very similar to those patients with coronary heart disease. Having led cardiac rehabilitation classes (exercise and education) as a junior physiotherapist I questioned why two patient groups with such similar risk factors were offered very different secondary prevention programmes.

Discussions with colleagues and an initial search of the literature indicated that the cardiac model of secondary prevention was effective in reducing cardiac mortality (Jolliffe et al., 2001). It also showed that both disease states were very similar, and that cardiac disease was the primary cause of death for TIA patients five years post TIA. This information indicated that there were substantial clinical arguments to suggest that the benefits of one form of secondary prevention (cardiac rehabilitation) may translate to a different disease state (stroke). In order to substantiate this theory it would be necessary to conduct research. Consequently, in 2007, as part of a Doctorate in Clinical Practice, a feasibility trial was proposed which aimed to evaluate if the cardiac model of rehabilitation was more effective than standard care in reducing cerebrovascular risk factors post Transient Ischaemic Attack.

This thesis is the product of that exploratory journey, from funding applications, to management of a portfolio study and finally the internal debate about the ethical implications and direction of future research. This journey begins in Chapter two, with an exploration of the physiological premise for this trial through a review of the causes of stroke and coronary heart disease and their associated risk factors. Chapter three then reviews the literature regarding current and enhanced secondary prevention strategies for both stroke and coronary heart disease patients. The results of these reviews would inform the study aims, objectives and design.

CHAPTER 2

Stroke & Coronary Heart Disease

2.1 Stroke Pathophysiology

Stroke is defined by The World Health Organisation (World Health Organisation, 1985) as *‘a syndrome of rapidly developing symptoms and signs of focal, and at times global, loss of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin’*. The consequences of a stroke vary depending on the degree of neuronal damage and the effect can be transient or produce prolonged symptoms ranging from mild to severe disability and death.

Approximately a third of all strokes are considered ‘severe’, leaving the person with significant disabilities, which may include reduced visual, cognitive and communication skills, paralysis, spasticity, depression and other mental health problems (National Audit Office, 2005). By contrast, patients with a minor stroke may have one or a number of these symptoms but to a level that does not greatly impair normal function. Clinically this is classified as having disabilities registering less than three on the National Institute for Health Stroke Scale (Coull et al., 2004). Transient Ischemic Attack’s (TIA’s) are a form of a stroke also caused by inadequate cerebral or ocular blood supply but with symptoms fully resolving within 24 hours (Warlow, 2001). Technically, a TIA and a stroke are one and the same disease but with differing levels of clinical severity. Both cerebrovascular events are therefore in effect a continuum, with the 24 hour definition for a TIA being an arbitrary marker (Warlow, 2008). Consequently, for the purpose of this thesis, unless specified separately, the term stroke will be used to refer to all stroke patients (i.e. stroke and TIA) and evidence will be sought from the literature relating to both stroke and TIA patients. However, due to the physical limitations resulting from a severe stroke, only patients diagnosed with a TIA or minor stroke have been included in this feasibility study.

2.2 Stroke and Coronary Heart Disease

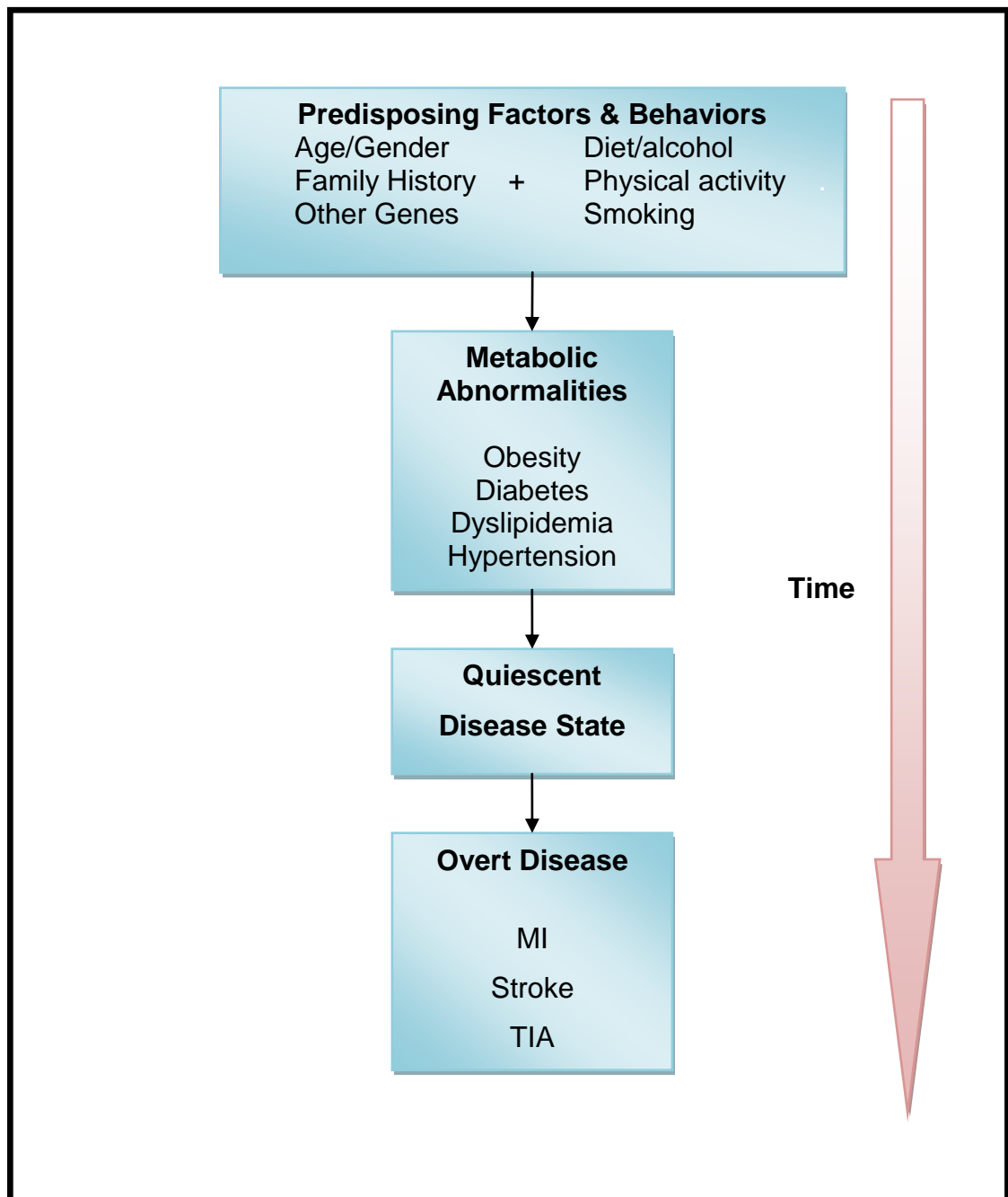
The term Stroke defines a wide variety of physiological disease states and presentations. The commonality is an alteration in cerebral blood flow, but the underlying pathology can vary. This has important implications for secondary

prevention strategies. Of the estimated 110,000 strokes in the UK each year, approximately 80% will be the result of ischaemic infarction with the remainder being attributable to haemorrhage (15%) or of uncertain cause (5%) (Warlow, 2008). Though less frequent, haemorrhagic strokes often result in a greater level of neuronal insult due to the mass effect of increased pressure. Consequently they are rarely associated with TIA's or minor strokes and, as they have a different pathophysiology, will not be considered further in this thesis.

As with stroke, coronary heart disease is an umbrella term for a number of different physiological states and presentations. However, unlike stroke, the underlying cause is more uniform, and occurs as a result of narrowing, or blockage in, the coronary arteries by atheroma. This can lead to angina, coronary thrombosis, heart attack, heart failure, and/or sudden death (Department of Health, 2000).

A shared physiological feature of both ischaemic stroke and coronary heart disease is the underlying role that large vessel atherosclerosis plays. This is the most common cause of both stroke and coronary heart disease (Warlow, 2008), with the development of atheromatous plaques (Figure 1) being intrinsically linked to the risk factors that both disease processes share as a consequence of genetic pre-dispositions and modern Western lifestyles. Although the atheromatous plaques themselves do not automatically lead to stroke or coronary heart disease (the majority will remain asymptomatic), when the plaques become unstable, and rupture, the ensuing atherothromboembolism can result in cerebral or myocardial infarction with ensuing ischaemic tissue damage (Warlow, 2008).

Figure 1 Progression of atherosclerosis



(Libby et al., 2005 pg1121)

The commonality in cardiovascular and cerebrovascular disease processes is reflected in the vascular risk factors. The list of risk factors is extensive and can be categorised as modifiable and non-modifiable (Table 1). The modifiable risk factors can be further divided into those for which pharmacological and surgical interventions can have a significant effect and those for which behavioural lifestyle factors are also thought to have an impact.

Table 1 Occlusive vascular risk factors

Stroke and Cardiac Modifiable Lifestyle Risk Factors	Stroke & Cardiac Non-modifiable Risk factors	Stroke and Cardiac Pharmacologically Modifiable Risk Factors
Cigarette-smoking	Age	Hypertension
Physical inactivity	Male sex	Dyslipidemia
Diet	Ethnicity	Diabetes mellitus
Alcohol	Genotype	
Social deprivation	Low birth weight	
Stress / depression		
Obesity and body fat distribution		
Hypertension		
Dyslipidemia		
Diabetes mellitus		

(Yusuf, 2004, Goldstein, 2006, NICE, 2007, Mozaffarian et al., 2008)

Much of the evidence for stroke and cardiac risk factors comes from the same large cardiovascular epidemiological studies. Though the extent of causality is not always apparent, these studies have shown a clear association between stroke, coronary heart disease and the above risk factors (Warlow, 2008 pg278, Yusuf, 2004).

Whilst stroke and coronary heart disease risk factors appear identical, differences in the pathophysiology are reflected in the relative weighting of these risk factors. Table 2, shows the estimated global contribution of the modifiable risk factors for each disease. These estimates show notable differences between stroke and coronary heart disease, particularly in regard to blood pressure, cholesterol, diet and activity. However, as all stroke subtypes are grouped together, it is possible that there could be less variation with coronary heart disease if non ischaemic strokes were to be excluded.

Table 2 Contribution of major risk factors to stroke and CHD disease burden

Risk Factor	Stroke*	CHD*
High blood pressure	72%	58%
High cholesterol	27%	63%
Obesity (BMI)	23%	33%
Diet (Low fruit & vegetable)	12%	28%
Physical inactivity	9%	22%
Tobacco	22%	22%
Alcohol	0%	0.2%

* Contributing risk factors expressed as a population attributable fraction. (Ezzati et al., 2003)

Analysis of the co-morbid factors provides further evidence of the common vascular disease process. Retrospective audits have shown that up to 70% of stroke patients have underlying coronary heart disease, although 40% will be asymptomatic (Gates et al., 1987, Adams et al., 2003). The long term consequence of this was demonstrated in Clark et al's., (2003) longitudinal study. This highlighted how, in the ten years post TIA, 70% of deaths would be due to vascular disease, with more being attributable to coronary heart disease (57%) than cerebrovascular disease (36%). At ten years the cumulative risk of subsequent vascular events for patients with minor stroke and TIA is as high as 47.8% (45.3–50.3) and 35.8% (32.3–39.3) respectively (van Wijk et al., 2005). For stroke patients the risk (mean yearly recurrence rate) is particularly high initially (15%) (Lin et al., 2007), gradually declines during the first three years, but rises thereafter and continues to remain high (5.7%) over the following ten years (van Wijk et al., 2005).

The shared underlying atherosclerotic pathology and high secondary event risk across all vascular territories has focused attention on the primary and secondary prevention of coronary heart disease and stroke. Since the introduction of national guidelines (Department of Health, 2000, Department of Health, 2007) , stroke services have followed the lead of cardiac services with the prescription of similar medications and interventions, such as thrombolysis. However, whereas coronary

heart disease patients are offered extensive cardiac rehabilitation programmes to reduce the risk of further cardiac events, stroke patients traditionally receive only a short piece of lifestyle advice.

To investigate why this anomaly occurs, a search of the literature was undertaken to ascertain whether there is any evidence to suggest that stroke patients may also benefit from a cardiac rehabilitation styled programme. The review will consider and compare the evidence for the effectiveness of the current stroke and coronary heart disease secondary preventative strategies, with particular emphasis on modifiable lifestyle factors. The conclusions from the review will inform the design of the study.

CHAPTER 3

Literature Review

3.1 Search Strategy

A literature search was undertaken to identify studies relating to cardiac rehabilitation and secondary stroke prevention. Searches were conducted in the following electronic databases: Medline, CINAHL, and the Cochrane Library using the following search terms:

- Stroke or cerebrovascular accident or CVA or Transient Ischaemic Attack or TIA AND exercise, or health behaviour or lifestyle change
- Stroke or cerebrovascular accident or CVA or Transient Ischaemic Attack or TIA AND heart or cardiac or myocardial AND rehabilitation
- Cardiac Rehabilitation or Heart or cardiac or myocardial AND rehabilitation or exercise or education or counselling

In addition, reference lists of retrieved articles were examined for further trials, reviews and meta-analyses. A full copy of the search strategy is available in appendix 1 and 2 (pg 148-154).

3.2 Stroke Secondary prevention

The current guidance for secondary prevention of ischaemic strokes is based on targeting the modifiable risk factors and their symptoms (RCP, 2008). Although a comprehensive approach is advocated, this is predominantly concerned with medical interventions and is based on extensive secondary preventative pharmacological trials. By comparison, advice regarding lifestyle risk factors is based upon evidence gained from primary prevention studies as *'little research...(into lifestyle risk factors)... has concentrated specifically upon secondary prevention'* (RCP, 2008 pg 66).

Traditionally, both pharmacological and lifestyle secondary preventative interventions are delivered by doctors and nurses on stroke wards and in TIA clinics. This is followed up in primary care with reviews and advice from General Practitioners, stroke clinics and community nurses. As a method of delivering secondary prevention this current model has developed over time and in line with

clinical guidelines. However, evidence for the effectiveness of this clinical advice is variable.

A national survey of 8,200 medical records from 235 sites across the UK found '*major deficiencies in delivery of secondary prevention after stroke*' (Rudd et al., 2004 pg 280). This study was primarily concerned with adherence to pharmacological therapies and was able to give an indication of both processes and outcomes. This indicated that even within the controlled environment of a hospital, many patients were not receiving the appropriate medications (9% for anti-thrombotics, 26% for statins and 22% for hypertensive medication). Six month follow up data was not provided for adherence to anti-thrombotic and statin medication, though it was available for hypertensive medication. This showed that although 84% of patients were still taking their hypertensive medication, 59% of these patients still had elevated blood pressure recordings.

A subsequent study of 300 male TIA and stroke patients from 24 British towns, showed that medication prescription and adherence had improved over time (1999 – 2005) (Ramsay et al., 2007). However, by 2005 only a third of male stroke patients were receiving a combination of antiplatelet, blood pressure lowering and statin therapy. Although antiplatelet prescription was reasonably high, the results from this primary care study suggest that there are lower rates of prescription and adherence in primary care especially for the older TIA patients. The authors therefore concluded that secondary prevention for cerebrovascular disease was less advanced than that for coronary heart disease, and the presence of coronary heart disease had a strong influence on the likelihood of patients receiving treatment. The findings from both studies suggest that even when there are standard evidenced based guidelines, adherence and implementation with the current service delivery model is sub-optimal.

Previous international studies indicate that these findings are not exclusive to the UK health system for both pharmacological and lifestyle risk factor management. In Boston (USA), Joseph et al., (1999) conducted an observational study of 66 stroke patients who were seen in an outpatient clinic more than two times (range 2 – 17) over a two year period. In this instance data from the notes showed that only 86% of hypertensive patients were receiving medication, and only 51% of these

had their blood pressure adequately controlled. Similarly, after two years 55% still had elevated lipid levels, 69% of diabetic patients had elevated glucose levels, none of the smokers (30% of patients) had stopped smoking and forty eight per cent of patients sustained a further vascular event during this period.

A comparable Canadian study reviewed the adequacy of risk factors management through stroke prevention clinics. Mouradian (2002) prospectively examined the notes of 119 patients seen in clinic. They found that one year after the stroke, blood pressure and cholesterol management had only improved by 20% ($P<0.001$) and 32% ($P<0.001$) respectively since the incident event, and that there was no significant improvement in either diabetes management or smoking cessation.

A limitation of both these studies is the inability to generalise to the wider population as they were conducted at just two sites, with relatively small participant numbers, and in the Joseph et al.,(1999) study, 98% of participants were male. However, they do provide further evidence to Rudd et al's., (2004) observation that the current medical model of care is not providing effective interventions sufficient to reduce the risk of subsequent strokes.

With the exception of smoking, the above studies have predominantly reported on pharmacological therapies and their outcomes. Within the current NHS system the healthcare professionals are also responsible for delivering lifestyle advice along with the prescription of medicines. A number of studies have investigated the process and outcomes of this advice. In 2004, Rudd et al., examined the prevalence of consultations on lifestyle advice. They found that such advice was recorded as having been given in only 37% of stroke consultations. The fact that, unlike pharmacological prescriptions, there is no legal requirement to record all aspects of clinical conversations, means this recorded number of lifestyle consultations could be an under-representation of the actual provision of such advice. Alternatively, the delineation in legal requirements for note taking may emphasise the low priority the medical profession attaches to lifestyle factors in relation to conventional medical interventions (Williams and Calnon, 1994).

In 2002 a national American phone survey of 51,193 people recorded 2.4% respondents as having had a stroke. In contrast to Rudd et al's., (2004) study, 61% recalled being given dietary advice and 64% being given exercise advice by

their doctor (Greenlund et al., 2002). This survey also investigated the effect of the physician advice and found that those people who received advice were more likely to have changed their diet and exercise levels (85% and 76% respectively) than those who did not receive diet and exercise advice (56% and 40% respectively). Although this was a comprehensive random survey across 20 states, the self-reported nature of the feedback could result in an over estimation of health benefits as participants may be naturally inclined to provide what they think is the right answer rather than report accurate findings (Denscombe, 2004).

Clinical studies that measured the effect of the current advice given for lifestyle and medical secondary preventative measures indicate that the current methods are less effective than Greenlund et al's., (2002) study would suggest. A prospective study by Redfern et al., (2000) reviewed the data from 717 patients on the South London Stroke Register. This showed that at three months post stroke only 28% of patients had stopped smoking, 3.6% still drank and at one year 36% were still obese. At the time it was suggested that these adverse findings may reflect a lack of medical input post discharge so a subsequent review of the data was undertaken. This review (Redfern et al., 2002) examined the contact these patients had had with medical professionals and revealed that 84% of the patients were seen by either their GP and/or a specialist Physician (70%) and community nurse (14%) in the first three months post stroke. These results suggest that the current service model for secondary prevention is either insufficient, ineffective or possibly both.

The above studies indicate that the current approach for the delivery of secondary stroke prevention is inadequate, with poor control of risk factors, especially those that require behavioural lifestyle modification. On the evidence of a national audit, Rudd et al., (2004 pg 285) concluded that less than half of stroke patients are receiving sufficient treatment to prevent subsequent strokes. They suggested that *'more effective ways of informing the public about minimisation of risk factors for vascular disease'* were required. As a possible solution to this they noted that *'considerable resources have been devoted to coronary artery disease prevention, especially for younger patients; risk factor management is similar for cerebrovascular disease and it may be time to combine efforts with the establishment of vascular risk reduction initiatives, rather than running parallel*

services'. The following section therefore considers the secondary prevention approach taken by cardiac services and reviews how this compares with stroke secondary prevention.

3.3 Cardiac Rehabilitation

Cardiac rehabilitation is now an established part of the cardiac care management model, with the expectation that more than 85% of patients are offered access to such programmes (Department of Health, 2000). Research into these secondary prevention programmes has evolved significantly in the past three decades and Certo's (1985) review provides an important insight as to why and how these programmes developed. Certo (1985) highlights how governments first became concerned with the social and financial effects of heart disease in the 1930's, when 80% of male survivors were unable to return to work and therefore claimed disability benefits. At the time, high mortality and secondary recurrence rates led to a very conservative approach to patient management. It was not until the 1960's that the original concept of an outpatient programme for a graded return to physical and social activity was shown not only to be safe, but also beneficial for patients (Hellerstein, 1968). Since then, cardiac rehabilitation programmes have become an accepted part of cardiac disease management within Western societies and there has been extensive research into the medical benefits of such programmes.

The World Health Organisation defines cardiac rehabilitation as *'the sum of activity and interventions required to ensure the best physical, mental, and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume their proper place in society and lead an active life'* (World Health Organisation, 1985). Interestingly, this emphasises the social and holistic aims of cardiac rehabilitation programmes, which reflect the historical social consequences of cardiac disease. In contrast, Wenger et al., (1995) provides a more prescriptive medical model explanation, defining cardiac rehabilitation as *'comprehensive, long-term programmes involving medical evaluation, prescribed exercise, cardiac risk factor modification, education and*

counselling'. This definition probably better reflects modern clinical practice and the evidence found in the following literature review.

Though the aims of cardiac rehabilitation programmes are quite uniform, their delivery within and between countries can differ. Within Europe most programmes are broken down into four phases (Table 3), whilst in America phase's II & III are combined. Programmes are usually delivered via group sessions at specialist centres or occasionally individually at home (Department of Health, 2000, SIGN, 2002, Balady et al., 2007, NICE, 2007), and typically involve a variety of therapies including exercise, psychological input, risk factor education and drug therapy (Taylor et al., 2004). Programmes that provide all these inputs are termed comprehensive cardiac rehabilitation. These contrast with other forms of cardiac rehabilitation, which provide only exercise or psychological / educational input.

Table 3 Cardiac Rehabilitation Phases 1- 4

Phase	Intervention*
Phase 1	The initial stage following myocardial infarction or step change in cardiac condition. Includes medical evaluation, reassurance and education, correction of cardiac misconceptions, risk factor assessment, mobilisation and discharge planning.
Phase 2	The post-discharge stage: a period of psychological stress and feelings of social isolation and insecurity. Support can be provided by home visiting, telephone contact and by use of the heart manual or equivalent cognitive behavioral programme.
Phase 3	<p>Structured exercise and rehabilitation: structured exercise training together with continuing educational and psychological support and advice on risk factors.</p> <p>An individualised menu based approach which can include specific education to reduce common cardiac misconceptions, encourage smoking cessation and weight management, vocational rehabilitation and referral to cardiologist, psychologist or exercise physiologist if appropriate. Most patients will benefit from undertaking at least light to moderate exercise.</p>
Phase 4	Long-term maintenance: of physical activity and lifestyle changes.

*adapted from SIGN 2002

The variety of interventions and methods of delivering cardiac rehabilitation programmes means they are very complex to analyse. Consequently, when trying to understand the cause and effect of rehabilitation programmes the term 'black box' has been used to illustrate the difficulty in defining the degree to which each aspect of the intervention was responsible for the overall outcome (Taylor et al., 2004, Rodgers et al., 2005). This term has also been applied to stroke rehabilitation (Whyte, 2003). However, unlike stroke risk factor modification, there are numerous studies (in excess of 6,345 Medline 2008) which have evaluated the health and social effects of cardiac rehabilitation programmes. The extensive data from these trials has enabled researchers to meta-analyse the results and provide a comprehensive overview of the relative effects of cardiac rehabilitation programmes. The following review of these meta-analyses considers the strength

of the evidence and examines whether there are specific aspects of these complex interventions that could be particularly appropriate for stroke secondary prevention.

3.3.1 Cardiac Rehabilitation Research

Since cardiac rehabilitation programmes were first deemed both safe and beneficial (Hellerstein, 1968), they have become the main form of risk factor modification and there have been numerous studies evaluating their effects. These studies were originally quite small and there was considerable heterogeneity between the outcome measures. As a consequence, the evidence for cardiac rehabilitation was very variable and it was not until the data was subjected to meta-analyses that a consensus of opinion developed. This analysis was primarily concerned with mortality (Table 4 pg 23 and Table 5 pg 24) but a number of studies also recorded the effect these rehabilitation programmes had on vascular recurrence rates and modifiable risk factors (Tables 6 – 8 pg 28 - 30).

3.3.2 Cardiac Rehabilitation: Effect on mortality

The first large meta-analysis of note was by Oldridge et al, (1988). This analysed 10 studies (including the 10 separate WHO trials) all of which had an exercise and education component. The results from this analysis showed that rehabilitation programmes reduced all-cause mortality and cardiovascular mortality by 24% and 25% respectively. The powerful findings from this meta-analysis indicated that cardiac rehabilitation was as effective as some of the medications of choice at the time (Beta Blockers), and the authors therefore recommended that it should be considered a clinical therapy. However, in keeping the study entry criteria broad, Oldridge et al, (1988) did not try to attempt to unravel the 'black box' of interventions and explore the benefits of each aspect of cardiac rehabilitation.

Table 4 Cardiac Rehabilitation Meta-analyses; study characteristics

Study Year	Sample size	Study Sample	Components of intervention	Mean age (range)	Percentage of females	Duration of follow up	CASP Score*
Oldridge et al. 1988	4,347	MI	3 studies with risk factor management plus exercise or exercise advice. 7 studies with exercise & some risk factor management. All to last at least six weeks.	52 (47-55)	3 %	15 months (1 – 48)	7
O'Connor et al. 1989	4,554	MI	Exercise only (6 trials) or exercise plus other interventions (15 trials)	≈ 55 (25-70)	1.6%	12, 24, 36 months	7
Jolliffe et al. 2001	8,440	MI CABG PCI CAD	Any form of exercise based programme (in-patient, outpatient, community or home based). Could be exercise only or comprehensive programmes.	55	19%	29 months	9
Taylor et al. 2004	8,940	MI, CABG, PCI	Any form of exercise based programme (in-patient, outpatient, community or home based). Could be exercise only or comprehensive programmes.	55 (48-71)	20%	Mean: 15 months (6 - 72)	9
Clark et al. 2005	21,295	MI CAD	Trials providing all supervised forms of cardiac rehabilitation	52 (51-71)	3.4%	20months (6-60)	7

* Scored by the author according to the CASP - Critical Appraisal Skills Programme guidance. MI: Myocardial Infarction. CABG: Coronary Artery Bypass Graft. PCI: Percutaneous Coronary Intervention. CAD: Coronary Artery Disease

Table 5 Cardiac Rehabilitation Meta-analyses; Results

Author	Cardiac rehabilitation Programmes	Cardiac mortality Odds ratios	All- cause mortality Odds ratios
Oldridge et al 1988	Exercise only & Comprehensive	0.75 (95% CI, 0.62 to 0.93)	0.76 (95% CI, 0.63 to 0.92)
O'Connor et al 1989	Exercise only & Comprehensive	0.78 (95% CI, 0.63 to 0.96)	0.80 (95% CI, 0.66 to 0.96)
Joliffe et al 2001	Exercise only	0.69 (95% CI, 0.51 to 0.94)	0.73 (95% CI, 0.54 to 0.98)
	Comprehensive	0.74 (95% CI, 0.57 to 0.96)	0.87 (95% CI, 0.71 to 1.05)
Taylor et al 2004	Exercise only & Comprehensive	0.74 (95% CI, 0.61 to 0.96)	0.80 (95% CI, 0.68 to 0.93)
Clark et al 2005	All cardiac rehab programmes	N/A	0.85 (95% CI, 0.77 to 0.94)
	Exercise only	N/A	0.72 (95% CI, 0.54 to 0.95)
	Comprehensive	N/A	0.88 (95% CI, 0.74 to 1.04)
	Education only	N/A	0.87 (95% CI, 0.76 to 0.99)

A subsequent meta-analysis by O'Connor et al., (1989) investigated aspects of this 'Black Box' effect by analysing the effect of 'exercise only' trials in relation to comprehensive rehabilitation trials. Though they found similar benefits (a 20% reduction in all cause mortality) to Oldridge et al., (1988) with their combined data, neither the six exercise only trials nor the fifteen comprehensive rehabilitation trials managed to attain individual levels of significance. Whilst supporting Oldridge et al's., (1988) claims for the efficacy of cardiac rehabilitation, O'Connor et al's., (1989) findings further emphasised the difficulty in understanding the complexity of the interventions. As a result O'Connor et al., (1989) recommended that future

trials should exceed 4,000 participants in order to be able to ascertain a true cause and effect.

Analysis of the influence of the various inputs for cardiac rehabilitation was further addressed by the NHS Centre for Reviews and Dissemination (NHS Centre for Reviews and Dissemination, 1998). In addition to O'Connor et al's., (1989) categorisation of exercise-only and comprehensive cardiac rehabilitation, this review also considered a third category comprising psychological and educational interventions. The results were largely supportive of cardiac rehabilitation as a means of helping patients '*achieve better health*' and '*reduce the risk of death*'. However, these beneficial findings only existed in the comprehensive form of CR and were largely based on Oldridge et al's., (1988) and O'Connor et al's., (1989) analyses of cardiac rehabilitation programmes.

In the exercise-only trials, the review NHS Centre for Reviews and Dissemination (1998) concluded that whilst exercise had a '*positive impact on the physical aspects of recovery at no additional risk to the patient*' there was no beneficial effect on mortality, secondary recurrence rates or blood lipid levels (with the exception of triglycerides). These conclusions were largely based on Wenger et al's., (1995) review for the US Cardiac Rehabilitation Guidelines, which questioned the benefit of exercise-only rehabilitation. However, as this was a narrative review with methodology that was unclear and conclusions that did not always accord with the evidence presented (NHS Centre for Reviews and Dissemination, 1998), it was only possible to suggest, as O'Connor et al., (1989) did, that further larger studies were required. In the psychological and educational intervention-only category, the heterogeneity of interventions and also outcomes made it particularly difficult to draw any firm conclusions. Whilst the report (NHS Centre for Reviews and Dissemination, 1998) proposed that there was some evidence to suggest that these interventions may improve risk factors such as cholesterol, blood pressure and wellbeing, there was no strong evidence of a secondary preventative effect on mortality or recurrent cardiac events.

These reviews and analyses have shown that cardiac rehabilitation was collectively an effective secondary preventative form of treatment, but they have been unable to suggest why this was. In 2001 Joliffe et al., (Table 5) was able to

partially address this with a substantially larger meta-analysis which looked to determine the effectiveness of exercise only rehabilitation and comprehensive cardiac rehabilitation programmes. This Cochrane review proved to be a seminal analysis, and included a total of 51 trials with double the number of participants (8,440) compared to previous analyses (Oldridge et al., 1988, O'Connor et al., 1989). The results from the subgroup analysis for exercise only interventions (2,582 participants) found that there were significant reductions in cardiac mortality (31%) and all-cause mortality (27%) (Table 5). In contrast to previous reviews (Oldridge et al., 1988, O'Connor et al., 1989, NHS Centre for Reviews and Dissemination, 1998), this analysis suggested that not only was the exercise-only element clinically beneficial, but that it was even more effective than comprehensive cardiac rehabilitation.

A subsequent meta-analysis by Taylor et al., (2004) built on the evidence from Joliffe et al., (2001). This review did not seek to address the issue of cause and effect for the component parts of cardiac rehabilitation, but sought to address concerns that recent changes in the medical management of patients would nullify the benefit of rehabilitation programmes. With 50% of the 48 trials (8,940 patients) published since the routine introduction of PCI's (percutaneous coronary intervention) and statins in the 1990's, Taylor et al., (2004) concluded that exercise based cardiac rehabilitation programmes (i.e. both exercise-only and comprehensive programmes combined) significantly reduced cardiac and all-cause mortality even after the introduction of modern medical procedures (Table 5). As 65% of the trials in this study were the same as those in Joliffe et al's., (2001), and 50% were pre-1990, this may exaggerate the influence of cardiac rehabilitation in modern times. However it does substantiate Joliffe et al's., (2001) findings on the overall benefit of exercise based cardiac rehabilitation.

The final substantial review identified in the literature sought to examine the effects of the components of cardiac rehabilitation programmes. In this study, Clark et al., (2005a) included all forms of psychological, educational and exercised based cardiac rehabilitation programmes. This allowed them to conduct a four way meta-analysis of the data from 63 trials and 21,295 patients. The results from the meta-analysis showed significant reductions in all-cause mortality for all forms of cardiac

rehabilitation, be it the education-only component, exercise and education, or exercise only programmes (Table 5).

3.3.3 Cardiac Rehabilitation: Risk Factors and Recurrence rates

Though the effects of the cardiac programmes are consistent with regards to mortality, there is considerably more ambiguity in respect to risk factor modification. Though not reported in the earlier meta-analyses by Oldridge et al., (1988) and O'Connor et al., (1989), all three subsequent meta-analyses (Jolliffe et al., 2001, Taylor et al., 2004, Clark et al., 2005a) considered the influence of cardiac rehabilitation on some of the major cardiovascular risk factors and cardiac recurrent event rates. Tables 6 – 8 present the results, which provide an indication of the heterogeneity of the measures and results.

Table 6 Cardiac Rehabilitation Meta-analysis; Jolliffe et al., (2001)

Risk Factors and Recurrence rates

(Jolliffe et al., 2001)	Comprehensive Cardiac Rehabilitation	Exercise Only Cardiac Rehabilitation
Total Cholesterol	Significant reduction -0.57 mmol/L (95% CI -0.83 to -0.31)	No Significant reduction
LDL Cholesterol	Significant reduction -0.51 mmol/L (95% CI -0.82 to -0.19)	No Significant reduction
Triglyceride	Significant reduction -0.29 mmol/L (95% CI: -0.42 to -0.15)	No Significant reduction
Systolic Blood Pressure	No Significant reduction	No Significant reduction
Diastolic Blood Pressure	Significant reduction -2.24 mmHg (95% CI: -3.36 to -0.85)	No Significant reduction
Smoking	No Significant reduction	No Significant reduction
HRQoL	No Significant reduction	No Significant reduction
Recurrence Non- fatal MI	No Significant reduction	No Significant reduction

Table 7 Cardiac Rehabilitation Meta-analysis; Taylor et al., (2004)

Risk Factors and Recurrence rates

(Taylor et al., 2004)	All Exercise Based Cardiac Rehabilitation (Comprehensive and Exercise Only)
Total Cholesterol	Significant reduction 0.37 mmol/L (95% CI -0.63 to -0.11)
LDL Cholesterol	No Significant reduction
HDL Cholesterol	No Significant reduction
Triglyceride	Significant reduction 0.23 mmol/L (95% CI: -0.39 to -0.07)
Systolic Blood Pressure	Significant reduction 3.2 mmHg (95% CI: -5.4 to -0.9)
Diastolic Blood Pressure (mmHG)	No Significant reduction
Smoking	Significant reduction (OR=0.64; 95% CI: 0.50 to 0.83)
Recurrence Non- fatal Myocardial Infarctions	No Significant reduction

Table 8 Cardiac Rehabilitation Meta-analysis; Clark et al.,(2005a)

Risk Factors and Recurrence rates

(Clark et al., 2005a)	Combined: Comprehensive, Education / Counselling and Exercise Only
Total Cholesterol	17 out of 35 trials showed significant reduction
Medication adherence	8 out of 22 trials showed significantly better application. 11 showed no significant difference
Re-infarction rate	Significant reduction Exercise based: OR 0.73 (CI: 0.60 to 0.89) Non- Exercise based: OR 0.86 (CI: 0.72 to 1.03)

The variation in results presents a confusing picture from which it is difficult to draw any specific conclusions. For example, Jolliffe et al., (2001) found small but significant reductions in total cholesterol, LDL cholesterol and diastolic blood pressure for comprehensive cardiac rehabilitation patients. Conversely, he found no significant changes in risk factors for the exercise-only cardiac rehabilitation, in spite of the greater reductions in mortality for the exercise-only trials. A possible explanation for this may be the number of participants available for the sub-group analysis. With proportionally more comprehensive rehabilitation trials there were more data available in the comprehensive cardiac rehabilitation group (360 - 600 participants) in relation to the exercise-only group (50 – 120 participants). This also potentially explains why Taylor et al., (2004) reported more consistent changes in risk factors, as their combination of any exercise based rehabilitation provided a greater pool of data for analysis (200 – 1,900 participants).

Of particular note, and in contrast to both Jolliffe et al., (2001) and Taylor et al., (2004), is the fact that although cardiac mortality was reduced in all three studies, only Clark et al., (2005a) reported significant reductions in recurrent myocardial infarction rates (3% at 1 year, 23% at 5 years). This again may be due to the other studies not being sufficiently powered to detect a change, as Clark et al., (2005) included double the number of participants compared with the other two studies. Interestingly, when Jolliffe et al., (2001) combined the results for all 'adverse'

clinical outcomes (non-fatal infarctions and revascularisations), they reported a 20% reduction for both the exercise-only (OR 0.81 95% CI: 0.65 to 1.01) and comprehensive rehabilitation (OR 0.81, 95% CI: 0.69 to 0.96) groups. This apparent dissociation between mortality, recurrence rates and attributable risk factors is difficult to explain and, based on reductions in recurrence rates and modifiable risk factor results alone, it is unlikely that cardiac rehabilitation would be deemed an effective intervention. However, the consistent reductions in mortality suggest that there is a cumulative benefit caused by the fact that many of the risk factors act in a combined and, as yet, unknown manner (Rothwell, 2007, D'Agostino et al., 2008).

The variations seen within and between studies may in part be due to the limitations which affected all three reviews. Many of the original trials in the analyses were recognised as being small and therefore underpowered (Jolliffe et al., 2001). As all the reviews included the same core trials, this was a weakness in all six analyses. The methodology of the individual trials was also often inadequate, with only 16% of papers reporting a clear description of an appropriate method of randomisation (Jolliffe et al., 2001). Both Taylor et al., (2004) and Clark et al., (2005a) sought to quantify this and classified the research quality with a mean Jadad score (Jadad and Gagliardi, 2002) of just 2 (range, 1 - poor to 5 - robust). In addition Jolliffe et al., (2001) conducted a pooled analysis in respect to the quality of randomisation. This still showed clinically significant findings for both groups but suggested an over estimation of clinical effect as the reductions in mortality were substantially lower in the more rigorous trials.

The heterogeneous nature of the numerous small trials also created difficulties when pooling the results. This primarily affected the psycho-social measures, with eighteen different quality of life measures used in just eleven trials (Jolliffe et al., 2001). It also proved contentious when considering the effect on mortality over time. Taylor et al., (2004) does not give an indication of follow up periods but suggests these were too small to measure educational benefits. Jolliffe et al., (2001) did record follow up with a mean period of 2.4 years (6 months – 5 years). Although they did not do a regression analysis to explore this further, they noted that two of the studies with extended follow up periods found no interventional effect on mortality at 11 years (Bethell and Mullee, 1990) or 19 years (Dorn et al.,

1999). In contrast, Clark et al., (2005a), completed a sub group analysis which showed that mortality reduced from an odds ratio of 0.97 (CI, 0.82 to 1.14) at one year, to 0.53 (CI, 0.35 to 0.81) at two years and 0.77 (CI, 0.63 to 0.93) at five years. This is an important and significant difference, and suggests that the maximum effect of cardiac rehabilitation occurs over the 1 – 5 year period and diminishes thereafter. Again, the data from this sub-group analysis should be interpreted with caution since the number of participants was relatively low for the follow up (9462 participants year one to 2477 year five).

One area of uniformity was in the participant characteristics. These were overwhelmingly middle aged (mean age 53.5 years, range 47 – 71 years) and male (89%, range 80% – 97%) with a diagnosis of myocardial infarction (67%, Taylor et al., 2004). This limited pool of participants reflects the original perception of pre-mature male deaths and social incapacity as a result of heart attacks (Certo, 1985). As a consequence it is difficult to generalise the results to both the stroke and coronary heart disease population where the mean age of incident events for stroke (73.8 years) and myocardial infarction (70.9 years) is considerably older (Rothwell et al., 2005). This variation in age and gender profile within the trials does not reflect the disease burden for stroke and coronary heart disease, and could significantly alter adherence and outcomes if the rehabilitation programmes were to be applied to the broader populous. Whilst it is acknowledged that older people do have the ability to obtain similar physiological benefits from exercise as younger people (Jolliffe et al., 2001), it is possible that additional co-morbidities from aging, along with female perceptions of exercise, may affect a patient's ability and motivation to undertake and benefit from cardiac rehabilitation programmes.

Despite these discrepancies, the consistent findings from these studies confirm that cardiac rehabilitation is an effective means of reducing cardiac and all-cause mortality by up to 31% and 28% respectively post myocardial infarction. The evidence also suggests that these programmes can significantly improve cardiovascular risk factors, though this reduction is modest. On this basis, cardiac rehabilitation is given a level one classification in most of the contemporary international clinical guidelines (Wenger, 2008). Consequently, since the publication of these meta-analyses, subsequent trials have tended to concentrate

on enhancing the secondary preventative effect of cardiac rehabilitation rather than justifying its existence (Giannuzzi et al., 2008, Wood et al., 2008).

Whether stroke patients would benefit from an enhanced form of secondary prevention such as cardiac rehabilitation is unproven at this stage. However, a number of small studies in stroke have been conducted to examine different forms of enhanced secondary prevention. The following section reviews these studies to examine whether their evidence supports the use of cardiac rehabilitation based programmes for secondary stroke prevention.

3.4 Enhanced Stroke Secondary Prevention

To date (July 2008) there has been no single study which has evaluated the combined effect of a group education, exercise and counselling programme such as comprehensive cardiac rehabilitation in post stroke patients. However, a number of studies have examined the individual aspects of such programmes concentrating on education and counselling or exercise. The majority of these enhanced secondary prevention studies have been small and have had a limited period of follow up. They have therefore tended to evaluate their results via changes in behavioural risk factors rather than by morbidity and mortality outcomes. The following section reviews these studies to examine whether their evidence supports the use of cardiac rehabilitation based programmes for secondary stroke prevention.

3.4.1 Education and Counselling

As the current guidance and clinical approach to post stroke lifestyle modification centres on the provision of advice (RCP, 2008), it was postulated by Sauerbeck et al., (2005) that enhancing this might improve risk factor modification. In this study, 437 patients were consecutively recruited post stroke. Each participant had a risk factor reduction discussion with a nurse and was provided with pamphlets to explain and support risk factor reduction. Follow up with a telephone interview reported a successful outcome with a significant 43% ($p<0.02$) reduction in smoking being achieved. However, deficiencies in the study design and reporting make it difficult to replicate or generalise these findings. In addition to lacking a

detailed description of the nature of the intervention, the absence of a control group meant the results were reported as significant only in relation to an earlier observational study (Redfern et al., 2000), which was from a different country and socio-economic group.

Further studies have specifically examined the relationship between advice, knowledge and risk factor modification. As knowledge of stroke risk factors is known to be low both pre and post stroke (Rodgers et al., 2001), it has been postulated that enhancing a patient's knowledge could lead to behaviour change and therefore reduce their risk factor profile. In a primary prevention study, Willoughby et al., (2001) recruited 85 participants who voluntarily attended a stroke risk preventative screening programme during a national stroke awareness week. Following the screening each participant received a ten minute individualised educational counselling session with a nurse. On follow up at six months there were self-reported improvements in diet (54%), exercise (33%), weight loss (23%) and blood pressure (11%). Although suggestive of increased knowledge leading to lifestyle changes, these results should be interpreted with caution as they were from a self-selecting population (without stroke) who are likely to have constituted the 'worried well', and whose attendance at the clinic possibly reflected their pre-existing motivation for behavioural change.

Alternative methods for enhancing behavioural change through improved knowledge were explored with 60 participants recruited from a primary care register that were identified as being at risk of stroke (Miller and Spilker, 2003). In this study the participants received either no additional risk factor education (control group), five minutes of advice, or two fifteen minutes sessions of advice with motivational interviewing. The results showed that those receiving the greater amount of advice were likely to have significantly increased their knowledge of stroke risk factors ($p=.001$), and to report greater improvements in stroke risk reduction behaviours ($p=.006$).

A subsequent study of knowledge and risk factor modification following an enhanced educational programme also showed significant improvements in a number of risk factors (Sit et al., 2007). In this community based study of 190 participants with a recent history of minor stroke or TIA, the participants in the

intervention arm received eight two hour group sessions covering the main lifestyle risk factors and medications. On follow up the participants in the intervention arm showed a significant improvement in medication compliance ($P=.004$), knowledge ($p<.001$), diet ($p=.004$) and BP monitoring ($p<.001$). In addition there were non-significant improvements in cholesterol levels and hypertension.

Both this and the study by Miller and Spiker (2003) suggest that stroke patients are willing and able to moderately improve their behavioural risk factors through enhanced education and counselling programmes. However, there are limitations to these types of studies. In addition to the limitations of self-reported surveys (Denscombe, 2004), the nature of both interventions also meant that unless patients in the control arm receive a similar amount of clinical contact there is the possibility of a Hawthorne effect.

3.4.2 Exercise

In contrast to cardiac rehabilitation, there is no structured programme for exercise based risk factor modification post stroke. Though there is limited data on the cardiovascular effect of exercise post stroke, the national guidelines recommend that all patients undertake regular exercise (RCP 2008). This evidence is from primary preventative research and suggests that exercise, as measured by physical activity, could play an important role in stroke prevention. In 2003 a meta-analysis of 23 studies by Lee et al., (2003) showed that moderately and highly active individuals had a 20% and 27% respective reduction in cerebrovascular events and mortality. Although this analysis was based on a limited search of the literature (MEDLINE only), and concentrated on a predominantly young population, it showed similar reductions in mortality to exercise based cardiac rehabilitation programmes. A subsequent meta-analysis by Wendel-Vos et al., (2004) included an additional four studies and stratified the data for gender, country of study, leisure time and occupational physical activity levels. This study also only searched one data base (PUBMED). However, the results were broadly similar, showing moderate occupational and leisure time activity levels reduced stroke risk by 20-25% and 15% respectively. Though these are primary prevention studies the results suggest that exercise could provide a similar level of health

benefits for stroke patients as comprehensive cardiac rehabilitation does for coronary heart disease patients.

One of the major limitations of these and similar epidemiological studies is the subjective description of exercise levels and the use of physical activity questionnaires, since both methods limit the ability to define a dose response, as they are based on broad categories and self-reported estimates. This makes the results subject to a degree of bias, and the considerable variation in the definitions of activity levels within the studies limits the specificity of the final analysis.

To counter the inaccuracies of self-reported measures of physical activity it is possible to use a quantifiable physiological measure of cardio-respiratory fitness. Cardio-respiratory fitness relates to a person's ability to perform exercise for prolonged periods of time and is dependent upon the functional state of the respiratory, cardiovascular and muscular skeletal system (ACSM, 2000). The most common and robust form of measure is maximum oxygen uptake capacity ($\text{VO}_2 \text{ max}$), which is the product of maximal cardiac output (L/min) and arterial venous oxygen difference ($\text{mL O}_2/\text{L}$) (ACSM, 2000). In 2003, Kurl et al. published the findings from their population-based cohort study which assessed the $\text{VO}_2 \text{ max}$ of patients and their subsequent stroke risk over an eleven year period. Of the 2,011 male subjects, it was found that ischaemic stroke risk was 3.5 times greater for those measured as unfit. These findings also remained significant after adjustments for age, examination year, smoking, alcohol consumption, socioeconomic status and energy expenditure of physical activity as well as prevalent coronary heart disease, diabetes, systolic blood pressure, and serum low-density lipoprotein cholesterol level. Although this was a robust, primary preventive study that provided quantifiable data strongly linking cardio-respiratory levels with stroke risk, it should be noted that the results were based on the recordings from relatively young males (aged 42 – 60 at baseline) and with only one initial assessment of $\text{VO}_2 \text{ max}$ taken. Further such studies will be needed to assess how changes in $\text{VO}_2 \text{ max}$ over time may affect stroke risk and whether this is also applicable to the female and elderly population.

While these studies indicate that there is a consistent body of evidence linking exercise with primary stroke prevention there is limited data with regards to

secondary preventive mortality and recurrence rates. In the absence of mortality data a number of cardiac rehabilitation and stroke studies have analysed the effect of exercise on known risk factors. Using these risk factors (Table 1 pg 10) as proxy measures (Duke University Medical School, 2005) for mortality and recurrence rates, it is possible to evaluate the potential effect of interventions such as structured exercise.

In contrast to cardiac rehabilitation studies, most of the literature regarding exercise post stroke is based on interventions concerned with disability and functional outcomes rather than secondary prevention. However, in addition to the functional outcomes, a number of these studies have also examined whether cardio-respiratory fitness can be improved post stroke and have used this as a proxy measure to infer secondary preventative benefits as well as functional benefits.

One of the earliest studies examining cardio-respiratory fitness and exercise post stroke was by Potempa et al., (1995). This randomised controlled trial compared the effects of a ten week aerobic exercise programme to a ten week programme of passive range of movement exercises for forty two chronic stroke patients with mild to moderate disabilities. This was a well organised (CASP score: 8), if small, trial concentrating on younger stroke patients. The results showed that exercise capacity (VO₂ max) could be significantly improved in stroke patients, and that this correlated to functional improvements.

Since then there have been a number of further studies examining the cardio-respiratory response to exercise and its relation to function post stroke. An early meta-analysis by Meek et al., (2003) found just three trials with a total of seventy five patients which met their criteria of 'improving cardiovascular fitness and/or function'. Not surprisingly the mixed criteria and heterogeneous outcome measures limited their ability to combine results. Consequently, although each individual trial reported significant improvements in function (Teixeira-Salmela et al., 2001, Duncan et al., 1989) and cardio-respiratory fitness (Potempa et al., 1995) post stroke, the meta-analysis concluded that exercise was no better than no exercise with regard to functional recovery, quality of life or cardio-respiratory fitness post stroke.

A larger and more specific meta-analysis by Pang et al., (2006) considered the effect of aerobic exercise training in improving aerobic capacity in individuals with stroke. This included 480 participants from seven randomised controlled trials (including Potempi 1995) which were deemed of 'fair to good quality' (PEDro scale). The participants within the study were spread across the acute to chronic spectrum with mild to moderate disabilities post stroke (although one study also included 30% of patients post head injury). Unlike Meek et al., (2003) the more homogenous outcomes allowed for pooling of the data as measured by changes in VO₂ max or workload capacity post exercise. Importantly, these results showed that stroke patients could make small but significant improvements in cardio-respiratory function.

More recently two pilot studies have specifically examined the effects of secondary prevention exercise based programmes post stroke. In contrast to the above trials these studies used a range of additional risk factor measures to quantify the effect of exercise training. The first of these was a study by Yang et al., (2007) which reviewed the effect of a twelve week treadmill based exercise programme for fifteen stroke patients with known prior coronary artery disease. The results showed that the exercise not only significantly improved the participants aerobic exercise capacity but also reduced their cholesterol levels (total cholesterol and low density lipoprotein). However, the findings from this study should be interpreted with caution because of the exclusion of participants already undertaking exercise, the relatively small sample and the absence of a control group, which means the possibility of a placebo effect or a selection bias, cannot be ruled out.

A subsequent randomised controlled pilot trial of forty eight stroke patients by Lennon et al., (2008) examined whether an exercise programme based on the cardiac rehabilitation paradigm could have secondary preventative benefits. During this trial the chronic stroke patients in the intervention arm undertook two aerobic exercise sessions per week over a ten week period using static exercise bicycles. The primary outcome in this study was the Cardiovascular Risk Score, which is an algorithmic score that assesses future risk of cardiac events based on age, sex, smoking status, resting blood pressure, diabetic status, total cholesterol and high-density / low-density lipoprotein. Post exercise the participants in the

intervention group showed a significant reduction in their cardiovascular risk score as well as a significant improvement in their cardio-respiratory fitness levels. There was no significant change in total cholesterol, LDL, HDL, triglycerides, systolic and diastolic blood pressures or the Frenchay Activity Index and depression (HADS) scores. This study had limitations in that it was not truly analogous with cardiac rehabilitation and limited contact with health professionals in the control group could have created a Hawthorne effect. However, overall it was a robust study and one of the first such trials to show a definite link between cardio-respiratory exercise and secondary prevention of cardiovascular disease in stroke patients.

The above studies show that exercise and cardio-respiratory fitness can have a significant primary preventative effect for stroke (Lee et al., 2003, Kurl et al., 2003, Wendel-Vos et al., 2004), and that, through exercise, stroke patients are able to significantly improve their cardiovascular risk factors (Pang et al., 2006, Yang et al., 2007, Lennon et al., 2008). However, the role and impact of exercise in stroke secondary prevention requires further research (Meek et al., 2003, Gordon et al., 2004)

3.5 Recent Literature

The previous section was a summary of the relevant literature identified in the systematic search that shaped the trial design. Since then (July 2008), a subsequent literature review (appendix 2 pg 154) has identified more recent articles that are relevant to this trial and influenced the discussion. The following section summarises this literature in light of the study aims and objectives.

3.5.1 Secondary prevention

Since this feasibility trial began a number of secondary stroke prevention trials concentrating on behaviour modification have been published. McManus et al., (2009) followed up their original trial of additional nurse-led counselling sessions post TIA (Ellis et al., 2005) which had reported significantly higher participant satisfaction ($p=0.027$) in the intervention group. In their three year follow up study

they found that the initial intervention, three additional education and counselling sessions, did not lead to a long term improvement in any of the modifiable risk factors (BP, HbA1c, smoking and cholesterol), medication adherence, vascular recurrent rates, perceived health status or satisfaction scores.

Published in the same year, the ExStroke pilot trial (Boysen et al., 2009) explored whether it was possible to improve physical activity post stroke with the intention that this would have secondary preventative benefits. The intervention in this multicentre trial of 314 mobile stroke patients evaluated whether repeated instructions to increase physical activity would lead to a change in activity levels as measured by the Physical Activity Scale for the Elderly (PACE). With up to seven 30 minute visits and telephone calls over a two year period the intervention considerably exceeded that given in the McManus trial. However the results, as measured by the PACE, did not show any between group improvements in activity levels.

A subsequent trial of TIA patients (Gillham and Endacott, 2010) examined whether enhanced secondary prevention, in the form of additional advice and motivational interviewing via the telephone, improved participants lifestyle related risk factors and their behavioural 'readiness to change' (Miller and Spilker, 2003). The results showed no difference between the two groups in the 'readiness to change' primary outcome category, though there were significant improvements for the enhanced prevention group in both their diet and levels of exercise. This trial was similar, though substantially smaller than both the McManus et al., (2009) and Boysen (2009) trials (52 vs. 205 and 314 participants), with follow up at three months as opposed to three and two years.

On the basis of these three trials it is apparent that improving risk factors through changing lifestyle behaviours is difficult. That stroke patients are likely to have low levels of baseline activity both prior to their incident event (Boysen et al., 2009) and post event (Saunders et al., 2009) is perhaps not surprising. However it would appear from these stroke related studies that enhanced levels of counselling alone has a limited effect in reducing secondary risk factors. This would also infer that the current method of clinical advice post stroke is unlikely to have any long term

effect on behaviour and therefore alternative methods of lifestyle modification need to be explored.

The potentially sub-optimal care provided post stroke has been highlighted previously in this chapter (Redfern et al., 2002, Rudd et al., 2004, Ramsay et al., 2007). A more recent Canadian study set in the primary care environment (Saposnik et al., 2009) indicated that not only was there a low attainment of guideline recommended targets for cholesterol, BP and LDL post stroke, but that the attainment was also significantly lower than that achieved by patients with coronary artery disease (CAD). This study did have limitations when generalising to the current environment. Firstly, it was conducted between 2001– 2004 and not only has treatment progressed since that time, but it was also in a different health system to the UK. There was also no accounting for previous lifestyle modification interventions as well as there being a much smaller representation of stroke participants to CAD participants (647 vs. 3,817). However, despite these limitations, this large study substantiates the view that lifestyle and pharmacological secondary prevention methods can be significantly improved post stroke.

A number of recent studies have also explored the link between exercise and risk factors post stroke. Rimmer et al., (2009) examined the effect of exercise intensity on cardiorespiratory fitness and risk factors (blood pressure and lipids). Using a cluster repeated measures design, 55 chronic (6 months +) ambulatory stroke patients were assigned to exercise groups of - moderate intensity short duration, low intensity longer duration or conventional therapy. All three groups undertook 3 sessions per week for fourteen weeks. The results showed there was no change in cardiorespiratory recordings between the groups. However, there were significant within group improvements for the moderate intensity group in diastolic (8.7 mm Hg, $P=0.002$) and systolic (10.3 mm Hg, $P=0.048$) blood pressure, and total cholesterol (15.4 mmol/L; $P=.036$) and triglycerides (26.8 mmol/L; $P=.029$). Within the other two groups the only significant change was an improvement in triglycerides levels (33.4mmol/L; $P=.045$) for the low intensity group. Whilst this was a small non-randomised trial the findings highlight the lack of a physiological training effect from conventional therapy and suggest that the intensity of exercise could be an important factor for risk factor modification.

Perhaps more pertinent are two recent publications from Canada. The first of these was a feasibility study of an adapted cardiac rehabilitation programme for chronic (mean 30 months post event) stroke patients (Tang et al., 2010). This used a repeated measures design with a three month monitoring period followed by a six month adapted cardiac rehabilitation programme. This programme consisted of a weekly group exercise and education session allied to a home exercise programme. As with the trial by Rimmer et al., (2009) all participants were independently mobile and classified as having a mild stroke. However, in contrast to that study, the 44 participants in this trial showed significant within group improvements in cardiorespiratory capacity (VO_2 peak change = $1.2 \text{ ml.kg}^{-1}.\text{min}^{-1}$ $P=0.046$) but no change in blood pressure. Like Lennon et al., (2008), this trial indicated it was possible for stroke patients with a mild disability to undertake an adapted cardiac rehabilitation programme which involved the use of cycle ergometers for participants with limited mobility and an increased staff to patient ratio (1:2 for Lennon et al., 2008, 1:5 for Tang et al., 2010). Although this trial confirmed the feasibility of the process, the results should be viewed caution, as in addition to the lack of a control group and geographic clustering, the cardiorespiratory changes during the intervention were similar in scale to those observed during the monitoring phase. This would suggest issues with the re-test reliability of the outcome measure and a possible learning effect.

The second study from Canada by Prior et al., (2011) evaluated the feasibility and risk factors for TIA and mild stroke patients undertaking a comprehensive cardiac rehabilitation programme. With a similar rationale to the current trial (acronym Ex4TIA), this study recruited 110 participants consecutively from stroke clinics. Though classified as a standard cardiac programme, the programme differed from the equivalent UK programme in the duration (6 months) and intensity (2 sessions per week for up to 50 sessions) of the exercise interventions. The results showed that it was both feasible and safe (no related adverse events) for TIA and stroke patients to undertake CR programmes. They also showed significant improvements in aerobic capacity (131.4%; $P=0.001$), total cholesterol (20.30 mmol/L; $P=0.008$), total cholesterol/high-density lipoprotein (211.6%; $P=0.001$), triglycerides (20.27 mmol/L; $P=.003$), waist circumference (22.44 cm; $P=0.001$), body mass index (20.53 kg/m²; $P=.003$), and body weight (21.43 kg; $P=0.001$).

There were also non-significant but favourable changes in low-density lipoprotein (20.24 mmol/L), high-density lipoprotein (10.06 mmol/L), systolic (23.21 mm Hg) and diastolic (22.34 mm Hg) blood pressure, as well as a significant shift toward non-smoking ($P=0.008$). This study also evaluated depression (HADS) and quality of life (SF-12), though these results are yet to be published.

The main differences with the current trial were that it was not a randomised trial and so it was unable to distinguish between the effects of standard care and cardiac rehabilitation. The selection criteria also stipulated that participants must have at least one established risk factor in addition to a TIA / stroke in the past 12 months. In addition the intervention was considerably more intense than is common in UK cardiac rehabilitation programmes. Despite these differences, the findings are influential in light of this feasibility trial and will be further substantiated with the results from the subsequent definitive trial that is currently underway (MacKay-Lyons M et al., 2010).

3.5.2 Stroke Risk factors

The powerful findings from the INTERHEART study (Yusuf, 2004) which were discussed in section 2.2, have since been replicated in phase 1 of the INTERSTROKE study (O'Donnell and Xavier, 2010). Phase 1 of this case controlled stroke study only recruited 3,000 cases in comparison to 30,000 in the INTERHEART study of myocardial infarctions (MI). Whilst phase 2 will include an additional 10,000 participants, the findings from phase 1 do provide preliminary evidence to verify the previous estimates (Ezzati et al., 2003) of the influence of modifiable risk factors and their population attributable stroke risk (PAR). Table 9 (pg 44) compares the odds ratio's (OR) and PAR's for the two studies. This indicates that whilst both diseases share the same risk factors there are some surprising differences in addition to the commonly known risk weightings of hypertension, and lipids (more specifically apolipoproteins). Most notable is the influence of stress as a strong myocardial infarction predictor, but weak stroke risk factor. Conversely physical activity has a noticeably larger PAR for stroke than it does for cardiac disease.

These findings will help future secondary prevention programmes target their interventions to the risk factors with a high PAR, and the evidence from these studies shows how this will need to be slightly different for stroke and cardiac patients. However, despite some differences in risk weightings, both studies further highlight the influence of shared modifiable risk factors which account for an overwhelming 90% and 92% of the PAR for stroke and MI.

Table 9 Modifiable Risk Factors

Modifiable Risk Factors	INTERSTROKE study*		INTERHEART study**	
	OR	PAR	OR	PAR
Hypertension	2.37	34.5%	1.91	17.9%
Smoking	2.32	21.4%	2.87	35.7%
Waist-to-hip ratio	1.34	26.0%	1.62	20.1%
Diet	1.29	17.3%	0.7	13.7%
Physical Activity	0.69	29.4%	0.86	12.2%
Diabetes Mellitus	1.60	7.9%	2.37	9.9%
ApoB-ApoA1 ratio	1.30	35.2%	3.87	54.1%
Alcohol	0.79	1.0%	0.91	6.7%
Psychosocial Stress	1.30	4.7%	2.67	32.5%
Depression	1.47	6.8%	Not reported separately	

*Ischaemic Strokes (O'Donnell and Xavier, 2010) ** (Yusuf, 2004)

At a physiological level the link between ischaemic stroke and cardiac disease has also been further evaluated with imaging studies (Calvet et al., 2010, Amarenco et al., 2011) which show a strong correlation between cervicocephalic and coronary artery stenosis in stroke patients without known cardiac disease. This physiological link, allied to lifestyle risk factors, emphasises the shared atherosclerotic disease process, though it does leave unanswered the question as to why some people have a stroke whilst others develop cardiac disease. The answer to this is not immediately apparent and there is clearly much that still needs to be learnt about the interaction of genetics, modifiable risk factors and the

physiological disease response. However, the evidence since 2008 only seems to substantiate the premise that stroke patients are likely to benefit from cardiac rehabilitation in a similar fashion to patients with cardiac disease.

3.6 Summary

The burden of both stroke and coronary heart disease on the individual and society is huge. Both diseases share broadly the same underlying atherosclerotic pathology, age profile, risk factors and pharmacological interventions. However, their post hospital secondary prevention management programmes are very different.

The evidence from research would suggest that the current system pays little attention to modifying lifestyle risk factors post stroke and, perhaps not surprisingly, it therefore has a limited effect. In contrast, coronary heart disease patients are encouraged to undertake extensive cardiac rehabilitation programmes which reduce mortality by up to 31% through exercise and targeting lifestyle risk factors and medication compliance.

Evidence for whether stroke patients could also benefit from similar programmes is limited. Several small studies suggest that stroke risk factors can be reduced through enhanced education and counselling sessions, though as with coronary heart disease patients, the improvements are modest. Evidence for the role of exercise and secondary prevention is greater, although this is mainly from primary prevention studies.

On the basis of this literature review it would appear that there is good reason to suggest that stroke patients could substantially benefit from the adoption of a secondary prevention programme based upon the principles of cardiac rehabilitation. However, guidance as to the exact format and content of these complex interventions is less conclusive. The evidence from the meta-analyses suggests that exercise is the most consistent and effective factor in these programmes for reducing mortality. However, as Oldridge (1988 pg 949) noted, *'the specific and non-specific effects of rehabilitation are not easy to separate and*

it is difficult to control for the placebo and Hawthorne effects inherent in an intervention where a high level of attention, support, and counselling is given not only by staff to patient, spouse, and family but also by patient to patient'. As a consequence, studies focusing purely on exercise may not take into account informal support and the cumulative and holistic effect of education and psychological counselling. On the basis of the literature review and for the purposes of this trial it is would appear reasonable to suggest that stroke patients can significantly reduce their risk factors post stroke and this may be enhanced by undertaking a programme of comprehensive cardiac rehabilitation.

3.7 Aims

The aim of this research is to investigate the feasibility of conducting a randomised controlled trial requiring TIA and minor stroke patients to participate in a standard NHS comprehensive cardiac rehabilitation programme. The research will also investigate whether the outcome measures are suitable for assessing whether the intervention will significantly reduce the risk of secondary cardiovascular events, produce significant physiological changes associated with atherosclerotic disease, and enhance behavioural risk factor modification for patients, more effectively than standard care.

CHAPTER 4

Research Methodology

4.1 Introduction

The following chapter details the research design options and the rationale for the study design. It includes development of the research procedures and outcome measures, along with a description of the research environment.

4.2 Methodology

4.2.1 Research design and rationale

Research designs are the explicit plans for completing an objective (Polgar and Thomas, 2008). The main method for addressing research questions is through the use of quantitative, qualitative or combined research methodologies. In choosing a design format it was therefore important to consider what the objectives were and to review the design methodologies to ensure that the research process would answer the research question, by proving or disproving the hypothesis.

4.2.2 Quantitative approach

The research question suggests this study would sit within the positivism paradigm. Quantitative research is based on the deductive approach to research (Neuman, 2007 pg.113), and follows three theoretical stages from conceptualisation to operationalisation and finally empirical data gathering. For this study the conceptual rationale was to assess the feasibility of examining the causal relationship between one form of treatment (standard care) and a second form of treatment (standard care and cardiac rehabilitation). The subsequent conceptual hypothesis could then be implemented with a view to developing an empirical hypothesis which would produce results that are generalisable to the population studied.

Within the field of quantitative research there are four main design methodologies to be considered (Gauch, 2000). Of the four methodologies, the non-experimental designs (descriptive and ex-post facto) were not deemed applicable, as the aim of

the study was to prove causality through manipulation of the variable. For this study the ability to not only manipulate the variable, but to also have a control group and randomisation meant it was possible to conduct a *true experiment* (Bowling and Ebrahim, 2005) rather than a quasi-experimental design. The true experiment is considered to be the 'gold standard' means of evaluation (Torgerson et al., 2008) and within health research this is referred to as a randomised controlled trial (RCT), as the design allows for the '*assessment of the relative effectiveness of different regimes by comparing the event rates and (or) outcome*' in a controlled and reproducible manner (Earl-Slater, 2002 pg 286). The design chosen follows the Medical Research Council's Framework for the development and evaluation of RCTs for Complex Interventions to Improve Health (Medical Research Council, 2000). This is a five stage process which includes the; Phase I - 'Pre-Clinical' or theoretical or modelling, Phase II - exploratory trial, Phase III - main trial and Phase IV - long term implementation and surveillance.

The scale of the experiment was influenced by time constraints associated with post graduate research and the history of research within this field. In this instance the intervention was already established and extensively researched within a similar health arena (coronary heart disease patients). Therefore, it was not deemed necessary to conduct a phase I trial to establish safety and dose, but to proceed to a phase II exploratory trial to determine the feasibility and efficacy of applying the intervention in a different disease state (cerebrovascular patients).

4.2.3 Qualitative approach

Qualitative research is the examination of an individual's subjective perception of an experience within a social environment (Polgar and Thomas, 2008). Through investigation of participants' thoughts and feelings it is possible to give depth and understanding to the interaction and experience of participants within healthcare research. Qualitative research typically produces data that is descriptive in nature and based on language rather than numerical results. As this study was aiming to examine treatment effect in terms of measurable physiological and lifestyle changes, and thereby influence health service development, a qualitative approach was not appropriate as a primary method of enquiry.

However, it was acknowledged that as an applied scientific study the participant's interaction and their experiences in the process might have a significant impact on the results and applicability of the study. The research was therefore designed at an early stage to include a qualitative analysis of participants' experiences and thoughts regarding enhanced rehabilitation or standard care. This qualitative assessment ran parallel to the main trial but was felt to be beyond the scope and time available for this doctoral thesis. The qualitative study was therefore partly conducted by a pre-registration MSc student, although the original organisation, funding and on-going supervision was led by the author (H Kirk) and principle supervisor (Dr P Kersten). Findings from this work are referred to in the thesis discussion (section 6.5).

4.3 Study Design

Evidence from the literature review suggested that a cardiac rehabilitation based programme could be an effective method for enhancing secondary prevention post stroke due to similarities in the disease states. The format of the intervention was to be a comprehensive rehabilitation programme based on the recommendations of the British Association of Cardiac Rehabilitation (BACR, 2007). The method for delivery of the intervention was not so conclusive. Whilst previous trials had incorporated elements of cardiac rehabilitation programmes (Yang et al., 2007, Lennon et al., 2008), these were not delivered in the standard cardiac rehabilitation format that currently exists within the UK. In order to trial an intervention that followed current cardiac rehabilitation practice and that would be deliverable within NHS resources, it was decided that further investigation was required using an existing cardiac rehabilitation programme.

4.3.1 Objectives

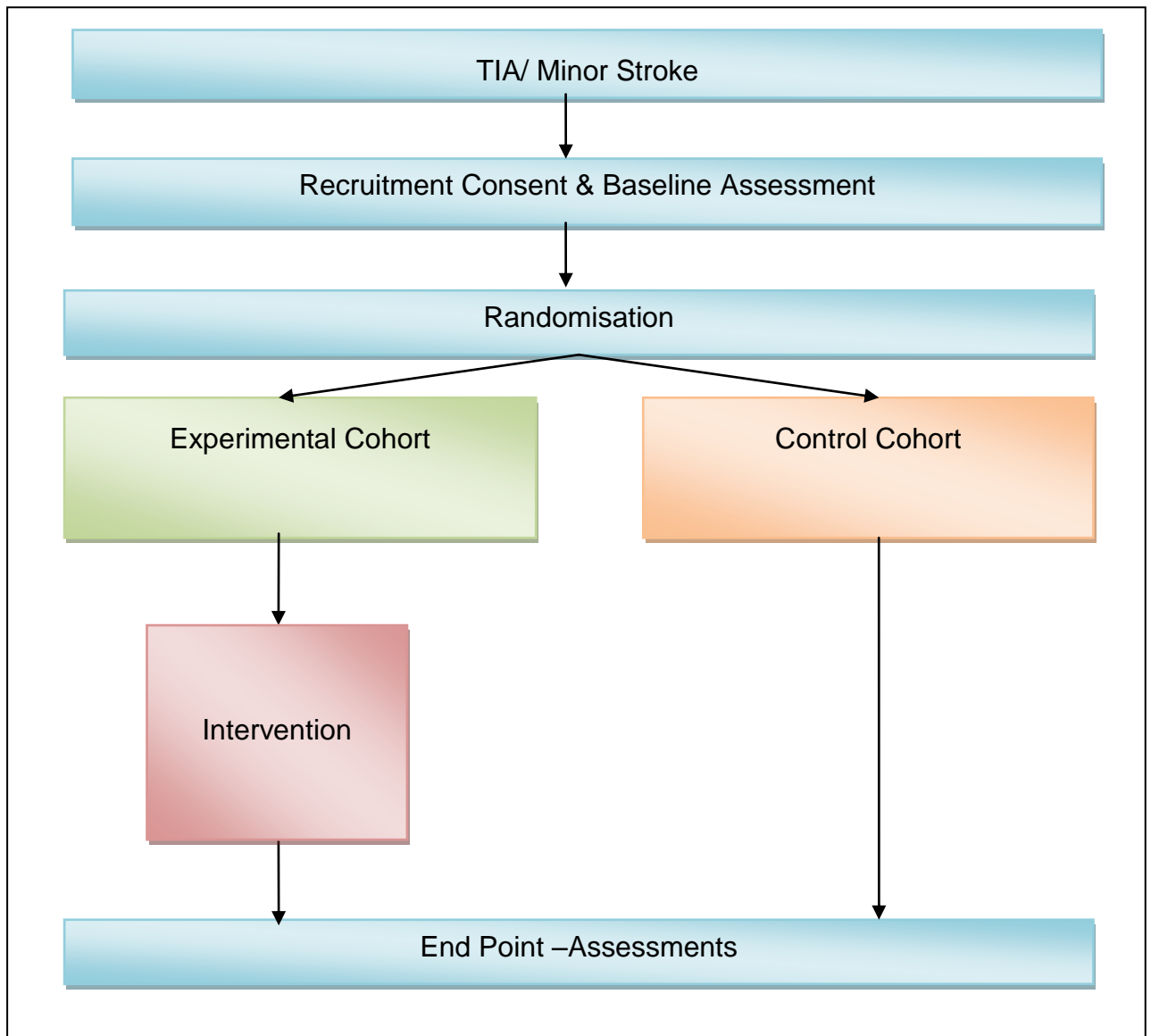
The study was designed as a feasibility trial which aimed to investigate the feasibility of stroke patients undertaking an NHS cardiac rehabilitation programme. The study also sought to ascertain if the outcome measures were suitable for determining whether the intervention (standard care and comprehensive cardiac rehabilitation) would cause a greater reduction in secondary preventative risk

factors post stroke, than standard care alone. In achieving these aims the study sought to meet the specified objectives of:

1. determining the applicability of the outcome measures for assessing if the intervention causes physiological changes associated with the atherosclerotic process
2. determining the applicability of the outcome measures for assessing if the intervention enhances lifestyle changes and HRQoL more effectively than standard care
3. testing the process of data analysis
4. determining if it is feasible and appropriate to proceed to a larger trial

Figure 2 gives an outline of the trial which was designed as a phase II feasibility study to evaluate whether the cardiac model of rehabilitation was more effective than standard care.

Figure 2 Study Design Summary



4.3.2 Sample

The decision to sample patients with a TIA or minor stroke was made on the basis that they would have confirmed cerebrovascular atherosclerotic disease yet have minimal restrictions in their mobility, speech or cognition. This would allow participants to undertake a comprehensive cardiac rehabilitation programme on a similar basis to coronary heart disease patients.

4.3.3 Recruitment

Patients with a confirmed diagnosis of TIA or stroke were recruited from the Stroke Unit, Acute Medical Units and TIA clinics at Southampton University Hospital Trust. After confirmation of the diagnosis by a physician, patients were screened to see if they met the inclusion and exclusion criteria outlined below. Appendix 3 (pg **Error! Bookmark not defined.**) details the clinical assessment process.

Inclusion Criteria

- Diagnosis (within 1 month of incident)
 - TIA - resolution of symptoms <24 hours of onset (not suspected Patent Foramen Ovale - PFO)
 - Minor stroke- NIHSS score <3
- GP within geographic locality
- Independently mobile (can use stick but no falls within past 2 months)
- Cognitive capacity to undertake group exercises (no apparent dementia)
- Able to give verbal and written consent

Exclusion Criteria

- Significant visual / speech impairment
- Previous experience of cardiac rehabilitation
- Current or recent participation in research
- Under 18 years old

If suitable for the study the patients were then approached by the physician, specialist nurse or research nurse and informed about the study. Patients who indicated an interest in the study were then provided with the participant information sheets (appendix 4 pg 156) and asked if they would be happy to be contacted by the researcher in the next few days. Patients who agreed to this were

given in excess of 24 hours before being contacted by the researcher, who ensured that they had understood the research. Those who wished to proceed with the study were given an appointment at the Wellcome Trust Clinical Research Facilities (WTCRF). This appointment was one month post TIA / minor stroke as all patients are required by law to wait one month before being allowed to drive again. At the WTCRF the assigned research nurse once more reviewed the study details with the patients before formally consenting them. Baseline and endpoint data were collected by the research nurses at one month and six months post event as per the standard operating procedures (appendix 7 and 8 pg 177-183).

In February 2010 two additional patient identification sites were added:

- Winchester & Eastleigh Healthcare Trust
- Lymington New Forest Hospital.

In both hospitals, patients were to be identified in TIA clinics following the same set procedures as at Southampton General Hospital.

4.3.4 Control Group

All participants received the standard care given to patients at the participating TIA and stroke clinics. This is generally delivered during the clinic day or on admission to the stroke unit and involves routine investigations (e.g. scans and ECG) to establish the likely cause of the event. Patients then receive pharmacological treatment in line with RCP Clinical Guidelines for Stroke (2008) to reduce the risk of future events. This medication is prescribed by the patients GP on receipt of the discharge letter, or letter from the clinic, and on-going monitoring and care is then the responsibility of the GP. However, if patients have complications or require further investigations they will be reviewed by the stroke physician in a subsequent clinic. In addition to pharmacological treatment, patients are also given lifestyle advice in line with the RCP Clinical Guidelines for Stroke (2008). Nationally, the frequency and content of this advice is not specified and frequently not recorded (Rudd et al., 2004).

4.3.5 Intervention group

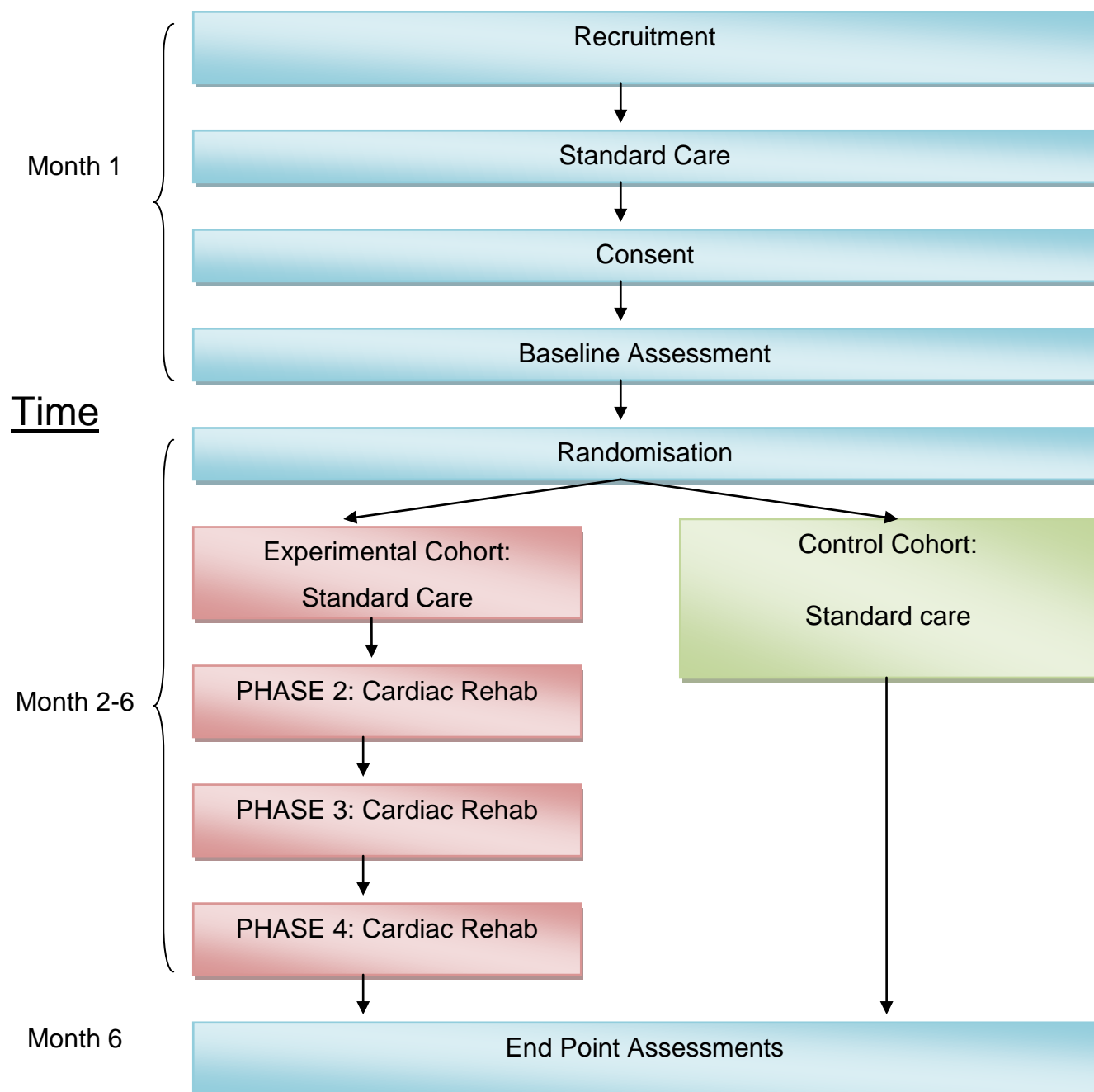
In addition to standard care post TIA, the intervention group also undertook additional rehabilitation based on the standard comprehensive cardiac rehabilitation programme as outlined by the BACR (2007) & SIGN (2002). There is an acknowledged variation in the organisation of these rehabilitation programmes (Coats et al., 1995) but the BACR has drawn up a list of core components (Table 10). For this research project the cardiac rehabilitation programme, was delivered by the Southampton Cardiac Rehabilitation team whose rehabilitation programme incorporated all six of the components listed in Table 10. These components are traditionally delivered in the four rehabilitation phases as outlined in Table 3 (pg 21). Due to the stroke ward and clinic discharge process being analogous to phases 1 & 2, participants in the intervention arm entered the trial for phases 3 & 4. A detailed description of the content of the Southampton Cardiac Rehabilitation programmes is listed in appendix 5 (pg 162).

Table 10 Cardiac Rehabilitation Core Components

1	Lifestyle I) Physical activity and exercise II) Diet and weight management III) Smoking cessation
2	Education
3	Risk factor management
4	Psychosocial
5	Cardio protective drug therapy and implantable devices
6	Long-term management strategy

(BACR, 2007)

Figure 3 Trial Summary



4.3.6 Randomisation & Data Access

Randomisation was used within this study so that any differences between the intervention or control group were likely to be due to chance rather than any bias in group assignment. This helps facilitate blinding and means that there is a greater probability that differences in the final outcomes were as a result of the intervention rather than selection bias or confounding variables (Schulz et al., 2010). Though simple (unrestricted) randomisation would be the optimum method for reducing the risk of bias, the relatively small sample size in this study meant this method could have produced disparate group sizes and for that reason block randomisation was used. Group allocation was produced by the Southampton Research Development Support Unit's computer random number generator with an even allocation ratio within block sizes of six.

Randomisation occurred following baseline data collection when the research nurse completed a referral form which included sufficient data for referral to cardiac rehabilitation. This was faxed to and processed by randomisation staff in a separate location. All group allocation was stored by the chief investigator (University supervisor) who did not have access to baseline or endpoint data. A detailed description of the randomisation procedures is provided in appendix 8 (pg 183).

4.3.7 Intention to treat

The study was designed to incorporate an intention to treat analysis. By collecting and analysing all available data the potential for bias is reduced by the maintenance of the original randomisation. This also adds validity to the analysis of intent rather than just treatment (Hollis and Campbell, 1999). This latter aspect was considered to be particularly important for an intervention such as cardiac rehabilitation which requires active participant involvement and therefore may not be adhered to by a proportion of participants. To counter this, participants were made aware that they were always able to leave the trial without it affecting their normal care or having to give a reason, but were also encouraged to complete their end point assessments whether or not they completed the intervention. The

full data set was to be reported in line with CONSORT recommendations (Schulz et al., 2010).

4.3.8 Blinding

To further reduce the chance of bias within the study it was important to ensure that blinding was included in the study design. The participatory nature of the intervention meant that it would not be possible to conduct a double blinded trial as the participants could not be blinded to their treatment allocation. However, the study was able to be conducted in accordance with the CONSORT single blinded RCT criteria (Zwarenstein et al., 2008). To achieve this, the randomisation only occurred after collection of baseline data, and the assessors were blind to group allocation for endpoint data collection and analysis.

4.4 Outcome Measures

The complex nature of cardiac rehabilitation programmes, combined with their broad holistic aims, meant that a variety of outcome measures were required to quantify the differences between the intervention and standard care. However, the relative short duration of funding for this doctoral study meant the primary clinical measures used in the main cardiac rehabilitation analysis (mortality and vascular recurrence rates), would not be appropriate. Therefore, as a measure of clinical effect, known vascular risk factors were the primary outcome measures (Table 9 pg 44). These measures were to be augmented with physiological measures of the atherosclerotic disease state (C-Reactive Protein, Fibrinogen), along with psycho-social measures of wellbeing (Short Form 36 – SF36 and Hospital & Anxiety Depression score - HAD).

Table 11 Outcome measures

Outcome	Lifestyle Risk Factors	Measurement Tool	Collection method
Primary	Future Cardiac Event Risk	Cardiac Risk Score	Cumulative risk score
Secondary	Future Vascular Event Risk (stroke & cardiac)	Cardiovascular Disease Score	Cumulative risk score
	Biomarkers	HsCRP	Blood sample
		Fibrinogen	Blood Sample
	Hyperlipidemia	Total Cholesterol	Blood sample
		High Density Lipoprotein	Blood sample
		Triglycerides	Blood sample
		Low Density Lipoprotein	Freidwald Equation
	Diabetes	Fasting Glucose	Blood sample
	Quality of Life	SF36	Self Assessment Questionnaire
	Activity	Exercise Frequency	Self Assessment Questionnaire
		Exercise Capacity	Physiological measure
	Smoking	Questionnaire	Self Assessment
	Diet	Questionnaire	Self Assessment
	Obesity	BMI	Physiological measure
		Hip to waist ratio	Physiological measure
	Depression	Hospital Anxiety Depression score	Self Assessment Questionnaire
	Hypertension	Blood Pressure	Physiological measure

The outcome measures were collected using the above methods. The self-assessment questionnaires and demographics were based on a format adapted from the 2008 National Database for Cardiac Rehabilitation. The following section provides a summary of the rationale and evidence base for the risk factors that were assessed.

4.4.1 Primary Outcome Measure

Cardiac Risk Score (CRS) (Wilson et al., 1998): The cumulative risk score was chosen as many atherosclerotic risk factors act in a combined and as yet, unknown manner (Rothwell, 2007, D'Agostino et al., 2008). The CRS is an algorithmic score which assesses future risk of cardiac events based on: sex age, resting systolic blood pressure, smoking status, diabetic status, total cholesterol and high-density lipoprotein cholesterol. Such scores are judged to improve reliability and accuracy when subjects have multiple mild abnormalities that act synergistically to increase risk (Wilson et al., 1998). It is based on the epidemiological data derived from the Framingham study, which has proven to be sensitive to changes in risk stratification for the stroke population (Wolf et al., 1991). Its use within a similar trial (Lennon et al., 2008) provided sufficient data to allow for power and sample size calculations for this study.

4.4.2 Secondary Outcome Measures

The lack of empirical data relating to lifestyle modifiable risk factors necessitated the use of a broad range of secondary measures which are related to known cardiovascular risk factors as outlined in section 2.4. This section provides a summary of the tests used to assess these risk factors and the rationale behind their use.

Cardiovascular Disease Score (CVDS) (D'Agostino et al., 2008): Unlike the CRS the CVDS is a cumulative risk score which assesses vascular risk for all the major cardiovascular diseases; coronary heart disease, stroke peripheral vascular disease and heart failure. As with the CRS it is an algorithmic score which assesses future risk based on age, resting blood pressure, smoking, diabetic status, total cholesterol and high-density lipoprotein cholesterol. It was not chosen

as the primary outcome measure as no suitable studies were identified that could have provided data for power and sample size calculations for this study.

C-Reactive Protein (CRP): This is an acute phase plasma protein produced in the liver and is a non-specific inflammatory biomarker. When measured in the blood with a high sensitive assay (hsCRP) it is thought to be a strong independent predictor of future myocardial infarction and stroke (Ridker, 2007a). The ability of cardiac rehab programmes to reduce levels of hsCRP has been shown in Milani et al's., (2004) study. The greatest debate with regards to CRP is whether it is a determinant of vascular disease and/or plays a causal role (Scirica et al., 2006, Ridker, 2007a). However, for the purpose of this study, significant alterations in hsCRP levels for either cohort would represent a valid change in future cardiovascular risk.

Fibrinogen: Fibrinogen is an acute phase protein and is central to the coagulation cascade. It is believed to play an active role in all stages of the atherothrombotic process (Koenig, 2003). Most of the studies to date have looked at its role in coronary heart disease where the upper third of patients have a relative risk of about 1.8 in relation to the lower third. Meta-analysis of TIA and minor stroke patients have also shown an increased risk of ischaemic events (Rothwell et al., 2004 b).

Hyperlipidemia: Total cholesterol has been an acknowledged risk factor for coronary heart disease for many years (Thom et al., 2006). For cerebrovascular events the evidence was originally less compelling (Goldstein et al., 2006) but with subsequent analysis and exclusion of haemorrhagic strokes, total cholesterol became an acknowledged risk factor for ischaemic cerebrovascular disease. The degree of risk varies from a 6% increased risk for every 1-mmol/L increase in total cholesterol (Bots et al., 2002) to 25% for every 1-mmol/L increase (Horenstein et al., 2002). Measurement of Triglycerides, HDL and LDL were required for the cardiac risk score algorithm.

Hypertension: There is a linear relationship between hypertension and stroke (Lewington et al., 2003). Up to 25% of adults are likely to be hypertensive although only 60% of them will be aware of it (Wilson et al., 2001). The Framingham Study showed that individuals with normal blood pressure (SBP <120

and DBP < 80mmHg) had a significantly lower lifetime risk of stroke (11%) than those with high blood pressure (SBP \geq 140 or DBP \geq 90 mmHg) (Seshadri et al., 2006).

Diabetes: The vascular complications of diabetes are stroke, myocardial infarction and peripheral arterial disease. Indeed diabetes both doubles the risk of ischaemic stroke and the chances of that stroke being fatal (Warlow 2008). Though improved diabetic control is not conclusively linked with reduced vascular complication (Warlow 2008), recent studies suggest that patients with both diabetes and a history of stroke are 7.95 times more likely to experience a fatal stroke than patients with no history of diabetes or stroke (Ho et al., 2003). The relatively short follow up period of this study meant that Hb1AC would not be an appropriate test and so fasting blood glucose samples were taken at both baseline and endpoint assessments.

Activity: Self reported activity levels are a strong predictor of primary stroke and vascular mortality (Lee et al., 2003, Wendel-Vos et al., 2004). In this study activity was measured by self reported activity frequency and intensity levels using the BACR (2007) audit questionnaire.

Exercise capacity is a determinant of V02 max which is itself a predictor of cardiac and all cause mortality (Kavanagh et al., 2002). Numerous sub-maximal tests to obtain a safe and efficient measure of exercise capacity have been developed. The test chosen for this study was the Astrand-Ryhming (1954) single stage 6 minute cycle ergometer test which requires participants to try and reach 85% of their age predicted maximal heart rate. This test is recommended by the American College of Sports Medicine (ACSM, 2000) and has been used extensively for estimating exercise capacity with good levels of validity and reliability (Kasch, 1984).

Smoking: Smoking is an independent risk factor for coronary heart disease through its association with atherosclerosis (Witteaman et al., 1993). In the same way it is an independent primary risk factor for first ever stroke, with a relative risk of 2 - 4 fold compared to non smokers (Wolf et al., 1988, D'Agostino et al., 2008, Bonita et al., 1999, Rodriguez et al., 2002, Kelly et al., 2008). As a risk factor for recurrent strokes, Burn et al., (1994) found that smoking was the only one of the

nine vascular risk factors which was significantly associated with stroke recurrence. Smoking was self-reported and recorded as number of cigarettes smoked each day and smoking activity in the previous four weeks.

Diet: Though there is little evidence for the influence of diet on secondary stroke prevention (Hooper et al., 2004), it is seen as a key factor in changing a number of modifiable cardiovascular disease risk factors such as hypertension, dyslipidemia and obesity (Salter et al., 2007). The provision of dietary advice for salt uptake (He and MacGregor, 2004) and reducing general cardiovascular risk factors (Brunner E et al., 2007) has shown modest reductions in blood pressure and cholesterol levels respectively. Analysis of the Framingham data (Gillman et al., 1995), showed a risk and age-adjusted reduction in stroke as consumption of fruits and vegetables increased, (RR=0.78 for each increase of 3 servings per day). Diet was therefore measured as the self-reported portions of fruit and vegetables eaten each day.

Obesity: Obesity is a known risk factor for vascular disease (NICE, 2007) and has traditionally been defined by body mass index (BMI). Recently there has been a move towards the measurement of proximal obesity by calculating waist to hip ratio (WHR), as this is a strong independent risk factor with greater odds ratios than BMI (OR, 3.0; 95% CI 1.8 to 4.8) (Suk S-H, 2003). For comparison with previous research, both physiological measures were recorded for this study.

Health Related Quality of Life (HRQoL): Fayers (2007) describes quality of life outcomes as the measure of the difference between the hopes and expectations of the individual and the individual's present experience, and health related quality of life concentrating on those factors that fall within the influence of health systems.

In recent years there has been an increase in the number and specificity of HRQoL measures. These are often tailored to particular conditions due to the specific problems associated with those conditions. In the case of stroke, factors such as social isolation, fatigue and depression are all recognised problems for many patients post event (Young 2003). However, for this trial, stroke specific measures such as the Stroke Specific Quality of Life Measure (Williams et al., 1999) were not used due to the impairment based nature of questions which were

not relevant for this subject group. At present all patients undertaking cardiac rehabilitation in the UK have their quality of life assessed as part of the national audit of cardiac rehabilitation. For research purposes this audit form was adapted to include the Short Form 36 (SF36) (Ware and Sherbourne, 1992) in place of the Dartmouth Co-op quality of life measure, as it was judged to have superior validity and reliability (Salter et al., 2007).

Depression: This is associated with a 3 – 4 fold risk of mortality for patients with coronary heart disease (Frasure-Smith et al., 1995). Consequently, SIGN (2002) recommend all cardiac rehab programmes monitor depression clinically using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Smith, 1983). In cerebrovascular disease, the emphasis on tackling depression has traditionally been post stroke and is related to levels of disability. However Kimberley et al., (2007) have recently shown a significant association (four fold relative risk) between depression and primary stroke/TIA in the under 65 population. Reliability and validity of the HADS subscales has proved to be consistently high (Moorey et al., 1991) and was therefore included in this study.

Qualitative Study Methodology

As part of the randomised controlled trial a qualitative study was undertaken exploring patients' experiences of standard care or standard care and cardiac rehabilitation care post TIA or minor stroke. Qualitative data were collected using semi-structured interviews (appendix 11 pg 189) from 22 RCT participants (17 males and 5 females; mean age 67 years: 12 were in the standard care group and 10 were in the cardiac rehabilitation group). Interviews were transcribed verbatim and subjected to thematic analysis using the procedural steps described by Braun & Clarke (2006).

Although the results are discussed in this thesis, the qualitative investigation represented a parallel but separate study. The principal researcher was Kaye Hillsdon, for whom this study was submitted as part of her Physiotherapy MSc. The fund holder and joint interviewer for this study was Hayden Kirk. Study supervision was by Dr Paula Kersten and Hayden Kirk. The detailed methodology and results from the study have been submitted for a separate publication.

4.5 Sample size and selection

Although this is a feasibility study a sample size calculation was conducted. Dr Peter Nichols (statistician – Faculty of Health Sciences) advised on the sample size calculation, which was based on the expectation of a reduction in Cardiac Risk Score (Wilson et al., 1998) (CRS) of 20% in the intervention group, a one-tailed test, with 80% power and 5% significance. To find a reduction in CRS of 20% from 12.0 (as found in Lennon et al., 2008) to 9.6, with a standard deviation of 4.0 requires 36 cases in each arm of the study. Allowing for a 10% attrition rate the trial was designed to recruit a total of 80 patients.

4.5.1 Recruitment Schedule

Recruitment of all participants had originally been through Southampton General Hospital, which operates a seven day a week TIA service with all urgent TIA patients (based on the severity of their TIA risk factors) being seen within 24 hours of referral and all others being seen within one week. Discussions with the Director of Stroke Services and TIA specialist nurse prior to the study suggested there were an estimated 500 attendees per annum at TIA clinics. Of these, approximately half were thought to have had a clinically confirmed TIA or minor stroke. This would mean that on average 20.8 patients a month would have been eligible for the trial (barring exclusion criteria). With consideration of the results from the consumer consultation (Figure 4. pg.67), it was anticipated that on average 13.5 patients would wish to be included in the trial each month. It was therefore anticipated that recruitment of all 80 participants would take a total of six months. However, taking into account exclusion criteria and unforeseen complications, an extra month was added to the recruitment schedule.

4.6 Patient & Public Involvement

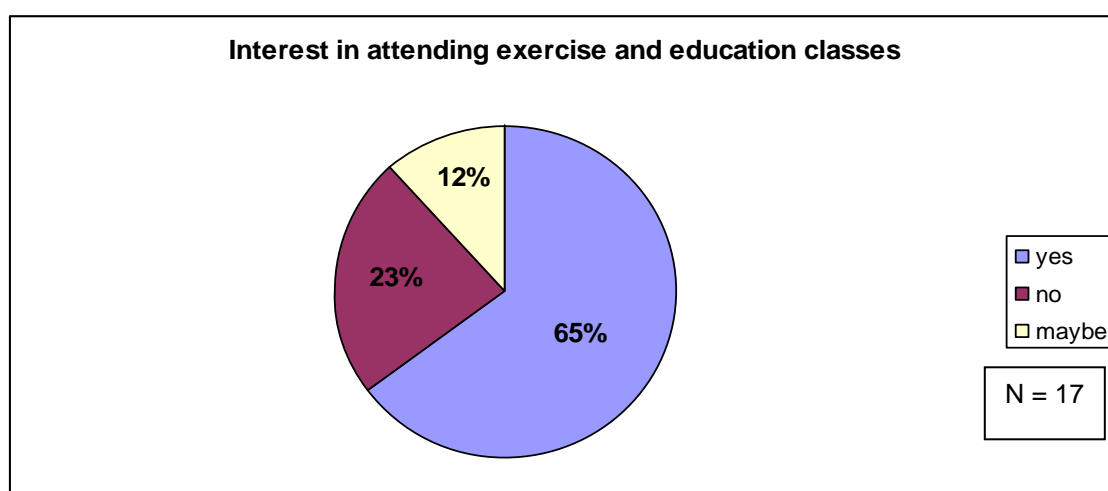
The study design incorporated service user opinions from the point of project inception. Although cardiac rehabilitation programmes have been used and refined over the past thirty years it was important to assess if a similar programme would be acceptable to people post TIA/Minor Stroke. Prior to applying for funding, a one month questionnaire survey was conducted which explained the

principles of a cardiac rehabilitation programme and asked patients attending a TIA clinic if they:

1. would be interested in participating in such a programme
2. would not be interested in participating in such a programme, or
3. may be interested in participating in such a programme

Figure 4, indicates the level of interest expressed. These results reflected the current participation levels for the cardiac rehabilitation programme at this site.

Figure 4 Potential interest in attending a Cardiac Rehabilitation



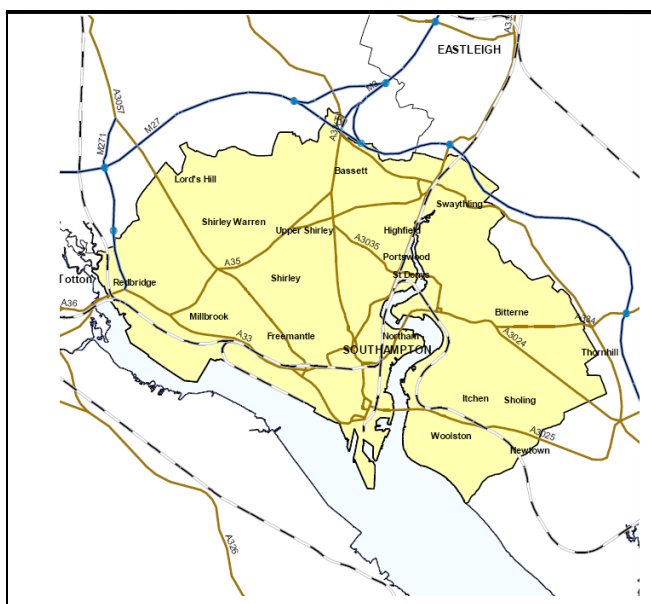
A second round of user consultation was conducted with six patients who had experience of stroke and TIA services and who form part of the University of Southampton Stroke User Group. Their opinion was sought on the methodology, format and potential ethical issues relating to the study. Their opinions were favourable and their suggestion to ensure inclusion of minor stroke patients was implemented. Service user involvement was included both in subsequent grant applications and also during the project in line with recommendations from the NIHR Involve database (NIHR, 2006). Collaboration with the Stroke User Group continued throughout the study with three patient representatives sitting on the advisory committee which met on two separate occasions to review reports from the research team, to input to the analysis, and to ensure project accountability.

4.7 Research setting

Recruitment was undertaken at Southampton General Hospital with additional patient identification undertaken at the Royal Hampshire County Hospital (Winchester) and Lymington New Forest Hospital. Consideration of the research setting was important due to the association between socio-economic deprivation and increased levels of cardiovascular disease:

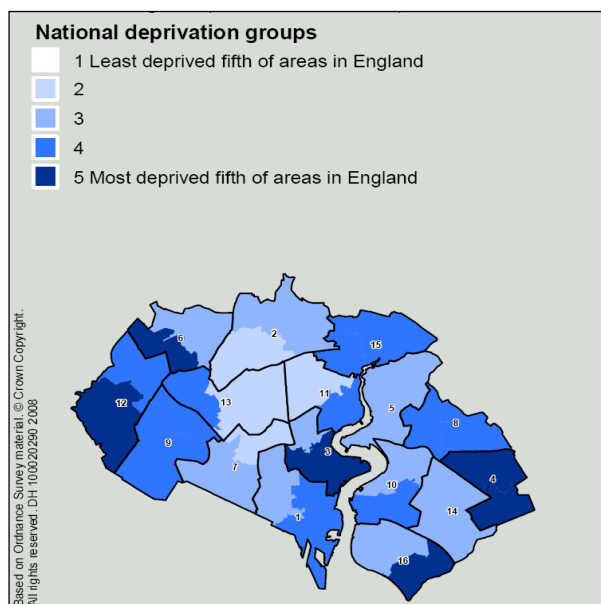
Geographically, Southampton is the largest city in Southern England (map 1.0) with a population of approximately 225,000 people. Southampton is a city based around a working port and as such has many of the inner city health and social issues associated with industrial cities. Map 2 shows Southampton Primary Care Trust (PCT) and gives an indication of the high levels of social deprivation which rank Southampton PCT as the 70th most deprived populous out of the 153 PCT's in England (APHO, 2008). Although situated within the city, Southampton General Hospital also provides secondary care for surrounding areas within the New Forest and Hampshire. Participants recruited from this district and from Royal Hampshire County Hospital (Winchester) and Lymington New Forest Hospital are from areas of comparatively low deprivation (map 3) (APHO, 2008).

Map 1 Southampton City



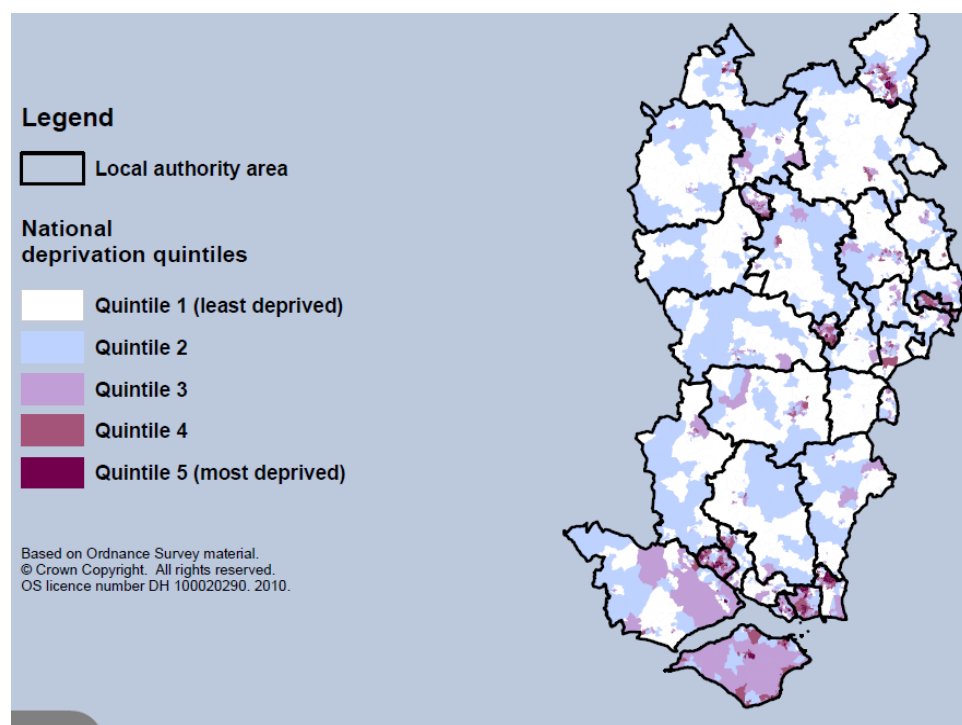
Source: APHO and Department of Health. © Crown Copyright 2008.

Map 2 Southampton City deprivation levels



Source: APHO and Department of Health. © Crown Copyright 2008.'

Map 3 Strategic Health Authority deprivation levels



Source: APHO and Department of Health. © Crown Copyright 2008

Clinical Setting: Southampton General Hospital (the main Southampton University Hospitals NHS Trust site) where all patients were recruited from is a large teaching hospital and its mid percentile ranking in the sentinel audit (2006) suggests it is fairly representative of hospitals with acute stroke services within the UK. The baseline and end point assessments were undertaken at the Wellcome Trust Clinical Research Facilities at Southampton University Hospital Trust. The intervention was delivered by the Southampton Cardiac Rehabilitation Team in their standard cardiac rehabilitation classes. These classes are held weekly at the Fleming Park Leisure Centre (Eastleigh) and Bitterne Park Leisure Centre, with patients and participants attending the centre that was most convenient for them.

4.8 Trial management

Responsibilities:

Hayden Kirk, as Chief Investigator (CI), undertook the design, conduct, analysis and reporting of the trial. He carried out duties in relation to responsibilities under the NHS ethics and research governance frameworks. In addition to the monthly meeting with the project / doctoral supervisors, the CI and principal supervisor (PK) met weekly in person or by teleconference to provide overall direction and supervision. The project Advisory Group met twice during the project to discuss reports from the research team, to input to the analysis and ensure accountability.

- Chief Investigator duties
 - Grant applications, financial monitoring and patient accrual reporting
 - Ethics and R&D applications and reporting
 - Development of standard operating procedures
 - Assessment, supervision and monitoring of research nurses
 - Participant recruitment and liaison with stroke and cardiac clinical teams
 - Recruitment and supervision of clinician for cardiac rehabilitation
 - Participant liaison (participant newsletter, appendix 16)
 - Investigation and reporting of adverse events

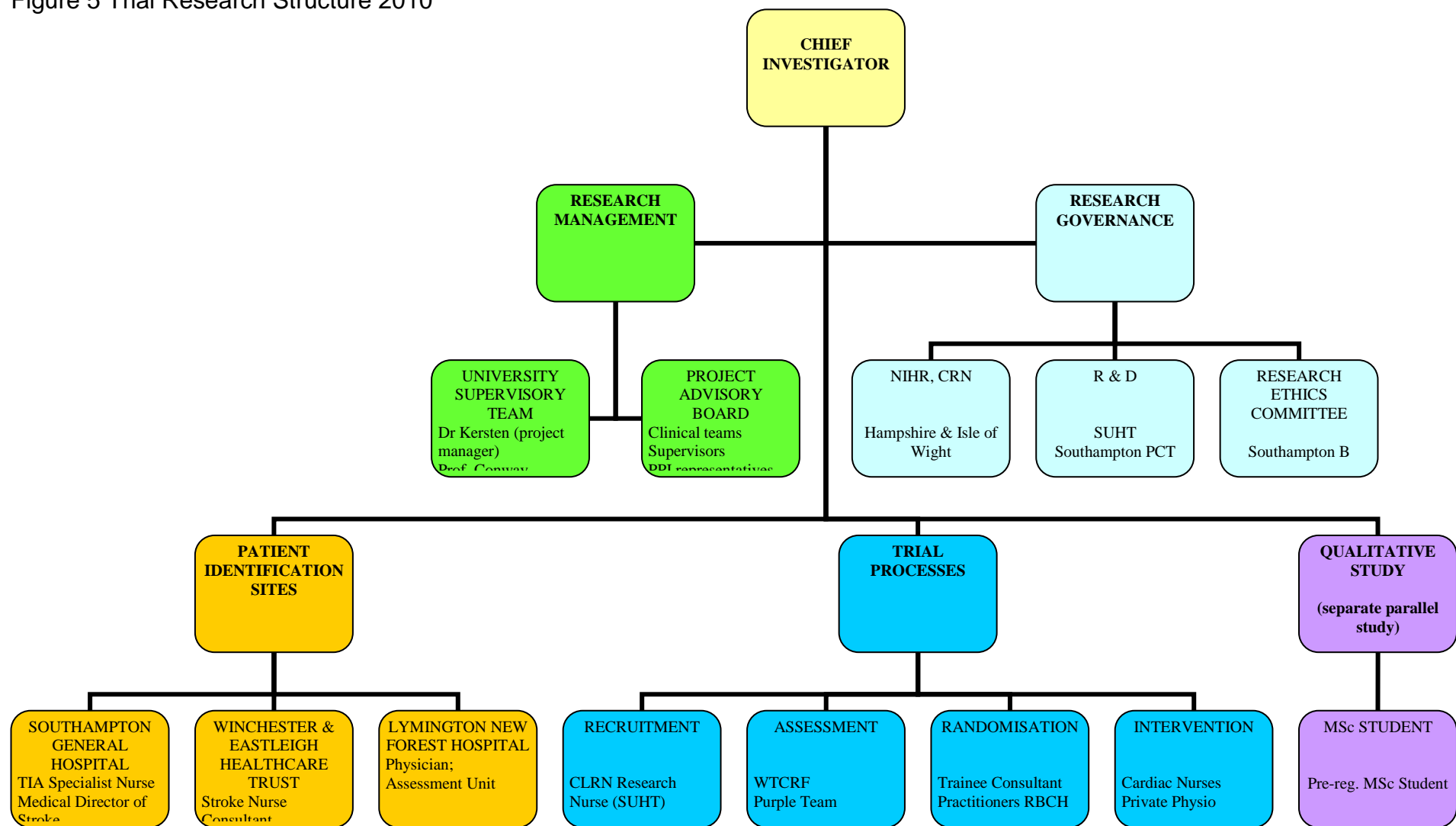
Internal Reporting:

The Chief Investigator produced and circulated a progress report and financial statement ahead of each advisory board meeting.

Team Structure

Figure 5. provides a diagrammatic representation of the trial research structure and personnel.

Figure 5 Trial Research Structure 2010



4.9 Data Analysis

Data was analysed on an intention to treat basis. As a randomised controlled trial the aim of the results section will be to make a group comparison between the experimental conditions (cardiac rehabilitation & standard care versus standard care) and the two independent sample groups (intervention and control). In order to make this comparison the one-tailed independent t-test was used. This was reliant upon the assumptions that:

1. the data is normally distributed
2. the data is interval data
3. variances between the groups are roughly equal
4. the scores are independent

To ensure that data was normally distributed it was visually checked through the plotting of histograms and verified with the Kolmogorov-Smirnov test. Variances between the groups was analysed using Levene's test.

For data that was ordinal (Table 12) the Mann-Whitney test was conducted to make a between group comparison. Additional analyses to explore the data further included a sensitivity analyses for those participants who completed $\geq 50\%$ of phase III of the cardiac rehabilitation intervention. A with-in group analysis was also conducted to evaluate whether any changes were as a result of between or with-in group alterations. Table 12 lists the outcome measures and test statistics. Data was analysed using the Statistical Package for the Social Sciences (SPSS) versions 17- 18.

Table 12 Test Statistics

Lifestyle Risk Factors	Measurement Tool	Data Form	Data Sets* (n = 24)	Test Statistic
Future Cardiac Event Risk	Cardiac Risk Score: Algorithm	Interval data: % risk score	2	Independent t-test
Future Vascular Event Risk	Cardiovascular Disease Score Algorithm	Interval data: % risk score	24	Independent t-test
Biomarkers	HsCRP	Interval data: mg/L	24	Mann-Whitney test
	Fibrinogen	Interval data: g/L	21	Independent t-test
Hyperlipidemia	Total Cholesterol	Interval data: mmol/L	24	Mann-Whitney test
	High Density Lipoprotein	Interval data: mmol/L	24	Independent t-test
	Total Cholesterol / HDL	Ratio data	24	Independent t-test
	Triglycerides	Interval data: mmol/L	2	Independent t-test
	Low Density Lipoprotein	Interval data: mmol/L	2	Independent t-test
Diabetes	Fasting Glucose	Interval data: mmol/L	24	Independent t-test
Quality of Life	SF36	Ordinal data	24	Independent t-test
				Mann-Whitney test
Activity	Exercise Frequency	Interval data: Exercise / week	24	Mann-Whitney test
	Cumulative Exercise	Interval data: Exercise / week	24	Independent t-test

Lifestyle Risk Factors	Measurement Tool	Data Form	Data Sets* (n = 24)	Test Statistic
	Exercise Capacity	ml kg ⁻¹ min ⁻¹	2	Independent t-test
Smoking	Cigarettes / day	Ordinal data:	24	Independent t-test
	Smoked in past 4 weeks	Nominal data	24	Mann-Whitney test
Diet	Questionnaire	Interval data: amount of fruit / day	23	Mann-Whitney test
Obesity	BMI	Ratio data	24	Mann-Whitney test
	Hip to waist ratio	Ratio data	24	Independent t-test
Depression	Hospital Anxiety Depression score	Ordinal data	24	Mann-Whitney test
Hypertension	Blood Pressure	Interval data: mmHg	24	Independent t-test
Demographics	Age	Interval data: years	24	Mean & Standard Deviation
	Gender	Nominal data	24	Baseline data
	Vascular Event: Stroke / TIA	Nominal data	24	Baseline data
	Number of pre-morbid Conditions	Interval data	24	Mean & Standard Deviation

*Number of complete data sets. Total number = 24 participants

4.10 Ethics

4.10.1 Ethics & Research Governance Approval

Ethical approval for this study was sought with a submission to the Southampton & South West Hampshire Research Ethics Committee (B) on the 13th March 2009. Ethical approval was given by this board on the 7th April 2009 (Appendix 9)

Substantial amendments: Three substantial amendments were submitted to Southampton & South West Hampshire Research Ethics Committee (B). They were applications to change the protocol to exclude patients taking Beta-Blockers from the exercise capacity test, to allow recruitment from the medical assessment unit and stroke ward and to increase the number of recruitment sites and recruiting personnel. The amendments were submitted on the: 18th May 2009, 24th July 2009, and 9th December 2009 and further details can be seen in appendix 10.

Southampton University Hospital Trust acted as sponsors for the study and R&D approval was obtained on 1st July 2009. Study ID: RHM MED0832

The intervention was delivered by the Southampton Cardiac Rehabilitation Team and Southampton City Primary Care Trust granted R&D approval for this on 13th July 2009. ID: MWP/006/09

As the two additional recruitment sites (Winchester & Eastleigh Healthcare Trust and Lymington New Forest Hospital) were classified as patient identification sites, R&D approval was not required.

The study was eligible for inclusion on the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio and was adopted as a portfolio study on 27th August 2009. ID: UKCRN 7348.

4.11 Funding

External funding was obtained through open grant applications to the Physiotherapy Research Foundation (PRF) and the Private Physiotherapy Education Foundation (PPEF). Hayden Kirk was the grant holder for both funding awards. Appendix 12 (pg 190) provides a summary of the funding allocation.

4.12 Summary

This chapter has described the rationale for the methodology, study design and outcomes measures used in this study. Chapter five presents the results.

CHAPTER 5

Presentation and Analysis of Results




5.1 Introduction

This section presents the results from the feasibility trial which aimed to investigate the feasibility of stroke patients undertaking an NHS cardiac rehabilitation programme and to ascertain whether the intervention (standard care and comprehensive cardiac rehabilitation) would cause a greater reduction in secondary preventative risk factors post stroke, than would standard care alone.

The results in this section are presented in table format. For those outcomes that fulfilled the criteria for parametric testing (independent samples t-test), the tables show the mean values and standard deviations for the baseline, study endpoint, change scores, confidence intervals and effect size. For those outcomes that required non-parametric testing (Mann-Whitney U), the tables show the median values and range for the baseline, study endpoint and change scores.

Due to the broad range of outcome measures, coloured arrows indicating the direction of change have been incorporated to help identify the significant findings. Thin blue arrows alongside the outcome measures indicate whether a higher or lower score is associated with a reduction in cardiovascular risk (Table 13).

Table 13 Data Indicators

Direction of Change	Indicator
Significant relative health improvement for the intervention group	
Denotes where a higher data score is associated with a reduction in cardiovascular risk	
Denotes where a lower data score is associated with a reduction in cardiovascular risk	

5.2 Recruitment

Recruitment was below the planned level as specified in the trial design. The implications and reasons for this are addressed in section 6.6.1 and appendix 13. Figure 6 (Consort data), highlights participant engagement throughout the study. Seventy four participants were initially assessed by clinical staff as being eligible for the trial. Two (2.7%) of these potential participants were subsequently excluded on further medical screening. The majority (n=48; 65%) of other participants chose not to participate due either to work commitments, difficulties with transport, a general lack of interest or 'other' reasons (e.g. child care, holiday) . Twenty four (32%) participants were consented and randomised. All twenty four participants returned for follow up.

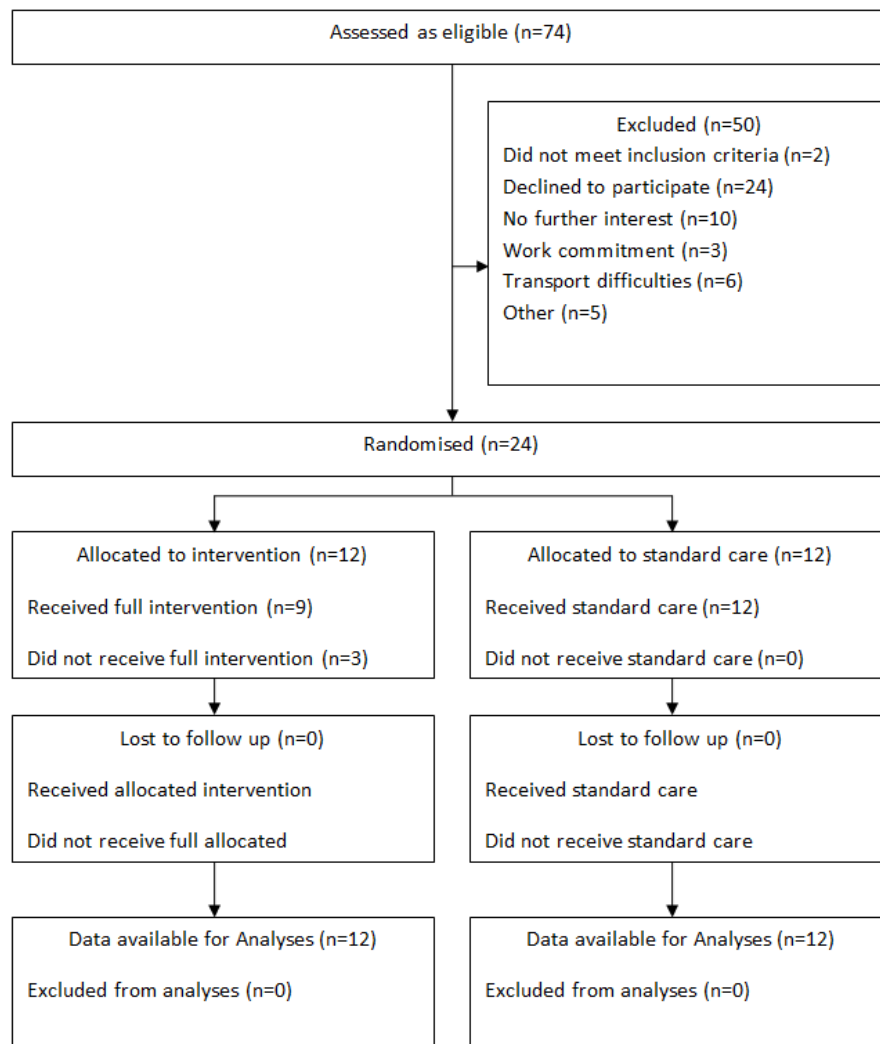


Figure 6 Consort statement

5.3 General Characteristics

Complete general characteristics data sets were obtained for all 24 participants. Of the 24, 18 (75%) were diagnosed as having had a TIA and 6 (25%) as having had a minor stroke. There was a greater, though not significant, proportion of participants with a TIA in the intervention group as opposed to the control group (Table 14). Demographic data showed that participants' ages ranged from 47 – 84 years. This wide range was reflected in the large standard deviations (7.3 – 11.4), though this was not statistically significant. Eighty three per cent of participants were classified as married, and 87% of them as being of 'white British' descent.

There was a strong emphasis towards male participation (79%), which was evenly distributed between the two groups.

Table 14 General Characteristics

Variable	Value	Control (n=12)	Intervention (n=12)
Sex	Male (%)	10 (83.3)	9 (75)
	Female (%)	2 (16.7)	3 (25)
Diagnosis	TIA (%)	8 (66.7)	10 (83.3)
	Stroke (%)	4 (33.3)	2 (16.7)
Age	Mean (SD)	66.8 (7.3)	67.5 (11.4)
	Median	69	69
	Range	53 - 78	47-84

Self-reported pre-morbid illness (Table 15) showed that participants had a number of accompanying illnesses, of which hypertension was the most common.

Table 15 Co-morbidities

Co-morbidities	Subjects (n=24)	Control (n=12)	Intervention (n=12)
Angina	2	1	1
Arthritis (osteo)	4	2	2
Cancer	1	0	1
Diabetes	2	0	2
Rheumatism	0	0	0
Osteoporosis	0	0	0
Hypertension	7	4	3
Chronic Bronchitis	1	1	0
Emphysema	0	0	0
Asthma	4	2	2
Peripheral Vascular Disease	3	2	1
Back problems / chronic pain	3	2	1
Other illness	4	1	3

5.4 Primary Outcome

5.4.1 Cardiovascular Risk Score

Although all participants returned for end point data collection, due to incorrect pathology documentation, insufficient triglyceride sample results were analysed to allow for the calculation of LDL cholesterol. This meant that it was not possible to calculate the algorithms for the Cardiac Risk Score (CRS). The CRS was therefore

replaced as the primary outcome measure with the Cardiovascular Disease (CVD) Score algorithm (this will be discussed in section 6.6.2). The CVD score was initially a secondary outcome measure as, unlike the CRS, there were no appropriate studies to provide the power calculations. However, as it produced a similar risk score based upon the same Framingham study data (D'Agostino et al., 2008) it was felt to be a suitable replacement as a primary outcome measure.

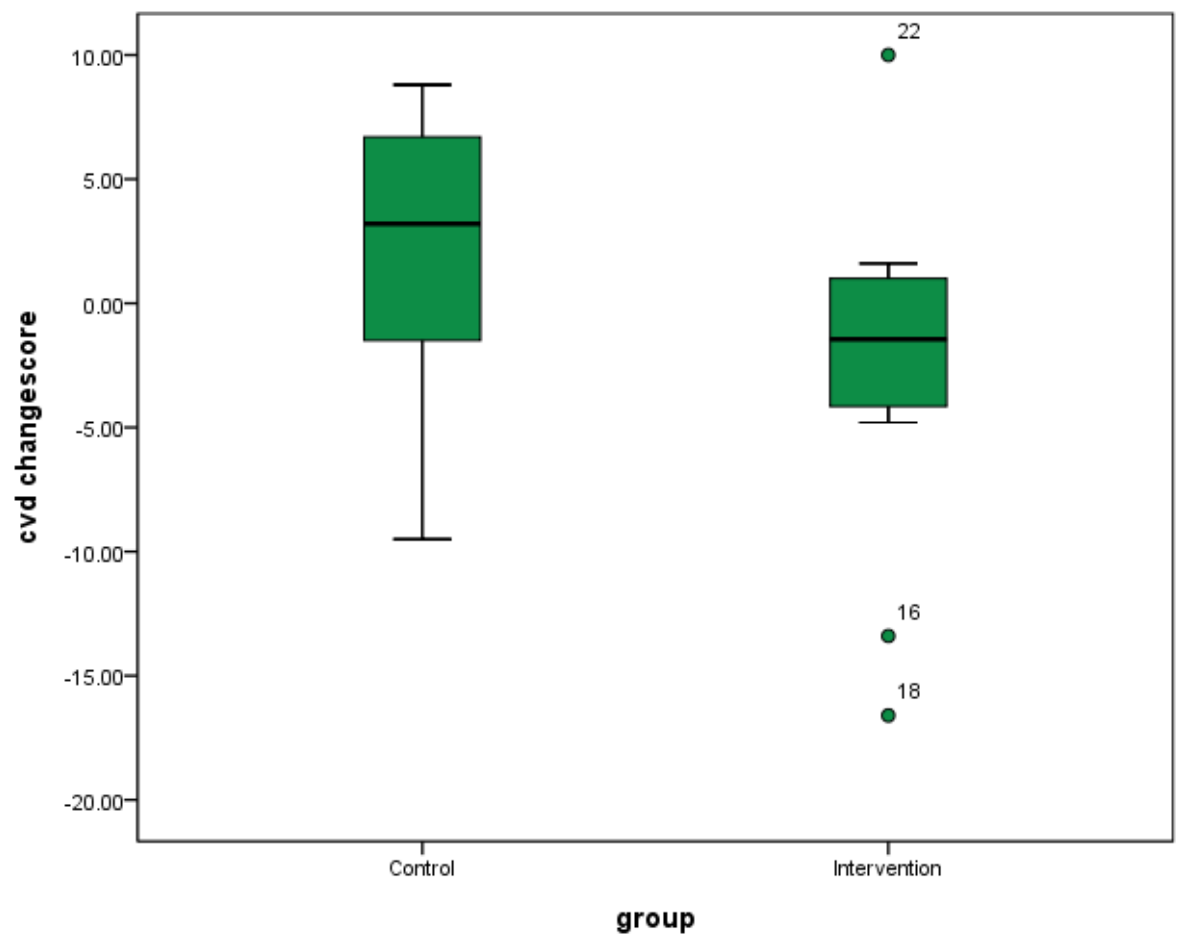
5.4.2 Cardiovascular Disease Risk Score

The results of the t-test showed that on average participants in the intervention group had a reduction in their CVD risk score ($M = 2.56\%$, $SE = 2$) whilst participants in the control group ($M = -2.1\%$, $SE = 1.6$) had an increase in their CVD risk score. Analysed as a one tailed t-test, the results showed that participants in the intervention group had a statistically significant improvement ($t(24) = -1.811$, $p=0.042$) in their cardiovascular risk change scores in relation to participants in the control group (Graph 1). This difference in scores represented a medium size effect ($r = 0.36$).

Table 16 Cardiovascular Disease Score

(mean±sd)	Control (n=12)			Intervention (n=12)			Significance		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	P value	95% CI	Direction of change
Cardiovascular Disease Score ↓	25.03 (15.4)	27.12 (16.1)	2.09 (5.5)	25.7 (22.8)	23.15 (18.3)	-2.55 (6.9)	0.042	-9.9,0.6	↑

Graph 1 Cardiovascular Disease Change scores



5.5 Secondary Outcomes

5.5.1 Biomarkers

On average, participants hsCRP change scores in the control group ($Mdn = -0.25$) showed a slight decrease in hsCRP levels, whereas the intervention group ($Mdn = 0.00$) showed no change in hsCRP levels. These changes were not statistically significant and represented a small effect size ($r = .08$).

Similarly, tests for the second biomarker, fibrinogen, showed the control group experienced a greater reduction in their fibrinogen change score ($M = 0.25$, $SE = 0.12$) than participants in the intervention group ($M = .20$, $SE = .10$). This difference was not significant ($t(21) = -0.336$, $p = 0.741$) and represented a small size effect ($r = 0.07$). It should be noted that testing errors in the pathology laboratories meant that in-complete data sets were obtained for one fibrinogen test in the control group ($n = 11$) and two fibrinogen tests in the intervention group ($n = 10$).

Table 17 Biomarkers

(mean±sd) (median-range)	Control (n=12)			Intervention (n=12)			Significance	
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	P value	95% CI
HsCRP(mg/L) ↓	3.50 (0.5,18)	2.00 (0.5,8)	-0.25 (-4,15)	2.00 (0.5,8)	2.00 (0.5,10)	0.00 (-5,5)	0.342	
Fibrinogen (g/L) ↓	4.28 (0.8)	3.98 (0.7)	-0.25 (0.4)	4.40 (0.5)	4.19 (0.5)	-0.20 (0.3)	0.370	-.39,.28

5.5.2 Cholesterol

Participants' total cholesterol change scores in the control group showed a slight increase in mean cholesterol ($Mdn = 0.20$), whereas the intervention group showed a slight decrease in total cholesterol ($Mdn = -0.25$). However, the

differences between the two groups were insignificant ($U = 51.50$, $z = -1.19$, *ns*) and there was only a small effect size ($r = -0.24$).

A similar trend was seen for HDL cholesterol scores, with participants in the control group recording a slight increase in their HDL cholesterol ($M = 0.03$, $SE = .04$), whereas participants in the intervention group ($M = -0.03$, $SE = 0.05$) had a small reduction in their HDL cholesterol scores. This difference was not significant ($t(24) = -.89$, $p > 0.05$) and the effect size was small ($r = 0.1$).

When each participant's total cholesterol and HDL cholesterol scores were expressed as a ratio, participants in the control group were shown to have had an increase in their HDL / total cholesterol ratio scores ($M = -0.06$, $SD = 1.17$), whereas participants in the intervention group had a small decrease in their HDL / total cholesterol ratio scores ($M = 0.02$, $SD = 0.48$). This difference was not statistically significant ($t(24) = -0.23$, $p > 0.5$) and there was no effect size ($r > 0.0$).

Table 18 Cholesterol

(mean±sd)	Control (n=12)			Intervention (n=12)			Significance	
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	P value	95% CI
Total Cholesterol ↓ (mmol/L)	3.75 (3,5)	3.55 (3,7)	-0.20 (-3,2)	3.95 (3,7)	3.80 (3,6)	-0.25 (-2,1)	0.177	
HDL Cholesterol ↑ (mmol/L)	1.10 (0.3)	1.10 (0.2)	0.02 (0.1)	1.25 (0.3)	1.22 (0.3)	-0.03 (0.1)	0.190	-0.7,1.9
Total Cholesterol / HDL ratio ↓	3.77 (1.09)	3.82 (1.37)	0.06 (1.17)	3.51 (1.05)	3.49 (1.04)	-0.03 (0.47)	0.41	-.84,.67

5.5.3 Diabetic status: Fasting Blood Glucose (FBG)

On average participants in both the intervention ($M = .13$, $SE = .1$) and control ($M = .11$, $SE = .12$) groups had a small reduction in their FBG readings. This

difference was not statistically significant ($t(24) = -.11$, $p > .5$) and the effect size was small ($r = .02$).

Table 19 Fasting Blood Glucose

(mean±sd)	Control (n=12)			Intervention (n=12)			Significance	
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	<i>P</i> value	95% CI
FBG (mmol/L)	5.49	5.38	-0.10	5.33	5.20	-0.12	0.457	-0.3,0.3
↓	(0.6)	(0.4)	(0.3)	(0.4)	(0.4)	(0.3)		

5.5.4 Blood Pressure

On average participants in the intervention group had a greater reduction in their systolic blood pressure (SBP) readings ($M = 4.58$, $SE = 4.69$) than participants in the control group ($M = -2.42$, $SE = 3.42$). This difference was not statistically significant ($t(24) = -0.373$, $p > 0.5$) and the effect size was minimal ($r = 0.006$).

In contrast, diastolic blood pressure (DBP) showed that participants in the intervention group had a marginally smaller reduction in their diastolic BP readings ($M = 4.42$, $SE = 2.42$) than participants in the control group ($M = 5.0$, $SE = 2.53$). Again this difference was not statistically significant ($t(24) = .17$, $p > 0.05$) and the effect size was minimal ($r = 0.001$).

Table 20 Blood Pressure

(mean±sd)	Control (n=12)			Intervention (n=12)			Significance	
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	<i>P</i> value	95% CI
SBP (mmHg)	134.33	131.92	-2.41	136.50	131.92	-4.58	0.356	-14.2,9.8
↓	(16.3)	(18.1)	(11.8)	(19.8)	(15.2)	(16.2)		
DBP (mmHg)	79.67	74.67	-5.00	79.42	75.00	-4.41	0.434	-6.6,7.8
↓								

(7.9)	(8.7)	(8.7)	(9.2)	(7.9)	(8.3)
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5.5.5 Obesity

On average, participants' Body Mass Index (BMI) change scores in the control group showed a slight increase in BMI ($Mdn = 0.25$), whereas the intervention group showed a slight decrease in BMI ($Mdn = -0.29$). However the changes were not statistically significant ($U = 51.00$, $z = -1.21$) and there was only a small size effect ($r = 0.25$).

Similar results were found for Waist to Hip (WtH) ratio's with participants in the intervention group showing a slight improvement in their WtH ratio change score ($M = -0.01$ SE = 0.01) in relation to participants in the control group ($M = 0.00$ SE = 0.00). This difference was not statistically significant ($t(24) = 1.2$, $p > 0.05$) and represented a small effect size ($r = 0.24$).

Table 21 Obesity

(mean±sd) (median-range)	Control (n=12)			Intervention (n=12)			Significance	
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	P value	95% CI
BMI ↓	27.61 (21,36)	27.87 (20,36)	0.25 (-1,1)	28.34 (23,43)	28.19 (23,43)	-0.29 (-2,4)	0.112	
WtH Ratio ↓	0.97 (0.06)	0.97 (0.07)	0.00 (0.02)	0.97 (0.07)	0.96 (0.07)	-0.01 (0.04)	0.121	-0.01, 0.05

5.5.6 Lifestyle: Smoking, Exercise & Diet

On baseline testing, four participants registered as having smoked within the past 4 weeks (control group n=1, intervention group n=3). At endpoint data collection all four participants continued to smoke along with an additional participant in the control group. These numbers are not sufficient to allow a between or within group comparison.

Exercise was assessed as a measure of cumulative exercise (amount of strenuous, moderate or mild activity per week) and whether or not participants thought they undertook 30 minutes duration of exercise 5 times a week.

On average participants in the control group undertook more cumulative weekly activity than those in the intervention group at the start of the trial (14.5 times per week as opposed to 9.83 times per week). However, by the end of the trial there was a reduction in cumulative activity in both groups. This reduction was significantly greater for participants in the control group ($M = -4.6$ $SE = 0.89$) than it was for participants in the intervention group ($M = -1.3$ $SE = 1.39$). This represents a statistically significant ($t(24) = -2.00$, $p=0.029$) change with a medium size effect ($r = 0.39$).

In answer to the question of whether participants undertook regular physical activity of at least 30 minutes duration on average 5 times a week, 75% of participants in the control group reported exercising this way. However by the end of the trial this level of physical activity had fallen by 25%. In contrast only 16% of participants in the intervention group reported taking 30 minutes of physical activity 5 times a week, but by the end of the trial this had increased to 50% of participants. This change in activity levels between the two groups represented a statistically significant improvement for the intervention group ($M= 0.33$ $SE= 0.65$ $p = 0.021$) in relation to the control group ($M= -0.25$ $SE= 0.45$) and was of a medium effect size ($r = .47$).

In contrast, there was no significant change in the portions of daily fruit and vegetable consumption between the intervention ($Mdn = 0.00$) and control group ($Mdn = 0.00$). The variation between the groups in table 22 represented a small effect size ($r = .12$).

Table 22 Exercise and Diet

(mean±sd) (median-range)	Control (n=12)			Intervention (n=12)			Significance		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	P value	95% CI	Direction of change
Cumulative Exercise ↑	14.50 (5.5)	9.83 (6.6)	-4.66 (3.1)	9.41 (7.7)	8.08 (5.7)	-1.33 (4.8)	.029	-6.7,0.1	↑
Exercise 5X 30 mins ↑	2.00 (1,2)	1.50 (1,2)	0.00 (-1,0)	1.00 (1,2)	1.50 (1,2)	0.00 (-1,1)	.021		↑
Diet ↑	4.00 (1,6)	4.00 (1,6)	0.00 (-1,1)	4.00 (2,6)	4.50 (1,6)	0.00 (-2,3)	0.267		

5.5.7 Health Related Quality of Life

Health Related Quality of Life (HRQoL) was assessed using the SF36. To assist with the interpretation of the results Table 23 provides a summary of the SF36 domains and their descriptions.

Table 23 SF36 HRQoL Definitions

Definition of scores*		
Domain	Lowest Possible (ceiling)	Highest Possible (ceiling)
Physical Functioning	Limited a lot in performing all physical activities including bathing or dressing due to health	Performs all types of physical activities including the most vigorous without limitations due to health
Role Physical	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health
Bodily Pain	Very severe or limiting pain	No pain or limitations due to pain
General Health	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality	Feels tired and worn out all the time	Feels full of pep and energy all of the time
Social Functioning	Extreme and frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role Emotional	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems
Mental Health	Feeling's of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time

*Ware 2000

5.5.7.1 Health Related Quality of Life: SF36 Physical Components

On average, participants in the intervention group improved in their SF36 Physical Functioning score ($M = 5.42$ $SE = 3.14$) whereas participants in the control group showed a deterioration during the trial period ($M = -6.83$ $SE = 3.22$). This difference registered as statistically significant ($t(24) = -2.720$, $p=0.012$) with a large size effect, ($r = 0.5$; Graph 2). However, according to Ware (2000), a sample

size closer to forty eight would be required for a 13 point change to register as statistically significant.

The Role Physical change scores for the control ($Mdn = 0.0$) and intervention ($Mdn = 0.0$) groups showed no significant change, with a minimal effect size ($r=0.08$).

Bodily Pain results indicated that participants in the control group had a reduction in their pain scores ($M = 4.75$ $SE = 5.02$), whereas participants in the intervention group ($M = -9.83$ $SE = 5.11$) showed a mean increase in bodily pain scores (Graph 3). This difference was not statistically significant ($t(24) = -2.034$, $p=0.054$) though it represented a medium size effect ($r = 0.39$)

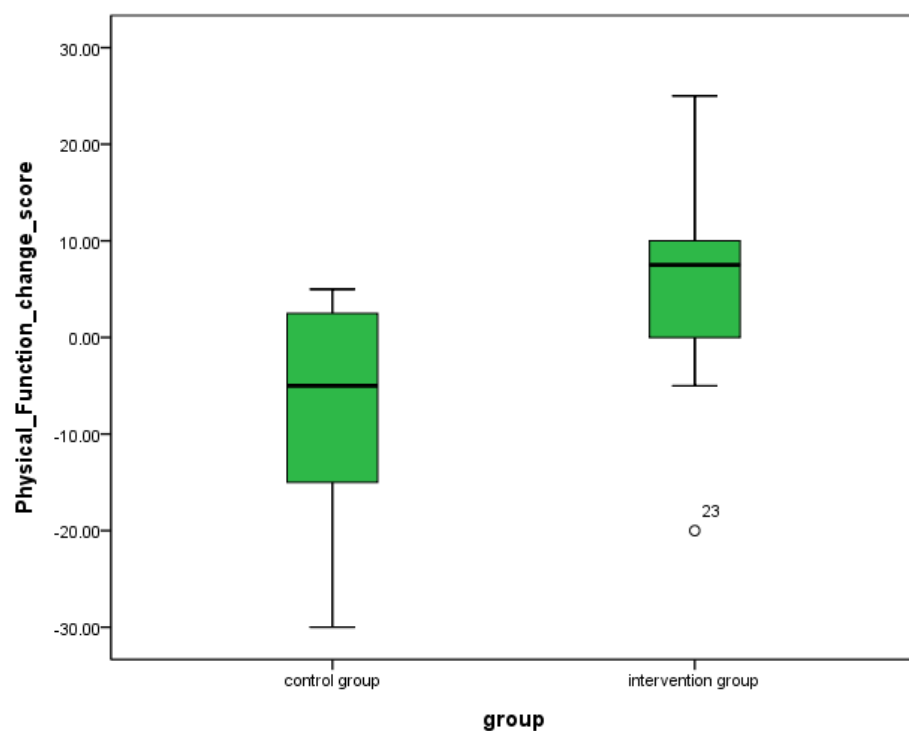
On average, participants in the intervention group showed an improvement in their SF36 General Health score ($M = 4.25$ $SE = 4.44$) in contrast to participants in the control group whose General Health score declined during the trial period ($M = -3.0$ $SE = 4.88$). This difference was not statistically significant ($t(22) = -1.09$, $p>0.05$; and represented a small size effect ($r = 0.2$) .

The Physical Component Summary (PCS) is an algorithmic calculation of the above four physical components of the SF36. Analysis of this data revealed that, despite the improvements in the Physical Functioning category, there was no statistically significant difference between the two groups in their overall PCS change scores ($t(24) = 0.314$, $p>0.05$, effect size, $r = 0.06$)

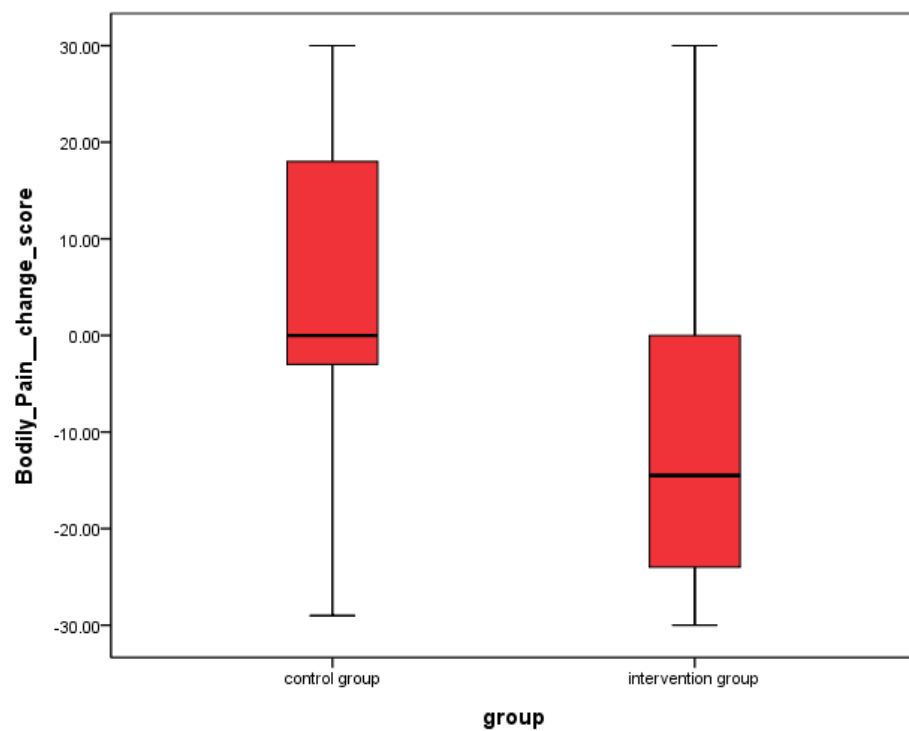
Table 24 SF36 Physical Component

	Control (n=12)			Intervention (n=12)			Significance		
	(mean±sd)								
(median-range)	Baseline	Endpoint	Change	Baseline	Endpoint	Change	P value	95% CI	Direction of change
Physical Functioning ↑	90.00 (12.4)	83.16 (17.3)	-6.80 (10.8)	70 (24.4)	75.40 (24.6)	5.40 (11.1)	0.012	-21.5,-2.9	↑
Role-Physical ↑	100 (0,100)	87.5 (0,100)	-4.16 (-100,100)	87.50 (0,100)	100.0 (1,100)	10.4 (-75,100)	0.705		
Bodily Pain ↑	51.75 (12.5)	56.50 (16.6)	4.75 (17.4)	52.91 (17.7)	43.08 (12.9)	-9.83 (17.7)	0.054	-0.28,29.4	
General Health ↑	78.8 (13.0)	75.83 (11.6)	-3.00 (16.9)	72.16 (18.4)	76.41 (17.6)	4.25 (15.3)	0.284	20.9,6.4	
Physical Component Summary ↑	47.35 (6.4)	47.42 (5.5)	0.06 (6.4)	43.71 (9.4)	43.0 (9.7)	-0.69 (5.3)	0.75	-4.2,5.7	

Graph 2 SF36 Physical Functioning Change Score



Graph 3 SF36 Bodily Pain Change Score



5.5.7.2 Health Related Quality of Life: SF36 Mental Components

Participants in the intervention group had a greater improvement in their Vitality score ($M = 10.4$ $SE = 5.82$) than participants in the control group ($M = -.83$ $SE = 6.56$). This difference was not statistically significant ($t(24) = -1.28$, $p > 0.05$) and represented a small size effect ($r = 0.26$).

On average, participants Social Functioning change scores for the intervention group ($Mdn = 6.25$) showed an improvement. There was no improvement in social functioning for the control group ($Mdn = 0.0$). The difference between the two groups was not statistically significant and the effect size was small ($r = 0.24$).

There was no change in the Role Emotional scores for either the control ($Mdn = 0.00$) or the intervention groups ($Mdn = 0.00$). However, there was a medium size effect seen in favour of the intervention group ($r = 0.37$).

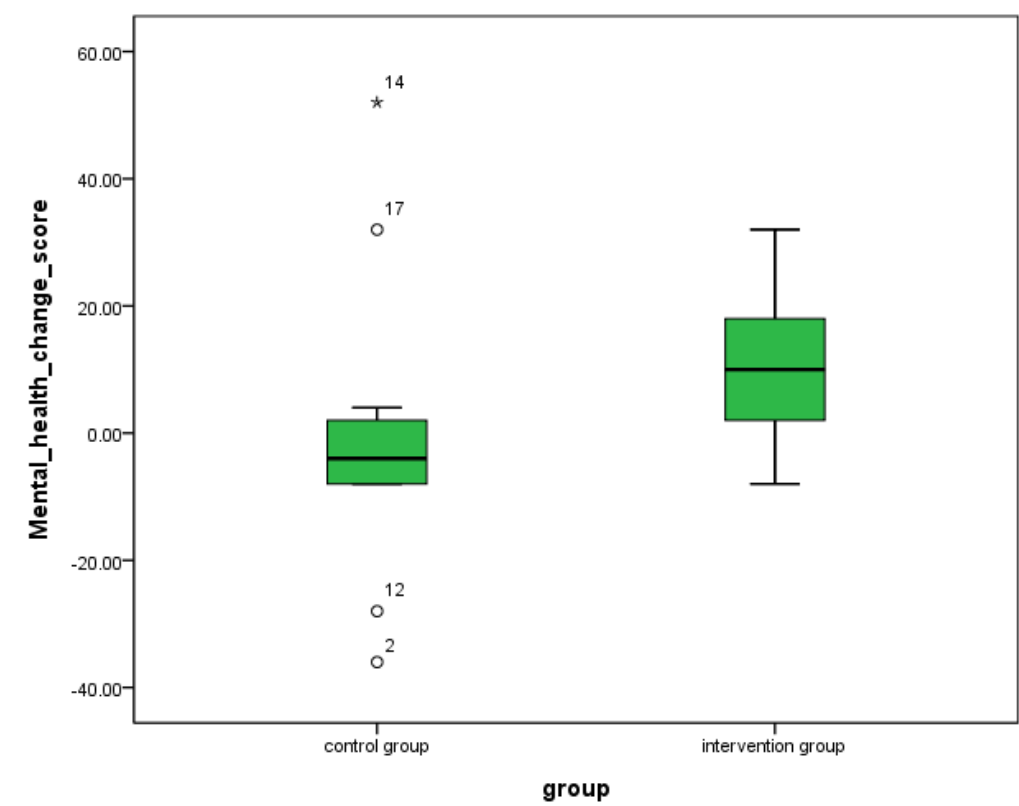
In contrast, Mental Health change scores for the intervention group ($Mdn = 10.00$) showed a significant improvement ($U = 36.5$, $z = -2.059$, $p = 0.039$) in relation to the control group ($Mdn = -4.00$). This 14 point difference in change scores represented a medium effect size ($r = 0.42$: graph 4 pg. 100) and also proved to be significant when the data was measured against the logarithmic sample size requirements suggested by Ware (2000) (Graph 5 pg. 102).

The Mental Component Summary score (MCS) is a similar algorithmic calculation to the PCS, accounting for the four mental components of the SF36. Analysis of this data revealed that the intervention group ($Mdn = 4.15$) showed a statistically significant improvement in their overall MCS score ($U = 36.0$, $z = -2.078$, $p = 0.038$) in relation to the control group, which experienced a slight reduction in their MCS score ($Mdn = -1.2$). This represented a medium effect size ($r = 0.42$; graph 6 pg. 102).

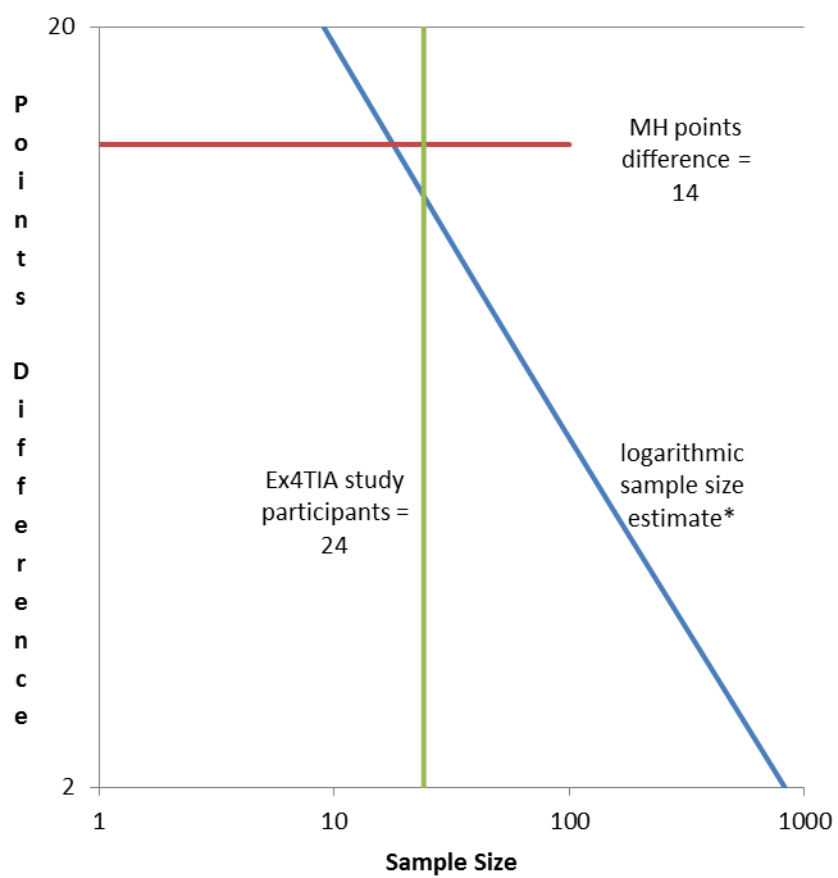
Table 25 SF36 Mental Health Component

(mean±sd) (median- range)	Control (n=12)			Intervention (n=12)			Significance		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	<i>P</i> value	95% CI	Direction of change
Vitality ↑	66.66 (15.1)	65.8 (16.8)	-0.833 (22.7)	51.66 (9.3)	62.08 (21.3.)	10.41 (20.16)	0.213	-29.4,6.9	
Social Functioning ↑	100.0 (25,100)	100.0 (37,100)	0.00 (-50,75)	87.5 (50,100)	100.0 (75,100)	6.25 (-25,50)	0.228		
Role-Emotional ↑	100.0 (33,100)	100.0 (0,100)	0.00 (-100,66)	83.3 (0,100)	100.0 (66,100)	0.00 (0,100)	0.070		
Mental Health ↑	88.00 (40,100)	84.00 (56,100)	-4.00 (-36,52)	84.0 (60,100)	92.0 (80,100)	10.00 (-8,32)	0.039		↑
Mental Component Summary ↑	57.2 (36,53)	54.70 (21,54)	-1.20 (-10,12)	54.00 (36,53)	59.70 (23,58)	4.15 (-6,12)	0.038		↑

Graph 4 SF36 Mental Health Change Score

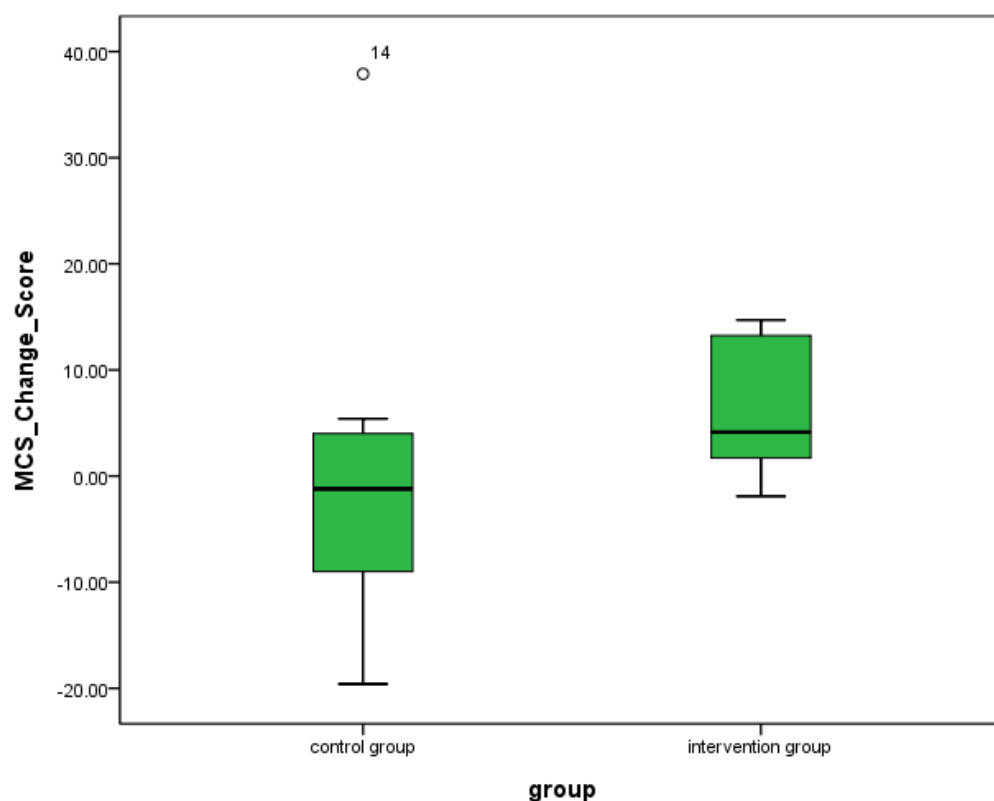


Graph 5 SF36 Mental Health Change sample size calculation



*Logarithmic sample size estimate based on data from Ware 2000

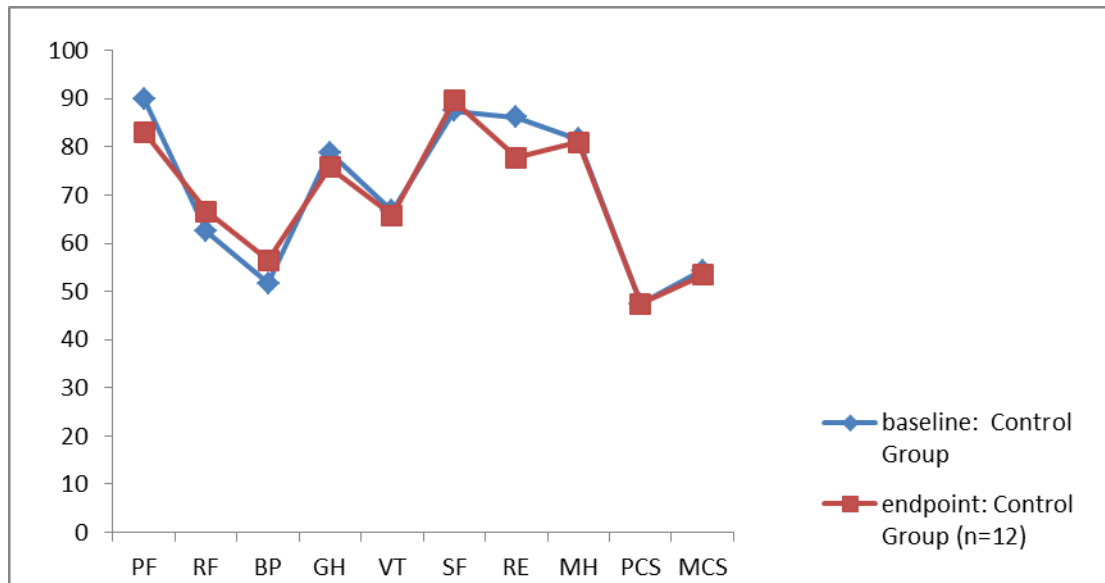
Graph 6 SF36 Mental Component Summary Change Score



5.5.7.3 Benchmarking the Ex4TIA HRQoL results

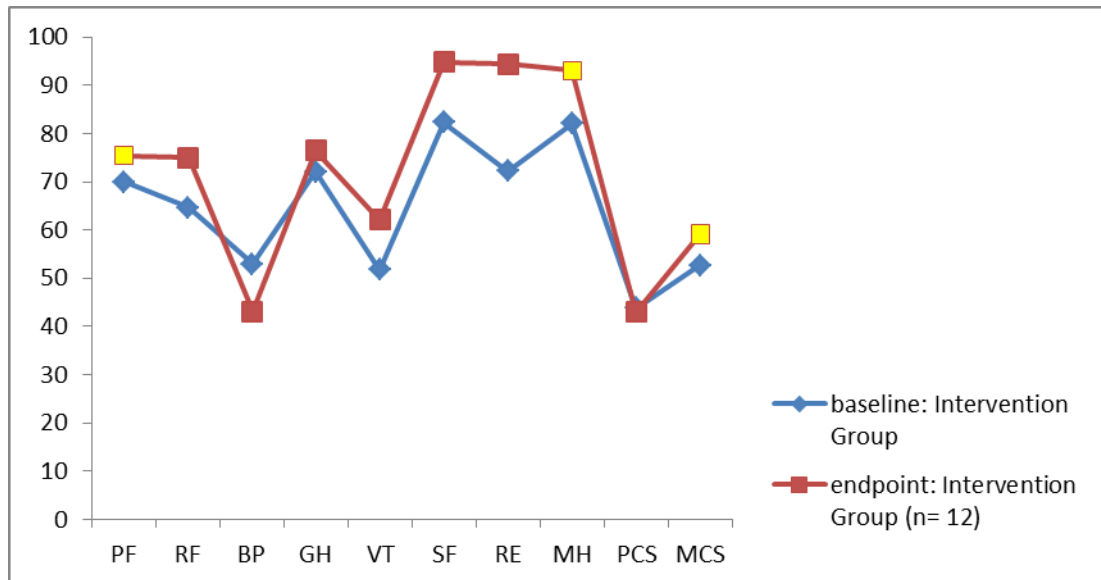
A more detailed examination of the standard care group data (Graph 7) shows that, with the exception of the physical functioning and role emotional scores, there was very little change in the ten domains during the five month trial period. In contrast, the participants in the cardiac rehabilitation group (Graph 8) showed an improvement in all but the bodily pain domain, with a noticeably consistent improvement in the mental health domains. A review of the quantitative data shows that the bodily pain score for the cardiac rehabilitation group was heavily skewed by participant 023, whose arthritis was aggravated by the cardiac exercises (though he still chose to persist with the exercises despite the discomfort they caused).

Graph 7 SF36 mean change scores for standard care group



PF: Physical Functioning RF: Role Physical BP: Bodily Pain GH: General Health
 VT: Vitality SF: Social Functioning RE: Role Emotional MH: Mental Health
 PCS: Physical Component Summary MCS: Mental Component Summary

Graph 8 SF36 mean change scores for the cardiac rehabilitation group



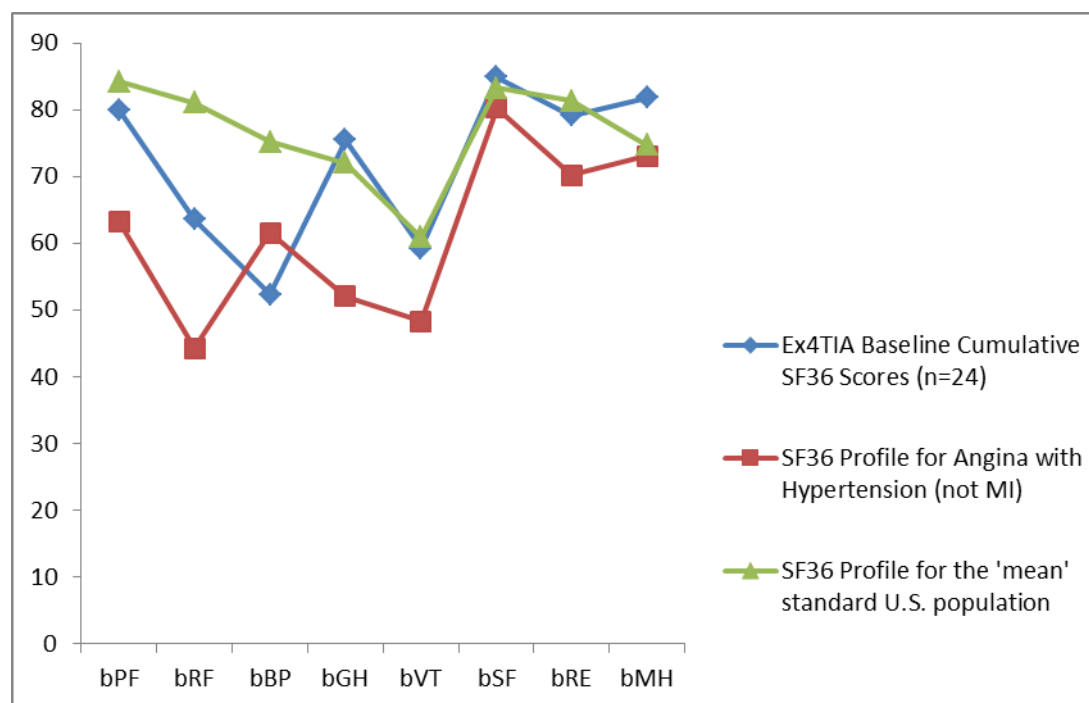
PF: Physical Functioning RF: Role Physical BP: Bodily Pain GH: General Health
 VT: Vitality SF: Social Functioning RE: Role Emotional MH: Mental Health
 PCS: Physical Component Summary MCS: Mental Component Summary

■ Indicates a statistically significant change relative to the control group

Although the standard care group had a greater mean Physical Functioning score at end point they showed a general decline during the trial (mean = -6.80). In contrast the cardiac rehabilitation group increased their perceived Physical Functioning abilities (mean = 5.40) during the trial. Interestingly, this relative decline (from a higher initial starting point) and improvement for the respective groups mirrors the changes for self-reported physical activity levels.

Comparison of the Ex4TIA data with similar (angina) audit data available from the Medical Outcomes Study (Graph 9) (Ware JE et al., 2000), shows that, with the exception of Bodily Pain, there was an evident trend between the stroke and angina disease cohorts. The notably higher latter three domain scores for the Ex4TIA stroke participants may partially reflect the differences in the 'normal' audit data that exist between the UK and US older adults populations (Ware 2000).

Graph 9 Baseline comparison of domain profiles



PF: Physical Functioning
VT: Vitality

RF: Role Physical
SF: Social Functioning

BP: Bodily Pain
RE: Role Emotional

GH: General Health
MH: Mental Health

5.5.8 Anxiety and Depression

On average participants' Hospital Anxiety and Depression Scores (HADS) were within the 'normal' range (0-7) for both groups. At the end of the trial participants in the control group showed no change in their anxiety levels ($Mdn = 0.00$), whereas data from the intervention group showed a slight reduction in anxiety levels ($Mdn = -1.00$), which represented a medium effect size ($r = .31$). However, the changes were not statistically significant.

A similar pattern was seen for the depression change scores, with no change in the control group ($Mdn = 0.00$) and a slight reduction in the intervention group ($Mdn = -0.50$). Again, these changes were not statistically significant and represented a small effect size ($r = .21$)

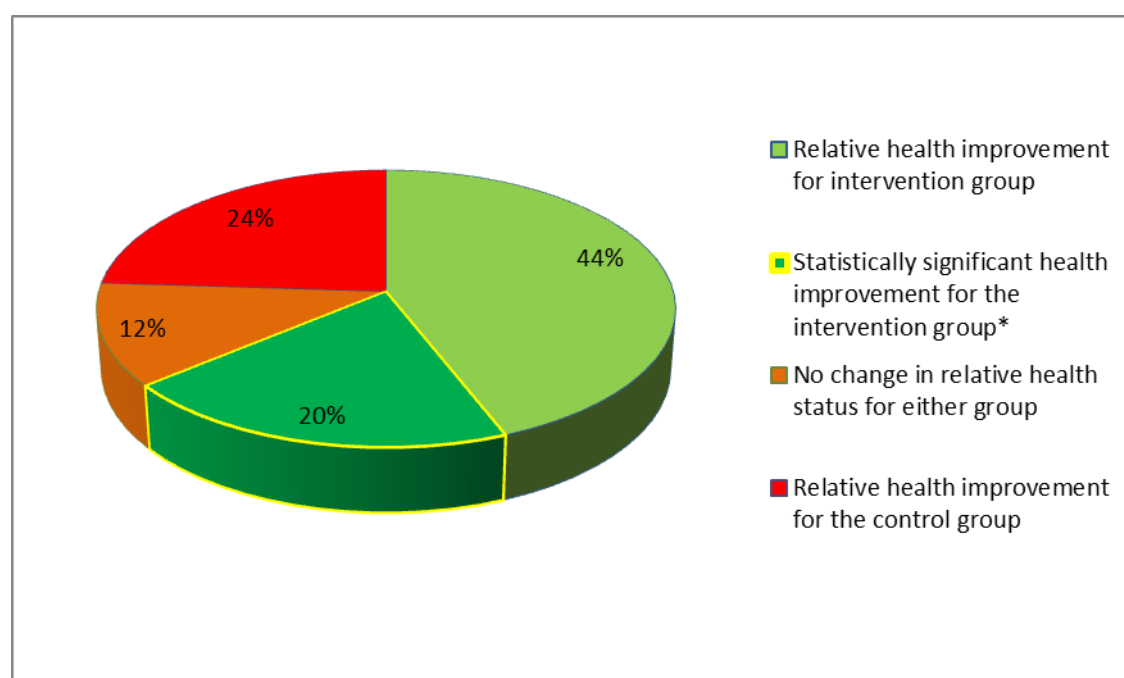
Table 26 Anxiety and Depression

(median-range)	Control (n=12)			Intervention (n=12)			Significance	
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	<i>P</i> value	95% CI
HAD Anxiety Scale ↓	3.50 (0,16)	4.50 (0,6)	0.00 (10,3)	4.50 (0,10)	3.00 (0,9)	-1.00 (-5,2)	0.127	
HAD Depression Scale ↓	1.00 (0,14)	2.00 (0,4)	0.00 (-13,1)	3.50 (0,7)	1.50 (0,8)	-0.50 (-6,2)	0.285	

5.5.9 Cumulative Outcome Summary

As a feasibility study with a wide variety of outcome measures, it was informative to get an impression of the trend of change for all 25 outcomes. Graph 10 provides a diagrammatic summary of the direction of change of standard care versus standard care and cardiac rehabilitation as illustrated by the percentage of outcomes measures showing a positive or negative trend.

Graph 10 Direction of change summary



*Statistically Significant outcomes; CVD risk score, weekly exercise, SF36 physical functioning, SF36 mental health, SF36 mental component summary.

5.5.10 Additional analysis

The previous analysis has been conducted on an intention to treat basis. However, the Consort data (Figure 6) illustrates that 3 participants did not complete the intervention. During the trial participant 008 completed just one out of a possible eight intervention sessions and participants 010 and 016 did not complete any of the interventions. Analysis of the CVD risk change scores with these data removed

reduces the sample size and power but demonstrates an increased statistical significance ($t(21) = 2.625$, $p=0.008$).

Examination of within group change using the paired samples t-test for parametric data or Wilcoxon Signed Rank test for non-parametric data provides an indication of whether the change in risk factors was due to the relative change between the intervention and control group, or whether there was a predominant change within each group. Analysis of the CVD data showed no significant within group change for the intervention ($t(12) = 1.276$, $p>0.05$) or control group ($t(12) = -1.304$, $p>0.05$). However, analysis of the secondary outcomes suggested that there were significant within group improvements in the intervention group for the SF36 Mental Health score ($p=0.014$) and the Mental Component Summary score ($p=0.006$). There was also an improvement in the intervention groups HADS anxiety score ($p=0.046$) which was not reflected in the between group change scores. Conversely, analysis of changes in the cumulative exercise levels suggested that changes between the groups was largely attributable to a reduction in exercise levels within the control group ($p=0.003$).

5.6 Qualitative Study Results

The results from the qualitative study have been separately submitted for publication. However, the preliminary results show that across both the standard care and cardiac rehabilitation groups four themes were identified; those concerning events that happened post TIA (i.e. information delivery and comparing oneself with others) and those that related to outcomes post TIA (i.e. psychological impact, attitudes and actions regarding risk factor reduction). The emergence of these four themes and the implications in terms of the main quantitative study are discussed in greater detail in section 6.5.

5.7 Summary of results

The results from this feasibility trial demonstrate that it is feasible to conduct a single blinded RCT requiring TIA and minor stroke patients to participate in an existing NHS cardiac rehabilitation programme. Evaluation of the recruitment data indicates that the trial design is appropriate but that fewer patients were suitable for the trial than predicted (see section 6.6.1).

Despite the limited sample size the results suggest comprehensive cardiac rehabilitation and standard care (intervention) causes a significantly greater reduction in cardiovascular risk post stroke, than standard care alone (control). There were also significant relative improvements for participants in the intervention group in terms of activity levels and health related quality of life. The suitability of the trial design, applicability of the outcome measures, adverse results and the implications for future health sector research are discussed along with the trial objectives in chapter 6.

CHAPTER 6

Discussion and Conclusion

6.1 Introduction

The burden of both stroke and coronary heart disease (CHD) on the individual and society is huge, and likely to increase with an ageing population (Department of Health, 2000, Department of Health, 2007, National Audit Office, 2005). Evidence from the literature review indicates that stroke and coronary heart disease share broadly the same underlying atherosclerotic pathology, age profile and risk factors (Rothwell et al., 2005 a, Yusuf, 2004, Goldstein, 2006, Gates et al., 1987, Adams et al., 2003, O'Donnell and Xavier, 2010), and that individuals who have had a stroke or myocardial infarction are at a high risk of subsequent events and death (van Wijk et al., 2005, Lin et al., 2007).

Despite these similarities, stroke patients do not have access to the effective secondary prevention programmes available to cardiac patients. To date, this is the first trial that has examined whether an intervention following a standard NHS cardiac rehabilitation programme would be a feasible and effective means for reducing cardiovascular risk post TIA and minor stroke. The results from this trial have shown that it is feasible for TIA and minor stroke patients to undertake cardiac rehabilitation and suggests that such programmes may provide a more effective means of reducing cardiovascular risk than standard care.

The following chapter provides a detailed interpretation of the results and feasibility of each outcome measure, reviewing this in light of recent sources of evidence. The subsequent sections consider the trial limitations and makes recommendations for future research based on the evidence from this trial and the literature review.

6.2 Trial Participants

The average age of participants in the trial (67.2 years) was lower than the mean age of for incident stroke (73.8 years) and cardiac (70.9 years) events as reported in the OXVASC study (Rothwell et al., 2005 a). This discrepancy in age is mirrored in data from the 2011 National Audit of Cardiac Rehabilitation (NACR) (Lewin, 2011) which reported the average age of cardiac rehabilitation participants to be 66.5 years. The fact that the average participation age is lower than the incident age may be a reflection of the reduced referral and participation rates for the elderly that are widely reported in cardiac rehabilitation programmes (Suaya et al., 2007, Wenger, 2008).

Further evaluation of the participant characteristics in the trial demonstrated additional similarities with the cardiac rehabilitation programmes. Self-reported co-morbidities showed that hypertension was the most common co-morbidity for both the cardiac rehabilitation patients (49%, Lewin 2011) and Ex4TIA trial patients (29%). The small number of participants in the Ex4TIA trial meant that a detailed comparison with the national cardiac data is not appropriate. However, it was noticeable that there appears to be a similar general trend towards the cardiovascular disease related co-morbidities and a spread of co-morbidities that would be expected with such similar age and vascular profiles (appendix 14 pg 193).

Representation of minority groups is traditionally low in cardiac rehabilitation with only 7% of patients classifying themselves as 'non-white British'. This proved similarly low in the Ex4TIA trial with only 12.5% of participants from 'non-white British' backgrounds. This low ethnic mix would also be expected in Southampton where 81% of the population are 'white British' (ONS 2010). However, whilst underrepresentation of minority groups is an important consideration in America (Mochari H et al., 2006), data from the NACR (2011) suggests that the uptake of phase III cardiac rehabilitation amongst different ethnic backgrounds is broadly reflective of myocardial infarction ethnic incidents rates in the UK.

Perhaps the most noticeable of the participant characteristics was the low representation of women. In this trial just 21% of participants were women, which is slightly less than the 26% of participants in phase III cardiac rehabilitation programmes (Lewin, 2011). It is arguable that this is not surprising based on the low levels of female participation (2% – 20%) in the cardiac clinical trials (O'Connor et al., 1989, Taylor et al., 2004). From a cardiac rehabilitation perspective, these figures indicate a substantial under-representation with respect to female myocardial infarction incident figures of 37% (Lewin, 2011). However, from a stroke perspective this represents an even greater under-representation as the sex ratio's for all cerebrovascular incident events are very similar for men and women (Rothwell et al., 2005 a). This is an important consideration in future trial design and recruitment as the experience from cardiac rehabilitation is that elderly women are less likely to be referred to or attend cardiac rehabilitation (Wenger, 2008). This is despite the fact that both genders receive equal benefit from cardiac rehabilitation, irrespective of age (Williams et al., 2006).

6.3 Primary Outcome

Analysis of the participants' cardiovascular risk score (D'Agostino et al., 2008) demonstrated that participants in the intervention group had a significant reduction ($p=0.042$) in the risk of future vascular events relative to the control group. This relative change in risk proved even greater when participants that did not complete the cardiac rehabilitation intervention were removed from the analysis ($p=0.008$). These results suggest that cardiac rehabilitation may be able to reduce the risk of further cardiovascular events for minor stroke and TIA patients.

The use of an algorithmic measurement such as the CVD score is considered to improve reliability and accuracy of risk when subjects have multiple mild abnormalities that act synergistically (Wilson et al., 1998). This would appear particularly pertinent to this study, as the reduction in cardiovascular risk is difficult to explain based upon an evaluation of the individual risk factors. Analysis of the individual risk factors demonstrates that, with the exception of self-reported levels of exercise, there were no significant reductions in each of the main risk factors (smoking, BP and cholesterol).

It is quite possible that the general trend towards an improvement in individual atherosclerotic risk factors for the cardiac rehabilitation group (Graph 10), meant that these factors acted in a combined and, as yet unknown manner to reduce overall risk (Rothwell, 2007, D'Agostino et al., 2008). This assertion, that changes in overall risk may be greater than the sum of changes to individual risk factors is supported by the evidence from meta-analysis of the cardiac rehabilitation literature. Both Jolliffe et al., (2001) and Taylor et al., (2004) (Tables 6 & 7 pg. 28) reported significant, though small, reductions in a variety of known risk factors. However, these are not only small, but inconsistent between the two meta-analysis and do not appear to reflect the significant reductions in mortality (26%) reported in both studies. Indeed, Jolliffe et al., (2001) reported no significant changes in any of the main risk factors for the one intervention (exercise only cardiac rehabilitation) that showed the greatest reduction (31%) in mortality.

It is important to acknowledge though, that there are limitations in the use of such algorithms. As the Cardiovascular Disease Score is based on data from the Framingham study, it is not validated for those with known cardiovascular disease or those over 74 years of age (2 in control group, 4 in intervention group). Further sub-group analyses with the data from participants over 74 years of age removed reduced the effect size to one of non-significance ($t=1.542$; $p=0.072$). This reduction can be partially explained by the reduced power of the data. However the use of such outcomes measures as a proxy for mortality will limit the validity of the results whilst there is an age restriction which is just one year greater than the mean age of incident stroke (Rothwell et al., 2005 a).

6.4 Secondary Outcomes

6.4.1 Change in activity

Self-reported activity levels are a strong predictor of primary stroke and vascular mortality (Lee et al., 2003, Wendel-Vos et al., 2004). In this study, activity was measured in the same format as the NACR (2007) audit questionnaire. This provided two self-reported measures of activity that were analysed in this trial.

1. Cumulative intensity and frequency of exercise per week.
2. Record of whether participants undertook an average of 30 minutes of physical activity 5 times a week.

The evidence from the trial demonstrated a significant improvement for the cardiac rehabilitation group relative to the standard care group for both measures respectively ($p=0.029$, $p=0.021$). Analysis of the data showed that in both outcomes the standard care group had higher levels of baseline activity. However, in the first measure there was a significantly greater reduction in activity in the standard care group. In the second measure of 30 minutes of physical activity 5 times a week, 50% of participants in both groups were taking the recommended 30 minutes of physical activity 5 times a week by the end of the study. This represents a 34% improvement for the cardiac rehabilitation group and a 25% reduction in activity for the standard care group. Interestingly, the improvement and end point activity levels for the intervention group are similar to those reported by cardiac rehabilitation patients in the 2011 NACR audit (from 34% at baseline to 49% at 12 months).

The discrepancy between the two similar self-reported outcome measures illustrates the inconsistency in the way that participants recall events and consider questions related to exercise intensity. Such self-reported questionnaires can also be subject to social desirability bias (Fisher, 1993). Though this should have been counteracted by the use of a control group, the fact that participants in the intervention group were made aware of the importance of exercise may have increased their desire to give a favourable response.

To overcome these subjective descriptions of exercise, quantitative estimates of VO₂max were to be obtained from the Astrand-Ryhming (1954) single stage 6 minute cycle ergometer test. As VO₂ max is a predictor of cardiac and all-cause mortality (Kavanagh et al., 2002), this study aimed to assess if there was a physiological reduction in risk for those undertaking the cardiac rehabilitation programme. Unfortunately, despite being recommended by the American College of Sports Medicine (ACSM, 2000) and having good levels of validity and reliability (Kasch, 1984), in practice the Astrand-Ryhming test procedure did not prove to be a suitable measure of exercise capacity as the intensity of the test meant that few participants were able to complete the procedure. Consequently, insufficient data were collected to allow with-in or between group analyses (a more detailed analysis can be seen in section 6.6.2 and appendix 15).

The first of the two recommendations from this feasibility trial would be that only one self-reported measure of activity is required in future trials. The second recommendation is to consider a more practical and safe form for assessing exercise capacity such as the incremental shuttle walk test (Ramsbottom et al., 1988, Keell et al., 1998).

6.4.2 Change in health related quality of life

In light of the cardiac rehabilitation aims of enabling individuals to 'preserve or resume their place in society and lead an active life' (World Health Organisation, 1985), it would seem reasonable to suppose that HRQoL would feature as a prominent measure of effectiveness. In reality, HRQoL has not featured strongly as a prominent outcome in any of the main cardiac rehabilitation meta-analysis (Jolliffe et al., 2001, Taylor et al., 2004, Clark et al., 2005a). The likely reasons for this are the medical model emphasis on measures of mortality and morbidity along with a general lack of consensus about the use of HRQoL measures (Jolliffe 2001, reports the use of eighteen different measures in 11 trials). However, since many of the anticipated benefits of the intervention are related to lifestyle changes, the impact of HRQoL could have an important effect on the individual participant's adherence to, and motivation for, lifestyle changes.

The results from the trial showed that the participants in the cardiac rehabilitation group had a significant improvement relative to the standard care group in three of the SF36 categories of HRQoL (Table 24 and 25 pg.96 and 99. Graph 8 pg. 103).

1. Physical Functioning
2. Mental Health
3. Mental Component Summary

The overall improvement in the social, emotional and mental health domains suggests that aspects of the cardiac rehabilitation programme provides more holistic benefit to participants than exercise induced risk reduction alone. This implies that participants undertaking cardiac rehabilitation had a greater improvement in the amount of vigorous activity they felt they could undertake and reduction in their levels of anxiety and depression (Ware JE et al., 2000) as a result of the cardiac rehabilitation. Whilst this subjective improvement in physical functioning is reflected in the self-reported increase in activity measure, the complexity of the interactions between physical and emotional wellbeing make it hard to quantify the importance of the improvement in the mental health component. Whether these improvements will have an effect on issues such as fatigue and depression which are commonly recognised problems for many patients post stroke (Young et al., 2003) is hard to quantify. In previous studies improvements in mental well-being have been linked to lifestyle changes through improvements in self-efficacy and readiness to change post stroke due to the potential to improve lifestyle risk factors (Ireland and Arthur, 2006, Miller and Spilker, 2003). Incorporating such measures in future studies would help quantify the potential emotional and social benefits of cardiac rehabilitation programmes for stroke patients.

The other means of quantifying the HRQoL measures is to benchmark with existing studies and audits. However, reviews of cardiac rehabilitation programmes do not provide much insight due to the fact that many trials used un-validated questionnaires, and those that do use validated questionnaires have tended to use psychological measures such as the HADS and Beck Depression Inventory rather than HRQoL measures (Jolliffe et al., 2001).

Comparison with the NACR data is also difficult due to their use of the Dartmouth COOP as an outcome measure and their presentation of results as a percentage of 'normal' scores. However, the fact that their most significant change (+29%), was in the domain of Physical Fitness appears to correlate with the EX4TIA finding of a significant improvement in the SF36 Physical Functioning domain. Also, when benchmarked with similar cardiovascular disease data (Graph 9 pg. 104, Ware JE et al., 2000), the Ex4TIA data showed a consistent disease profile which suggests that, despite the small sample size, it is unlikely that this represents a type I – 'false positive' error.

The findings from this trial suggest that cardiac rehabilitation can have a positive impact on aspects of participants HRQoL. This is an important finding in light of the fact that self-assessed health status can be a powerful predictor of mortality and morbidity (DeSalvo et al., 2006). The significant improvement in these domains may also be linked to changes in lifestyle risk factors such as levels of exercise. However, this link would require further investigation and may become more apparent if future studies were to include a measure of self-efficacy and readiness to change.

6.4.3 Change in anxiety and depression

Anxiety and Depression, as measured by the HAD scale, reduced on average in the cardiac rehabilitation group and increased in the standard care group. These between group changes were not significant, although within group analysis showed that there was a moderately significant reduction ($p=0.046$) in anxiety levels for participants in the cardiac rehabilitation group. The results show that the mean participant scores were all in the normal to low range for depression and anxiety (< 7). This is perhaps to be anticipated in light of the low levels of disability within both groups.

The lack of a between group change mirrors the results from Lennon et al's., 2008 trial of a stroke adapted cardiac rehabilitation programme. Comparisons with the NACR data are difficult as they report effect in terms of percentage of participants moving from the categories of borderline/clinically anxious or depressed to within

the 'normal' range. On this basis, the NACR data (Lewin, 2011) showed a statistically significant reduction in levels of both anxiety (6%) and depression (4%). These relatively small changes were detectable due to the large sample size (n = 13,795) and would therefore be less likely to be picked up in a small feasibility study. Interestingly, however, the NACR baseline measures of borderline /clinical depression were similar to those in the Ex4TIA study (Table 27).

Table 27 Comparison of the NACR and Ex4TIA study HADS scores

Domain	NACR Baseline % of patients	Ex4TIA Baseline % of patients
HADS Anxiety: Normal range	70	75
Borderline / clinically anxious	30	25
HADS Depression: Normal range	83	92
Borderline / clinically depressed	17	8

In relation to primary prevention data there is evidence to suggest that depression is associated with an increased risk of stroke and death (Kimberly et al., 2007, Frasure-Smith et al., 1995). However, with low levels of depression within either group (20% scored >7, 4% scored > 11), it is questionable whether the HADS is a good indicator of clinical or psychological benefit for patients with TIA's or mild strokes. Future studies may gain a better insight into the psychological impact of a TIA or minor stroke and its impact on rehabilitation change through the adoption of HRQoL and measures rating self-efficacy and readiness to change.

6.4.4 Change in lipids

There was no evidence of a change in total cholesterol. This is in contrast to the evidence from cardiac rehabilitation programmes (Jolliffe et al., 2001) which showed small but significant reductions in total cholesterol (-0.57mmol) for the comprehensive (but not exercise only) rehabilitation programmes. There was also no evidence of a change in HDL cholesterol or the total / HDL cholesterol ratio. This is in line with the cardiac rehabilitation programmes (Jolliffe et al., 2001)

which did not show any reduction in HDL cholesterol and did not report on the total / HDL cholesterol ratio.

The lack of a significant change in either group is perhaps not surprising, for although lifestyle factors can influence cholesterol levels (Jenkins et al., 2011, Burr et al., 1989), this influence is not considered as strong as the effect of pharmacological interventions in secondary prevention programmes (Carlsson, 1998). Examination of baseline medications indicated that 85% of participants were taking a statin at the start of the study (median simvastatin dose = 40mg), which would be in line with the hospital policy of routine prescription of statins in TIA clinics. However, a more detailed review of the data showed that although there was only a minimal mean total / HDL cholesterol ratio change of 0.09 in favour of the cardiac rehabilitation group, this equated to a reduction from 5 to 3 participants in the high ratio category (NICE 2008). In contrast, all five participants with a high score in the standard care group remained in the high category. Though these relative changes are not individually significant, their cumulative effect may play an important role when acting in combination with other factors to reduce overall risk.

In light of the above information it would be appropriate to include a measure of both total and HDL cholesterol in future larger trials. It would also be important to ensure the collection of triglycerides to allow for the calculation of LDL cholesterol (an explanation of the lack of an LDL measure is provided in section 6.6.2). Future studies would also benefit from a greater understanding of the influence of statins through the detailed monitoring of prescribed dosage at baseline and endpoint data collection.

6.4.5 Change in Blood Pressure

Elevated blood pressure is the most important risk factor for stroke (Warlow, 2008). A reduction of just 10mmHg and 5mmHg in systolic and diastolic blood pressure can reduce the risk of a subsequent stroke by up to 30% (Rodgers et al., 1996). In this trial there was no evidence of a significant change in either systolic and diastolic blood pressure. Though the standard care and cardiac rehabilitation

groups both showed respective mean reductions in systolic blood pressure (-2.41 and -4.58) and diastolic blood pressure (-5.0, -4.41), these were not statistically significant for between or within groups analysis.

Comparison with the NACR audit data shows a small, non-significant, change of 2% of patients moving from being classified as normal rather than hypertensive ($\geq 140/90$ mmHG) at 12 weeks. This contrasts with the Ex4TIA data which showed no change in hypertensive classification in either group. Evidence from meta-analysis of the cardiac rehabilitation trials indicates a contrasting response, with varied small reductions in either diastolic (Jolliffe et al., 2001) or systolic blood pressure (Taylor et al., 2004). Measurement of blood pressure is also subject to the same debate about lifestyle and pharmacological influences that exists for the analysis of cholesterol. Keeping detailed records of alterations in blood pressure medications in a future trial could provide useful information on the influence of the medications, as well as the monitoring and adherence of the hypertension management plan. In light of recent suggestions that blood pressure variability may play an important role in cerebrovascular risk (Rothwell, 2010), it may also be appropriate for future trials to monitor blood pressure variability pre and post intervention.

6.4.6 Change in obesity

There was no significant change in either BMI or WtH ratio for participants in this study. Though obesity is a known cardiovascular risk factor (Suk S-H, 2003), there is little evidence from the cardiac rehabilitation trials to allow for a comparison of the data. In the Ex4TIA trial the WtH ratio data suggests that both the standard care (WtH ratio 0.97) and cardiac rehabilitation group (WtH ratio 0.96) were in the high risk category for stroke (male OR, 3.8; 95% CI, 1.8 to 5.0; female OR, 2.5; 95% CI, 1.6 to 4.0) (Suk S-H, 2003). Similar results from the BMI data indicates that participants in both groups stayed within the overweight range ($25 - 30\text{kg/m}^2$) according to the WHO categorisation (World Health Organization, 2000).

Interestingly, the small BMI reductions seen in this trial contrasted with the data

from the Lennon et al., (2008) trial of chronic stroke patients which showed significant within group BMI increases for participants in both the standard care ($P = 0.008$) and cardiac rehabilitation based exercise programme ($P = 0.012$). Lennon et al., (2008) did not measure WtH ratio's but reported that there was no change in waist circumference.

Although reducing BMI to $<30\text{kg/m}^2$ is a stated aim of the British Heart Foundation (BHF) cardiac rehabilitation programmes (Lewin, 2011), the NACR report showed that twelve weeks after completing the programme, there was no change in the number of patients (27%) over this figure. This lack of effect does bring into question the relevance of BMI as a measure of risk reduction. Although it is recommended by the BHF, its questionable validity as a measure of stroke risk (Walker et al., 1996, Suk S-H, 2003), and its inability to account for frame size and muscularity (Jeukendrup and Gleeson, 2005), have cast doubt on its use as a sensitive measure of stroke risk and lifestyle change.

6.4.7 Change in diet

All participants that completed the cardiac rehabilitation intervention programme participated in a one hour dietary advice session. The results showed that there was no evidence of dietary change between the standard care and cardiac rehabilitation group, as measured by the daily portions of fruit and vegetables consumed. Previous behaviour modification programmes have shown that dietary content can be significantly improved post TIA (Gillham and Endacott, 2010, Sit et al., 2007) and analysis of the Framingham data (Gillman et al., 1995), has shown a modest risk and age-adjusted reduction in stroke as consumption of fruits and vegetables increased, ($RR=0.78$ for each increase of 3 servings per day). However, with Ex4TIA participants recording mean daily portions of 3.5 (standard care) and 4.1 (cardiac rehabilitation) fruit and vegetables per day, they were not far below the national recommendation of five fruit and vegetable portions per day. It may therefore be unrealistic to expect a significant increase to the extent required in the Framingham data. There was no evidence from the cardiac rehabilitation research or the NACR data to make a comparison with the Ex4TIA results.

6.4.8 Change in blood glucose

There was no evidence of a change in fasting blood glucose (FBG) levels between the standard care and the cardiac rehabilitation group. Examination of the data indicates that the mean FBG levels were within the 'normal' range of 4 – 6 mmol/L. This equates to 16% (standard care) and 8% (cardiac rehabilitation) of participants in the impaired / diabetic range at baseline and 8% (standard care) and 0% (cardiac rehabilitation) at endpoint. Although there is little comparable data in the stroke and cardiac rehabilitation trials, the fact that patients with both diabetes and a history of stroke are 7.95 times more likely to experience a fatal stroke than patients with no history of diabetes or stroke (Ho et al., 2003) suggests that controlling blood glucose would reduce the risk of cardiovascular disease. Future trials with a longer follow up period may gain a greater insight into the effect of cardiac rehabilitation and diabetic control by the addition of Hb1AC measures. These measures provide a better indication of average glucose levels over a three month period and are known to be affected by exercise (Marcus et al., 2008).

6.4.9 Biomarker changes

High sensitivity C-Reactive Protein (hsCRP) was chosen as a biomarker due to its strong association to inflammatory atherothrombotic disorders such as myocardial infarction and stroke (Rost et al., 2001, Cao et al., 2003, Everett et al., 2006, Ridker, 2007b), and the ability of cardiac rehab programmes to reduce levels of hsCRP (Milani et al., 2004). However, when the change scores were compared within this trial there was no significant change between the cardiac rehabilitation and standard care groups.

A more detailed analysis of the data demonstrates a non-significant trend towards a reduction in hsCRP levels (mdn = 3.50mg/L to mdn = 2.00mg/L) for the standard care group from the high risk category (3 mg/L) to the 'average risk' category (2 to 3 mg/L), (Pearson, 2003), though this was not a significant with-in group change ($p=0.25$). In comparison there was no change in the intervention groups hsCRP levels (mdn=2.00mg/L).

It is not immediately apparent why the control group should have experienced the greater reduction in hsCRP. It is possible that, as hsCRP reduction is strongly linked with the use of statins (Ridker, 2010), the greater self-reported use of statins within the control group (11 participants at baseline, 12 at endpoint) in relation to the intervention group (9 at both baseline and endpoint) may have contributed to the reduction in hsCRP seen in the standard care group.

Like hsCRP, levels of fibrinogen were recorded due to its long association with cardiac disease (Drouet, 1996) and minor strokes / TIA's (Rothwell et al., 2004 b). The evidence from this trial indicates that there was no change in fibrinogen levels between the standard care and cardiac rehabilitation groups. Closer examination of the data reveals that two participants (18%) in the standard care group and one participant (10%) in the cardiac rehabilitation group had elevated levels of fibrinogen (> 5g/L) at baseline and that these figures did not change at endpoint testing.

Since undertaking this trial, more recent evidence from the literature (Whiteley et al., 2011, Whiteley et al., 2009) would suggest that, although both hsCRP and Fibrinogen are associated with an increased risk of subsequent vascular death (stroke and MI), this risk is no greater than for non-vascular deaths. Therefore, until further evidence of causation is available it is questionable whether future trials will benefit from the inclusion of hsCRP or fibrinogen measures.

6.5 Qualitative Study Discussion

Participant opinions regarding their experiences of standard care and the intervention are important in understanding whether it is feasible and ethical for stroke patients to be undertaking cardiac rehabilitation in a larger definitive trial. Whilst reported in-depth in a separate academic submission, the below paragraphs highlight the main findings and how these may relate to the results from the quantitative trial.

In general, participants' experiences of health provision were positive for both groups. Of the four identified themes (information delivery, comparing oneself with others, psychological impact, attitudes and actions regarding risk factor reduction) there were some consistent trends between and within the two groups.

Perhaps not surprisingly, cardiac rehabilitation was found to have positive effects on people's confidence and motivation to exercise. Participants attributed this to the camaraderie of the group, approachability of staff and supervision during exercise which were positive influencing factors. Notably, these attributes are similar to those reported in studies exploring cardiac patients' experiences of cardiac rehabilitation (Clark et al., 2005b, Wingham et al., 2006, Jones et al., 2009). This is also in line with studies showing that peer support can help individuals to make sense of their condition, increase their confidence post event, and develop an awareness of self-management skills (Reed et al., 2010). Whether this correlates with the changes seen in the SF36 mental health categories is supposition, though as Ireland and Arthur (2006 pg. 301) noted in their study of health behaviours and stroke risk *"...a minor stroke event in an older adult represents a significant loss, one that can compound other recent or concurrent losses. These losses represent experiences that inform perceptions of self-efficacy in implementing the risk reduction behaviours."* Therefore, it is possible that anything that improves self-efficacy may have a beneficial effect on behavioural change and risk reduction.

There were also a number of criticisms of cardiac rehabilitation, with a few individuals identifying that committing to weekly rehabilitation classes was quite a burden. The burden of attending the sessions was the possible reason for a 25% drop out rate. This is in line with the cardiac rehabilitation referral to participation dropout rate of 25% (Lewin, 2011).

Education was a common theme for both groups, as the diagnostic period was identified as being a particularly stressful time for many participants, impacting on their ability to recollect details of information they had received. As a consequence participants often sought additional information. For some participants in the cardiac rehabilitation group the formal sessions enabled them to seek answers to

questions that were either not asked or were insufficiently answered whilst receiving standard care. However, others perceived the educational sessions as being only partially relevant to their own circumstance or just vaguely informative. The criticism of the educational sessions is possibly a reflection of the lack of stroke disease specific information and a weakness in the study design. Whilst the theme of lack of information was consistent throughout, it was most evident in the standard care group. Patients' perceptions of inadequate information provision are well documented in stroke care (Smith et al., 2009) and the evidence of poor secondary prevention recollection in this study appears to substantiate the suggestion that the current methods for delivering secondary prevention advice in the clinic or on the ward are insufficient and ineffectual (Redfern et al., 2002, Rudd et al., 2004, Ramsay et al., 2007, Saposnik et al., 2009).

The theme of comparison with oneself and others appears to link with the psychological impact and risk reduction behaviours shown by the participants. For a number of participants there was a low perception of risk and for one participant the risk comparison with cardiac patients led her to drop out of the cardiac rehabilitation classes. For others the psychological impact of the stroke had a marked effect on them. Whether this correlates with pre-existing high levels of 'readiness to change' is not known as this was not measured. However, it would seem likely that for those participants who were psychologically affected, the cardiac rehabilitation programme offered them guidance and support in a way that is lacking in standard care. Whether this is linked with the relative improvements in risk, exercise and HRQoL seen in the quantitative study is again supposition but a theory that would warrant greater exploration in future studies.

The findings from the qualitative research enriched the trial by helping provide meaning and context to the data presented in this study. There were some acknowledged limitations to this study linked to the main trial limitations (section 6.6); the main specific limitation being the convenience sampling strategy which was employed as a result of the slow rate of recruitment in the main trial. Despite these limitations, this study suggests that the majority of participants that undertook cardiac rehabilitation benefited from the support and advice in a manner that participants in standard care did not. Future cardiac rehabilitation trials

involving TIA and stroke patients should ensure that they cater for the specific educational needs of this group, and explore possible links between the class format, self-efficacy and readiness to change.

6.6 Feasibility: Limitations & recommendations for future trials

Feasibility studies are traditionally pieces of research conducted before a main study to provide estimates of important parameters which will help inform the main study design (Arain et al., 2010). Section 6.4 reviewed the effects of the intervention and the applicability of each outcome measure. However, for two of the outcome measures additional recommendations in relation to trial design were made and these are summarised in section 6.7.2. The following section reviews the trial design and its limitations, the causes and consequences of which provide an indication of the feasibility of proceeding to a larger trial as well as providing a balanced picture of the quality of the evidence from this trial.

6.6.1 Recruitment

The study recruited a total of 24 participants over an eleven month period. As part of a part time Clinical Doctorate degree the trial recruitment period could not have been extended beyond the 11 month period. At the end of recruitment, the study had 48 participants fewer than the planned total requirement, as calculated on the outcome data from Lennon et al's.,(2008) trial. The following paragraphs examine the potential reasons for this, the implications and lessons learnt.

'Recruitment into health care randomised trials is notoriously difficult, particularly trials that use sequential recruitment' (Torgerson et al., 2008 pg.154). A review of trials funded by the Medical Research Council and NHS HTA programmes found 45 per cent of trials failed to achieve more than 80 per cent of their recruitment rate (McDonald et al., 2006). Unfortunately, this was also the case with this trial. Discussions with the research team and a review of the audit data suggest that there are a number of reasons as to why recruitment was slower than anticipated.

Possibly the most significant cause was an initial over estimation of the number of confirmed TIA patients that were suitable for the trial. The original number of confirmed TIA's was based on the Consultant and TIA clinic nurse providing an estimated number of patients seen in clinic. As section 4.5.1 illustrated, this would have meant that there were a total of 250 confirmed TIAs' per annum. With an expected level of recruitment (65%), based on the previous patient consultations, the expectation was to recruit thirteen participants per month. However, the results showed that during the trial recruitment averaged two participants per month (appendix 13 pg 191).

The subsequent audit figures indicate that the initial estimation of patients seen in TIA clinics was probably only slightly higher (3%) than the expected number of TIA's based upon stroke and TIA ratio data from the OXVASC study (Rothwell et al., 2004 a). It appears that the greater discrepancy was in the number of confirmed TIA's deemed eligible for the study. The fact that the diagnosis is based on clinical history and presentation means that there can be quite a wide degree of uncertainty in the diagnostic process. A poor history, no residual clinical features and a number of known stroke and TIA mimics (e.g. seizures, migraine, syncope) mean that quite often patients are classified as a possible or probable TIA and treated pharmacologically even when they are not a definitive classical TIA. Anecdotally it appears that the clinical team were only approaching and recruiting those patients with a confirmed, rather than possible, TIA. If this is the case, then the audit data in appendix 13 suggests that this is approximately 30% of the clinic patients rather than 50% of patients as initially thought. The other underestimation was a higher than anticipated number of patients with a confirmed TIA or minor stroke who had co-morbidities, which subsequently excluded them from the trial. In the planning stage an extra month had been added to the recruitment process to account for these exclusions, which would equate to sixteen per cent of confirmed TIA patients. Examination of the audit data (appendix 13) suggests that as many as 80% of patients could be excluded due to comorbidities.

One further reason for reduced recruitment was an over-estimation of the number of eligible participants who were prepared to take part in the study. The initial pre-study audit (figure 4 pg 67) had indicated that 65% of participants would be

interested in undertaking an exercise and education programme. Of the participants approached in the TIA clinic or on the stroke ward only 45% of those who agreed to consider it actually took part in the trial. It is difficult to be sure as to why this figure was so low but reviewing the reasons given and feedback from the user group suggests that there was a low priority to rehabilitation post TIA due to a perception of low risk and a historical view of TIA's and minor strokes being a 'natural consequence of aging' . This potential low priority for secondary prevention contrasted with the relatively intense commitment required for the intervention, and was thought to be an important factor in the slow recruitment. The lack of available support from the Stroke Research Network and a weak research culture in the clinical setting was also a potential limitation in relation to more research active sites.

Comparison with similar studies is difficult as the two studies (Tang et al., 2010, Lennon et al., 2008) that recruited chronic stroke patients did so on a voluntary community basis. However, the trial by Prior et al., (2011) also recruited consecutive patients from TIA clinics. Interestingly, their data suggests a similar recruitment rate to the Ex4TIA trial with just 22% of patients meeting the selection criteria and 56% of patients consenting.

To counter the low recruitment rate in the Ex4TIA trial, two additional patient identification sites were opened. Unfortunately, without a research presence on either site they were not to prove successful. The implications of the reduced sample size were that a Type II error could have occurred as the study was inadequately powered to demonstrate a difference between the groups. To minimise this risk, all outcomes were analysed on an intention to treat basis. One strength of the study was that data was available for all participants, including those that dropped out of the intervention. This high return rate was attributed to extensive participant information provision. This would be important in any future studies and an example of the participant literature can be seen in appendix 16.

6.6.2 Outcome Measures

As a feasibility study, this trial included a high number of varied physiological and lifestyle measures. Many of the recommendations regarding the suitability of the individual outcome measures have been covered previously (section 6.4). However, two of measures were limited, not by the applicability of the data, but by limitations in the trial design and operating procedures.

The first of these was the primary outcome measure, the Cardiac Risk Score which was to be derived from an algorithm incorporating a number of known risk factors (pg. 61). During data entry it became apparent that triglyceride levels (which are required for the calculation of low density lipoprotein levels) were only reported in 10% of blood samples. This meant that not all the data necessary to populate the CRS algorithm was collected. On reflection, the fact that this missing data was not identified earlier was unintentionally due to a desire to maintain blinding, and unfamiliarity with the pathology laboratory reports which meant that the individual reports were not routinely checked.

The second design limitation was the lack of data from the exercise capacity test. This test was to be conducted using the Astrand Rhyming (1954) procedure and was one of the secondary outcome measures. The test requires the participants to cycle on a static exercise bicycle at a predetermined work rate with their heart rate monitored. If their heart rate reaches a consistent level after six minutes (85% of predicted maximum heart rate) then the test is stopped and the results are extrapolated and applied to an algorithm so that their VO₂ max can be estimated. This test was therefore dependent upon heart rate calculations which proved to be an issue for a number of participants. The association between cardiac and cerebrovascular disease meant that a number of participants had a history of cardiac problems and were on medication to control their heart rate. This pharmacological control of heart rate would give an artificially low heart rate reading and so those participants were excluded from this test (Substantial Amendment appendix 10 pg 187). The fact that the test was also moderately intensive potentially caused adverse events in two of the participants. As a result of these adverse events a Reasonable, Reasoned & Thorough review was

conducted (appendix 15 pg 194). The outcome of the review was that the standard operating procedures for the test were changed to exclude any participants with a history of cardiac disease or with any abnormalities on their ECG recording. This meant the complete data sets were only produced for two of the twenty four participants.

6.6.3 The Hawthorne effect

The effect of participants responding to being in an experiment rather than any of the changes being as a direct result of an intervention itself can create a Hawthorne effect (Torgerson et al., 2008). This may have had an influence on the results from this trial as participants were not blinded as to which arm of the trial they were in and there were considerable differences in the amount of staff contact between the intervention and control arm of the trial. However, as one intentional aspect of the intervention is increased staff contact it could be argued that if the results do show a significant change between groups this is not a type 1 error but actually the intended outcome of the intervention.

6.6.4 Bias

Biases can give an incorrect estimate of effect (Torgerson et al., 2008) and must therefore be minimised in the study design and reported in the study analysis. To counter potential biases, participants were randomly assigned to either group to safeguard against recruitment bias and allow for comparisons to be made. Collection of outcome data was also restricted, being undertaken solely by the research nurses at the Wellcome Trust Clinical Research Facility. This reduced the risk of ascertainment bias as the nurses were not involved in the design, analysis or presentation of the results.

However, despite these precautions, a number of potential biases could have occurred in the study. Participation in intensive trials such as cardiac rehabilitation can be biased towards age, gender and socio-economic groups (Mosenifar, 2007). The issue of health inequalities is a considerable problem for public health provision and in obtaining generalisable trial results. The implications for this study

was the potential for a natural selection bias to occur, as the majority of participants entering the study may have been the 'worried well' who are naturally more inclined to undertake health initiatives to reduce the risks associated with cardiovascular disease. This is perhaps an unavoidable bias in this type of study and in public health in general. Whilst this bias cannot necessarily be avoided, a recommendation for future studies would be to use a form of socio-economic data gathering and modelling so that this suspected bias can at least be quantified, if not mitigated.

6.7 Recommendations for future trials

As a feasibility trial, this study indicated that it was both safe and appropriate to conduct an RCT involving TIA and minor stroke patients in cardiac rehabilitation programmes. However, a number of valuable lessons have been learnt which would strengthen any future definitive trial. The following section highlights the main recommendations, which focus on recruitment, the use of outcome measures and piloting of standard operating procedures prior to trial commencement.

6.7.1 Recruitment recommendations

The possible reasons for the slow recruitment rate in this study have been addressed in section 6.6.1. The implications and recommendations for future trials are that:

- A multi-site trial is undertaken. This will require collaboration with the cardiac rehabilitation teams so that a local cardiac rehabilitation programme is available for all participants.
- The TIA clinical team are encouraged to recruit all patients classified as a possible, as well as probable TIA as long as they have one elevated risk factor (O'Donnell and Xavier, 2010). Whilst this could potentially reduce the specificity of the results, until further epidemiological data is available for TIA patients it is not possible to associate clinical presentation with secondary risk (Rothwell, 2005 b)

- The phase III cardiac rehabilitation programme includes stroke specific talks and literature.
- Obtain support for recruitment from the local Stroke Research Network

A power calculation for future trials was conducted with an on-line calculator (Lenth, 2012). Using the results from the primary outcome (CVD score) a two tailed test with a difference of means of 4.64, a combined standard deviation of 6.59 and a power of 90% and significance of 5%, indicates a future study would need to recruit a total of 88 participants. Allowing for a 25% drop out rate, 55 participants would need to be recruited in each group (110 in total). On the basis of the recruitment experience of this trial (section 6.6.1), for a trust with 500 TIA clinic patients per annum it would take approximately 50 months to recruit 110 participants. We would therefore recommend that 6 sites would be required to participate in a year long trial.

6.7.2 Outcome measure recommendations

As a feasibility trial, a large number of outcome measures were taken and their results and the implications of these have been covered in previous sections. The majority of outcomes in this trial provided important and appropriate information. However, subjecting participants to unnecessary investigations has ethical implications, and the following section outlines the main recommendations following this trial.

- Primary Outcome: Ideally, mortality and morbidity figures with a five year follow up would allow for a direct comparison with data from the cardiac rehabilitation studies. These data should be collected in future trials along with risk scores. Such scores are increasing in number as they provide useful quantifiable information. In addition to the limitations discussed in section 6.6.2, future scores will have increased validity if based on the UK population.

- The inclusion of a socio-economic data alongside, or separate from, the risk score would also provide important information on the known relationship between cardiovascular risk and social demographics (Redfern et al., 2000)
- Extending the data collection period: Data from the cardiac rehabilitation trials suggests that the secondary preventative effect (Jolliffe et al., 2001, Clark et al., 2005a), and effect on outcomes such as depression, change over time. It is therefore recommended that an annual follow up be undertaken for up to five years.
- Self-efficacy and readiness to change scores are incorporated.
- Biomarkers: The collection of biomarkers such as hsCRP or fibrinogen should not be undertaken until further evidence of causation is available.
- Activity levels: This feasibility trial suggests that the cardiac rehabilitation programme may be an effective means for reducing future vascular events. This was despite the fact that it only provided one structured session of exercise per week for a 6 – 8 week period. This is below the ACSM (2000) recommended level of exercise and that provided in similar trials (Lennon et al., 2008, Prior et al., 2011). However, it was not clear how much exercise participants took outside of the intervention. In future trials the use of an exercise diary may help with the calculation of an exercise dose response and also negate the need for the retrospective self-reported measures of activity questions.
- Exercise capacity: To include a more practical form for assessing exercise capacity such as the incremental shuttle walk test (Ramsbottom et al., 1988, Keell et al., 1998).
- Discontinue with the collection of the HAD score.
- Ensure collection of triglycerides for the calculation of LDL.
- Collect Hb1AC in addition to fasting blood glucose.

6.7.3 Standard Operating Procedures

In accordance with Good Clinical Practice guidelines standard operating procedures had been devised and reviewed by all the research staff involved in the trial (pg 72). However, lessons were learnt from this trial which would improve the implementation of operating procedures in a follow up trial. As highlighted in section 6.6.2, two of the outcome measures (LDL cholesterol and exercise capacity) could not be collected due to limitations in the trial design and operating procedures. In both instances, had the procedures been fully piloted with an age matched individual it is likely that the issues regarding the suitability of the exercise capacity test and pathology collection procedures would have been apparent before the trial began, An additional recommendation to piloting the assessments would be the implementation of a prospective data checker that is independent to the trial analysis. This role would ensure that any errors in data collection are picked up and reported immediately.

6.8 Implications for the future

The results from this feasibility trial contribute to the expanding knowledge base of alternative methods for secondary prevention post minor stroke and TIA. However, this is just one of many steps required to improve the long term health status of patients post stroke.

This trial was conducted following a systematic process analogous to the original and updated guidance for developing and evaluating complex interventions (Medical Research Council, 2000, Medical Research Council, 2008). The following section summarises the process and the knowledge gained along the way and the implications for future research and clinical practice.

The updated MRC guidance for complex interventions provides a template for developing and evaluating such interventions (Figure 7). This is a more fluid process than the original guidance and there is an acknowledgement that the process may not necessarily always follow a linear or even cyclical sequence.

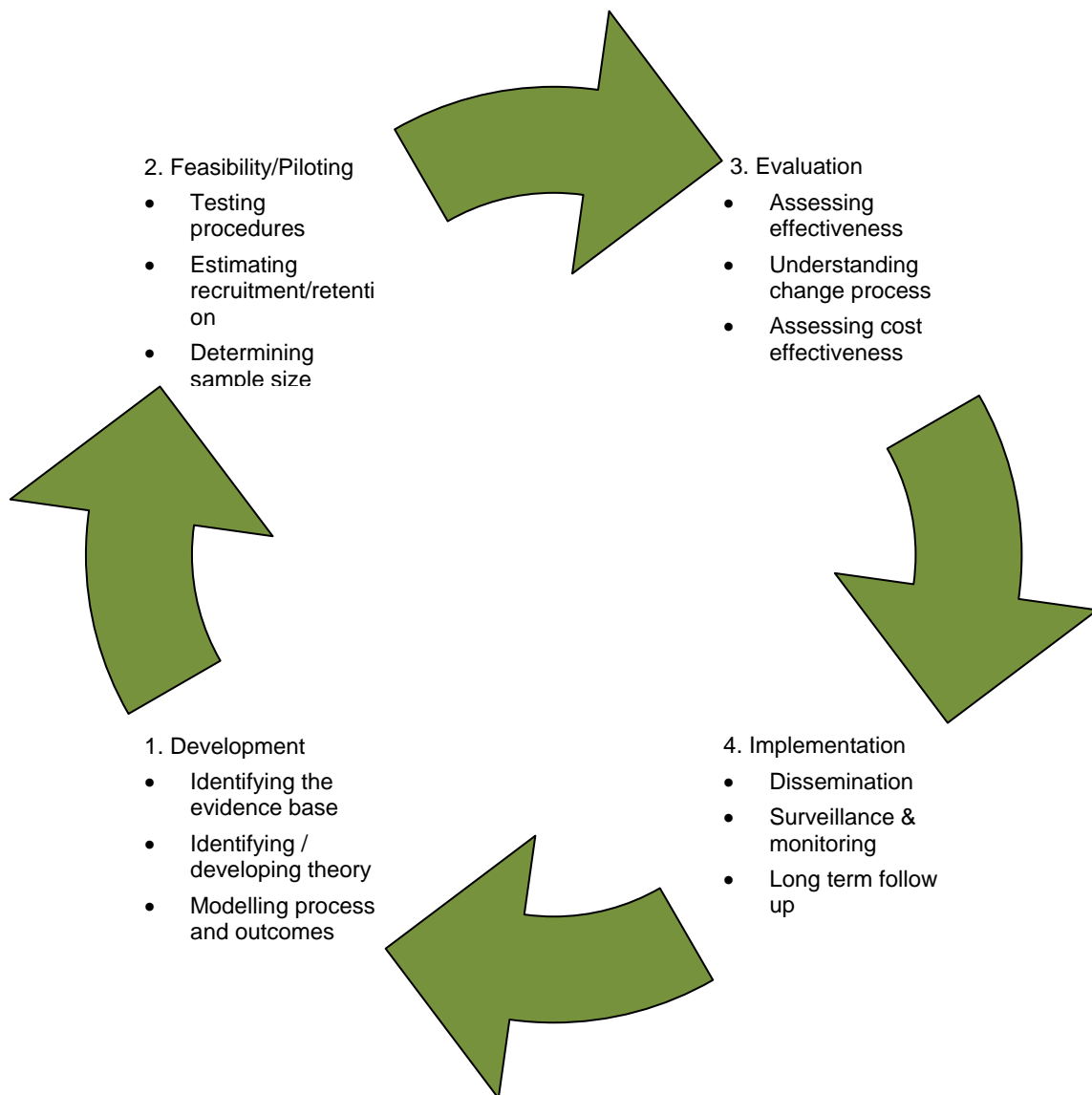


Figure 7 Key elements for research development and evaluation

In accordance with the developmental stage of the MRC process, Chapter One of the thesis provided a summary of the health care environment and clinical situation for the management of strokes and TIA's at the time when the research question was first proposed. This highlights the apparent inequity in treatment between cardiac and stroke secondary prevention. The inequity in treatment posed the first question which was whether there was a clinical rationale for these differing approaches to secondary prevention. Chapter Two sought to address this question by examining the pathophysiology for stroke and cardiac disease. This concluded that there were differences in the pathophysiology between stroke and cardiac disease with a greater predominance of large vessel disease in cardiac

patients. However, despite differences in the weighting of these risk factors both ischaemic strokes and coronary heart disease were found to share much the same lifestyle risk factors and atherosclerotic disease process.

Chapter Three sought to address a number of questions. The first was whether cardiac rehabilitation was an effective means of secondary prevention and if so, what form would be most suitable for this trial. The second question was whether there was any evidence that this effect could realistically be expected to translate to stroke patients. The evidence for the first of these questions showed that cardiac rehabilitation was an effective means of secondary prevention with consistent reductions in mortality. Though much of this evidence is now quite dated and changes in risk factors and quality of life measures were inconsistent or inconclusive, the reductions in mortality provide the evidence base upon which most cardiac rehabilitation services are developed. The second question examined the literature regarding lifestyle programmes for secondary stroke prevention. The strongest evidence for the potential to translate the benefits of cardiac rehabilitation programmes to the stroke community was the primary prevention exercise based studies. In contrast the literature suggested that additional educational based stroke behavioural change programmes often showed an increase in knowledge but these rarely translated to consistent improvements in cardiovascular risk factors.

The second MRC feasibility and piloting phase reflected the methodology and results section in chapters four and five. The MRC recognise that 'a key question in evaluating a complex intervention is about practical effectiveness - whether the intervention works in everyday practice' (Medical Research Council, 2008). This was felt to be a particular strength of this trial as the intervention was an already established NHS service. Sample size was calculated on the basis of a similar trial and recruitment rates were piloted post TIA clinic. The data from this study were sufficient to provide an indication of both feasibility and effectiveness. The results in chapter five suggest that cardiac rehabilitation programmes were potentially more effective in reducing cumulative risk (CVD score) and improving HRQoL and activity levels than standard care. Whilst existing NHS cardiac rehabilitation programmes were a feasible intervention for TIA and minor stroke patients,

recruitment in a trial environment was considerably slower than anticipated and chapter six outlined the adaptations to outcome measures and educational material which would be recommended in any future trials.

As is often the case in trying to answer one question, numerous other questions are developed. In this instance the question as to the path that future research should take has led to much debate. The traditional academic model and MRC guidance (2008) would suggest progressing to a definitive trial. However, for ethical, practical and clinical reasons it is important to first consider whether there is a need for further research in this field, and if so what form should this research take?

In trying to address the above question it is the author's opinion that there are three options that need to be considered. The following paragraphs highlight the rationale for each option based on the evidence from the trial and with acknowledgement to the clinical environment.

6.8.1 Option I

In line with the framework for the development and evaluation of RCTs for complex interventions it would appear appropriate to proceed from the feasibility trial to a definitive RCT. The positive findings from the trial allied to the high risk of recurrent vascular events (van Wijk et al., 2005) and the sub-optimal (Redfern et al., 2002, Rudd et al., 2004, Ramsay et al., 2007, Saposnik et al., 2009) secondary prevention programmes that currently exist post TIA and minor stroke clearly show that there is a clinical need for interventions that improve secondary prevention post stroke. These results, combined with results from similar trials, (Lennon et al., 2008, Prior et al., 2011) suggest that cardiac rehabilitation programmes potentially offer improved secondary preventative benefits for stroke patients in comparison to standard care. In order to develop a similar evidence base to that found in cardiac rehabilitation, the recommendation for option I would be to conduct larger multi-centre trials based on the format of the Ex4TIA trial and subsequent recommendations (pg 132). Based on the evidence from the cardiac rehabilitation literature, with mortality data as the main outcome measure, larger studies with in

excess of 4,000 participants will be necessary to ascertain a true cause and effect (O'Connor et al., 1989).

6.8.2 Option II

The second option is to say no to larger trials and to progress straight to the development of clinical services. This option is based on the premise that there is sufficient evidence of similarities in the cardiac and stroke disease processes that a successful treatment for one disease is likely to prove successful for the other (Gordon et al., 2004, Mead, 2009). Whilst there are acknowledged differences in the pathology of the diseases, primary prevention exercise data (Lee et al., 2003, Wendel-Vos et al., 2004) and the reduction in all-cause mortality (Jolliffe et al., 2001) post cardiac rehabilitation make a strong case that the benefits of lifestyle changes will be equally as applicable to stroke patients as to cardiac patients. If the evidence from this trial and other similar small trials substantiates the argument for cardiac rehabilitation style programmes for stroke patients, then it may be the case that future research should be observational, addressing the issues of access and clinical effect rather than proof of clinical concept (Horn et al., 2005).

6.8.3 Option III

The third option for further research is that an epidemiological study be undertaken first to develop a clinically and socially robust algorithmic risk measure based on secondary risk factors. Previous experience in stroke care has shown how a lack of data on prognosis can be the main barrier to effective treatment in routine practice (Rothwell, 2006 b). Whilst there are an increasing number of primary vascular risk scores; CRS (Wilson et al., 1998), CVD (D'Agostino et al., 2008), QRISK (Hippisley-Cox et al., 2008), ETHRISK (Brindle et al., 2006), these have not been validated for older patients or secondary events. Evidence of the overlap in the patient attributable risk (PAR) from the INTERSTROKE and INTERHEART studies indicates that the modifiable risk factors act in a combined manner which is not fully understood. This correlates with the cardiac rehabilitation trial data which

shows that risk factors, as individual proxy measures, are a poor indicator of risk or mortality. Option III would therefore seek to provide a robust measure which could be used in both the clinical and research environment and negate the need for large costly mortality based studies.

6.8.4 Options Appraisal:

In reality, a combination of both larger trials (option I) and service development programmes (option II) are already taking place. Definitive trials based on the Prior et al.,(2011) and Lennon et al., (2008) pilot trials, are due to be published and presentation of these results - CRAFTS trial (Lennon and Blake, 2009) and PREVENT (MacKay-Lyons M et al., 2010) will provide empirical data to help substantiate the clinical relevance of cardiac rehabilitation for stroke patients. The data from these trials will provide evidence of a change in cardiovascular risk (Lennon and Blake, 2009) as well as changes in each of the individual risk factors and health related quality of life measures (Lennon and Blake, 2009, MacKay-Lyons M et al., 2010). With an extended follow period of 12 months the PREVENT trial will also provide preliminary data on vascular event rates. However, experience from the cardiac meta-analysis would suggest that substantially greater numbers than the proposed 200 participants will be required to ascertain a true cause and effect.

The data from these trials is likely to be very important and will provide both operational data (i.e. recruitment and drop out rates) and outcome data which will influence the design and scale of the follow on trial from this study. The results will also provide additional data which will help establish the 'hard evidence' required to break down the barriers that currently surround the cardiovascular silos of cardiac and stroke care. At the same time lessons learnt from current exercise based service development initiatives in Scotland (Mead, 2009) and Cornwall will hopefully be fed back to the broader stroke community to inform the necessary service configurations for this patient group.

However, based on the experiences to date there are three fundamental limitations in proceeding straight to options I and II :

1. Justifying the financial outlay.
2. Accounting for the introduction of new confounding variables
3. Evaluating different models of complex rehabilitation initiatives

From a financial perspective RCT's, as exemplified in option 1, can be ethically criticised for their financial costs (Horn et al., 2005, Yang et al., 2010). This was apparent when reviewing the experience of the cardiac rehabilitation trialists which suggests that proceeding directly to larger mortality based trials could take up to thirty years and cost many millions of pounds to produce a definitive and accepted body of evidence.

Whilst the time and money may be ethically justified if a definitive body of evidence is produced, the second and third limitations listed above would cast doubt about the definitive nature of this work. When reviewing the development of the body of evidence for cardiac rehabilitation it became apparent that the extended period of research and the natural progress of medicine meant that by the time the evidence was established it was automatically out of date due to the introduction of confounding variables. In conventional medicine this is not such a problem, as when new interventions come along they are compared to the previous gold standard and are adopted if of proven benefit. However, whilst this theory appears to work well for pharmacological therapies, it does not translate so easily for surgery or complex service orientated interventions. The solution to this is to always conduct further trials. This occurred with cardiac rehabilitation following the regular introduction of statins, PCI's and ACE inhibitors, and was evaluated by Taylor et al., (2004) in their meta-analysis of cardiac rehabilitation. However, even in this meta-analysis a high proportion of the original data pre-dated the use of statins, PCI's and ACE inhibitors. As such the evidence base is likely to be weaker than it may appear and will need further updating in due course.

The third difficulty relates to the 'black box' problem posed by trying to evaluate the different models and components of complex research or service based interventions. A criticism of the MRC (2008) framework is that it assumed that interventions that follow the research and development guidance will reach a point

of stability (Mackenzie et al., 2010). In reality, complex organisational systems are characterised by flux, contextual variation, and adaptive (or possibly maladaptive) learning rather than stability (Mackenzie et al., 2010). Clinical experience from both the cardiac rehabilitation and stroke early supported discharge trials shows that implementation in real life rather than the 'bounded constraints' of a randomised trial can result in large departures from the intervention protocols which are not seen in less complex interventions. This creates an inability to define a dose response or cost benefit and so services are often configured on clinical preference rather than on evidence.

The costs and difficulties associated with researching complex interventions as listed above has meant that many clinicians and policy makers have traditionally progressed straight to service implementation as outlined in option II. This has the advantage over RCT's of low start-up costs, immediacy and the development of services in real world settings. Despite these advantages, such interventions are often criticised for their poor evidence of clinical and cost effectiveness (House of Commons Health Committee, 2009) and as such are at risk of being cut due to their weak evidence base. To increase the validity of such services, observational research studies have been proposed as a means of opening the 'black box' of complex rehabilitation interventions (DeJong et al., 2005). These studies allow for services to be evaluated in the real world environment where multiple variables and external factors can affect outcomes (Horn et al., 2005). This can account for the introduction of new confounding variables and provide a means of evaluating different models of rehabilitation. However, these studies do not prove causality (Horn et al., 2005, Yang et al., 2010) which is an essential requirement in an increasingly evidence based environment.

In order to address the limitations of options I and II, the development of a secondary preventive cardiovascular prognostic tool (algorithmic risk measure) through epidemiological research (option III) may first be necessary. Such a measure would provide a cost effective means of evaluating an intervention (option I) or service (option II). This would enable the evidence base to be regularly updated to account for the introduction of new variables. It would also

allow for new and existing services to be refined and benchmarked against a stable marker/outcome measure. It is therefore the author's opinion that option III would provide the greatest benefit to the clinical and scientific environment and should be a priority for future research in this field.

6.9 Summary

Current secondary prevention strategies for stroke patients are sub-optimal and reliant upon pharmacological therapies for managing a lifestyle related disease. The origins of the research were derived from increasing awareness of the shared risk factors and atherosclerotic pathology affecting cardiac and stroke patients. This led to the development of the clinical question as to whether TIA and minor stroke patients may benefit from a cardiac rehabilitation programme.

This is the first trial to demonstrate that it is feasible to conduct a single blinded randomised controlled trial requiring TIA and minor stroke patients to participate in an existing NHS cardiac rehabilitation programme. Despite the limited sample size the results suggest that relative to standard care, comprehensive cardiac rehabilitation could significantly improve cardiovascular risk, patient activity levels and health related quality of life post stroke.

Based on the evidence and experience from this study it is recommended that further research is conducted to ensure that future treatment is determined by need rather than historical clinical and cultural silos. It is the conclusion of this study that research into the development of a secondary preventive prognostic tool should be conducted as a priority, prior to proceeding to a definitive trial and subsequent observational studies.

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Appendix 1 Literature Search Criteria

Stroke and exercise/ health behaviour

#	Query	Limiters/Expanders	Last Run Via	Results
S13	S7 and S12	Limiters - Published Date from: 19900101-20081231; English Language; Exclude MEDLINE records; Human; Age Groups: All Adult Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	156
S12	S8 or S9 or S10 or S11	Search modes - Boolean/Phrase	CINAHL	352971
S11	lifestyle change	Search modes - Boolean/Phrase	CINAHL	350
S10	Health Behaviour	Search modes - Boolean/Phrase	CINAHL	17281
S9	exercise	Search modes - Boolean/Phrase	CINAHL	59400
S8	education	Search modes - Boolean/Phrase	CINAHL	290262
S7	S1 or S2 or S3 or S4 or S5 or S6	Search modes - Boolean/Phrase	CINAHL	32419
S6	tia	Search modes - Boolean/Phrase	CINAHL	545
S5	transient ischaemic attack	Search modes - Boolean/Phrase	CINAHL	147
S4	transient ischemic attack	Search modes - Boolean/Phrase	CINAHL	718
S3	cva	Search modes - Boolean/Phrase	CINAHL	342
S2	cerebrovascular accident	Search modes - Boolean/Phrase	CINAHL	480
S1	stroke	Search modes - Boolean/Phrase	CINAHL	32056

Stroke and Cardiac Rehabilitation

#	Query	Limiters/Expanders	Last Run Via	Results
S14	S7 and S13	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	17
S13	S11 and S12	Limiters - Published Date from: 19900101-20081231; English Language; Exclude MEDLINE records; Human; Age Groups: All Adult Search modes - Boolean/Phrase	CINAHL	265
S12	rehabilitation	Search modes - Boolean/Phrase	CINAHL	77177
S11	S8 or S9 or S10	Search modes - Boolean/Phrase	CINAHL	114235
S10	myocardial	Search modes - Boolean/Phrase	CINAHL	30811
S9	cardiac	Search modes - Boolean/Phrase	CINAHL	38622
S8	heart	Search modes - Boolean/Phrase	CINAHL	81776
S7	S1 or S2 or S3 or S4 or S5 or S6	Search modes - Boolean/Phrase	CINAHL	32419
S6	tia	Search modes - Boolean/Phrase	CINAHL	545
S5	transient ischaemic attack	Search modes - Boolean/Phrase	CINAHL	147
S4	transient ischemic attack	Search modes - Boolean/Phrase	CINAHL	718
S3	cva	Search modes - Boolean/Phrase		342
S2	cerebrovascular accident	Search modes - Boolean/Phrase	CINAHL	480
S1	stroke	Search modes - Boolean/Phrase	CINAHL	32056

Cardiac Rehabilitation

#	Query	Limiters/Expanders	Last Run Via	Results
S12	cardiac rehab*	Limiters - Published Date from: 19900101-20081231; English Language; Exclude MEDLINE records; Age Groups: All Adult Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	155
S11	S4 and S10	Limiters - Published Date from: 19900101-20081231; English Language; Randomized Controlled Trial Search modes - Boolean/Phrase	CINAHL	49
S10	S5 or S6 or S7 or S8 or S9	Search modes - Boolean/Phrase	CINAHL	415623
S9	counseling	Search modes - Boolean/Phrase	CINAHL	19808
S8	counselling	Search modes - Boolean/Phrase	CINAHL	4810
S7	education	Search modes - Boolean/Phrase	CINAHL	290262
S6	exercise	Search modes - Boolean/Phrase	CINAHL	59400
S5	rehabilitation	Search modes - Boolean/Phrase	CINAHL	77177
S4	S1 or S2 or S3	Search modes - Boolean/Phrase	CINAHL	114235
S3	myocardial	Search modes - Boolean/Phrase	CINAHL	30811
S2	cardiac	Search modes - Boolean/Phrase	CINAHL	38622
S1	heart	Search modes - Boolean/Phrase	CINAHL	81776

Stroke and exercise/ health behaviour

#	Query	Limiters/Expanders	Last Run Via	Results
S13	S7 and S12	Limiters - Date of Publication from: 19900101-20081231; English Language; Human; Age Related: All Adult: 19+ years; Publication Type: Meta-Analysis, Review Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE	213
S12	S8 or S9 or S10 or S11	Search modes - Boolean/Phrase	MEDLINE	800151
S11	lifestyle change	Search modes - Boolean/Phrase	MEDLINE	746
S10	Health Behaviour	Search modes - Boolean/Phrase	MEDLINE	29412
S9	exercise	Search modes - Boolean/Phrase	MEDLINE	193737
S8	education	Search modes - Boolean/Phrase	MEDLINE	608042
S7	S1 or S2 or S3 or S4 or S5 or S6	Search modes - Boolean/Phrase	MEDLINE	145634
S6	tia	Search modes - Boolean/Phrase	MEDLINE	5386
S5	transient ischaemic attack	Search modes - Boolean/Phrase	MEDLINE	839
S4	transient ischemic attack	Search modes - Boolean/Phrase	MEDLINE	3434
S3	cva	Search modes - Boolean/Phrase	MEDLINE	1541
S2	cerebrovascular accident	Search modes - Boolean/Phrase	MEDLINE	2596
S1	stroke	Search modes - Boolean/Phrase	MEDLINE	139330

Stroke and Cardiac Rehabilitation

#	Query	Limiters/Expanders	Last Run Via	Results
S14	S7 and S13	Limiters - Date of Publication from: 19900101-20081231; English Language; Age Related: All Adult: 19+ years; Publication Type: Meta-Analysis, Randomized Controlled Trial Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE	81
S13	S11 and S12	Limiters - Date of Publication from: 19900101-20081231; English Language; Human Search modes - Boolean/Phrase	MEDLINE	6389
S12	rehabilitation	Search modes - Boolean/Phrase	MEDLINE	218848
S11	S8 or S9 or S10	Search modes - Boolean/Phrase	MEDLINE	1168763
S10	myocardial	Search modes - Boolean/Phrase	MEDLINE	304861
S9	cardiac	Search modes - Boolean/Phrase	MEDLINE	467154
S8	heart	Search modes - Boolean/Phrase	MEDLINE	888599
S7	S1 or S2 or S3 or S4 or S5 or S6	Search modes - Boolean/Phrase	MEDLINE	145634
S6	tia	Search modes - Boolean/Phrase	MEDLINE	5386
S5	transient ischaemic attack	Search modes - Boolean/Phrase	MEDLINE	839
S4	transient ischemic attack	Search modes - Boolean/Phrase	MEDLINE	3434
S3	cva	Search modes - Boolean/Phrase	MEDLINE	1541
S2	cerebrovascular accident	Search modes - Boolean/Phrase	MEDLINE	2596
S1	stroke	Search modes - Boolean/Phrase	MEDLINE	139330

Cardiac Rehabilitation



#	Query	Limiters/Expanders	Last Run Via	Results
S18	S15 or S17	Search modes - Boolean/Phrase	EBSCOhost MEDLINE	130
S17	S14 and S16	Search modes - Boolean/Phrase	MEDLINE	89
S16	meta-analysis	Limiters - Date of Publication from: 19800101-20081231; English Language; Age Related: All Adult: 19+ years Search modes - Boolean/Phrase	MEDLINE	5022
S15	S12 and S13	Limiters - Date of Publication from: 19800101-20081231; English Language; Age Related: All Adult: 19+ years; Publication Type: Meta-Analysis Search modes - Boolean/Phrase	MEDLINE	97
S14	S12 and S13	Search modes - Boolean/Phrase	MEDLINE	100696
S13	S7 or S8 or S9 or S10 or S11	Search modes - Boolean/Phrase	MEDLINE	1009248
S12	S1 or S2 or S3 or S4 or S5 or S6	Search modes - Boolean/Phrase	MEDLINE	1327474
S11	counseling	Search modes - Boolean/Phrase	MEDLINE	57196
S10	counselling	Search modes - Boolean/Phrase	MEDLINE	14394
S9	education	Search modes - Boolean/Phrase	MEDLINE	608042
S8	exercise	Search modes - Boolean/Phrase	MEDLINE	193737
S7	rehabilitation	Search modes - Boolean/Phrase	MEDLINE	218848
S6	coronary disease	Search modes - Boolean/Phrase	MEDLINE	183258
S5	ischemia	Search modes - Boolean/Phrase	MEDLINE	166277
S4	ischaemia	Search modes - Boolean/Phrase	MEDLINE	19985
S3	myocardial	Search modes - Boolean/Phrase	MEDLINE	304861
S2	heart	Search modes - Boolean/Phrase	MEDLINE	888599
S1	cardiac	Search modes - Boolean/Phrase	MEDLINE	467154

Appendix 2 Updated Literature Search Criteria

The original literature searches (appendix 1) were re-run for the period December 2008 to March 2012. The below table provides a summary of the final search results.

Search Criteria	Database	Results
Stroke and exercise / health behaviour	CINAHL	84
Stroke and cardiac rehabilitation	CINAHL	113
Cardiac rehabilitation	CINAHL	55
Stroke and exercise / health behaviour	MEDLINE	0
Stroke and cardiac rehabilitation	MEDLINE	0
Cardiac rehabilitation	MEDLINE	11

Appendix 3 Stroke physician checklist for study eligibility

 <p>University Hospitals NHS Trust</p>	<div style="border: 1px solid black; padding: 5px; display: inline-block;"> Appendix 1 Ex4TIA Trial </div>	
<u>Stroke physician checklist for consideration of study eligibility</u>		
		YES NO
1. Diagnosis (within 1 month of incident)		
a. TIA - resolution of symptoms <24 hours of onset (not suspected PFO)	<input type="checkbox"/>	<input type="checkbox"/>
b. (OR) minor stroke- NIHSS* score <3	<input type="checkbox"/>	<input type="checkbox"/>
2. Lives within geographic locality (see below GP postcodes)		
SO 14, 15, 16, 17, 18, 19, 30, 31, 32, 33, 40, 41, 42, 43, 45, 50, 51, 52, 53, BH 25	<input checked="" type="checkbox"/>	<input type="checkbox"/>
3. Independently mobile (can use stick but no falls within 2 months)		
	<input checked="" type="checkbox"/>	<input type="checkbox"/>
4. No significant visual / speech impairment		
	<input checked="" type="checkbox"/>	<input type="checkbox"/>
5. Cognitive capacity to undertake group exercises (no apparent dementia*)		
	<input checked="" type="checkbox"/>	<input type="checkbox"/>
6. Able to give verbal and written consent		
	<input checked="" type="checkbox"/>	<input type="checkbox"/>
7. Age >18yrs		
	<input checked="" type="checkbox"/>	<input type="checkbox"/>
8. Considered medically Fit for Exercise (SIGN* 2002 guidance)		
	<input checked="" type="checkbox"/>	<input type="checkbox"/>
9. No previous experience of cardiac rehabilitation		
	<input checked="" type="checkbox"/>	<input type="checkbox"/>
10. No current or recent participation in research.		
	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<p>If the patient scores any NO's (other than 1.a or 1.b) then please document but do not give study invitation letter. If scores are all YES's then please inform the patient of the EX4TIA study, provide them with study invitation letter and ask if they would mind being phoned by the university researcher to answer any questions they may have and ascertain if they would like to be involved in the study.* Please see accompanying documentation sheet for</p> <ul style="list-style-type: none"> - National Institute for Health Stroke Scale (NIHSS) - Mini Mental Test (MMT) if doubts regarding cognitive capacity - SIGN Exercise Risk Guidelines 2002 		
<div style="display: flex; justify-content: space-between;"> <div> Patients details (Apply stick label): </div> <div> Clinic date: / / </div> </div> <div style="margin-top: 5px;"> Name _____ </div> <div style="margin-top: 5px;"> Contact Details _____ </div>		

Participant Information Sheet

A study evaluating if cardiac rehabilitation is effective in reducing risk factors post TIA?

We would like to invite you to take part in a research study.

Before you decide if you would like to participate, it is important for you to understand why the research is being done and what is involved. Please take time to read the following information carefully.

What is the purpose of the study?

Stroke is a common condition with one occurring every 5 minutes in the UK and about one in six people having a stroke at some point in their life. Transient ischaemic attacks (TIA's) are warning signs of a stroke and indicate risk of stroke and heart disease is increased. There is overwhelming evidence that control of the risk factors following a stroke or TIA reduces the risk of a subsequent stroke. Risk factors include certain lifestyle choices such as smoking, diet, physical activity, and alcohol consumption, as well as medical conditions such as high blood pressure, high cholesterol, and diabetes. This study will help us to establish whether a different approach to addressing risk factors is beneficial for patients following a TIA or stroke.

Why have I been invited?

You have been invited to participate in the study as you have been diagnosed as having a minor stroke or TIA within the past month.

Do I have to take part?

That is up to you to decide. We will describe the study and guide you through this information sheet with you, trying to answer any questions that you may have. If after reading this you are still interested we will ask you to sign a consent form to

show you have agreed to take part; a copy of the consent form will be given to you, one will be placed in your medical notes, and one will be retained by the researcher.

Participation in the study will not affect your usual standard of medical care or stroke clinic follow up in any way. Your participation is voluntary and you are free to withdraw at any time without giving reason and without your medical care or rights being affected.

Please ask if anything is not clearly explained in this document or if you would like more information. Take your time to decide whether or not you wish to take part and discuss it with others if you wish.

What will happen if I take part?

The study is a randomised controlled trial which means we are comparing different management approaches after stroke /TIA to find out if one is better for reducing risk factors related to stroke and cardiac disease

Within the study each patient is randomly assigned to one of two groups, each of which will receive standard advice. This involves relevant clinical investigations, lifestyle advice, changes to medication as appropriate and follow up by the GP. One of the groups (intervention group) will additionally undertake an exercise and education programme (commonly referred to as Cardiac Rehabilitation). Those patients that are assigned to this (intervention) group will be contacted by the Southampton cardiac rehabilitation nurses and enrolled in their established cardiac rehabilitation programme. This requires attendance of eight, 2 hour sessions, once a week at Bitterne Leisure centre or Fleming Park in Eastleigh –(whichever is closest for you). These sessions are run by the nurses for individuals similar to yourself and involves light to moderate levels of exercise and interactive educational sessions about such topics as medication, TIA's, lifestyle and exercise. In accordance with clinical trial practice, you will not know which group you are in at your initial assessment and will have a 50% chance of being assigned to either group after this assessment. However we do not know at this stage whether the additional exercise and educational support is of any benefit.

This study will operate from April 2009 to August 2010, but each participant's involvement will be for only five months. For all participants we will need to collect data when they start and finish the trial so that we can assess if the standard care or Cardiac Rehabilitation was more effective. This would include two, 2 hour hospital out-patient appointments at the Wellcome Trust Clinical Research Facilities, Southampton General Hospital. At these appointments a number of measures will be taken relating to risk factors associated with vascular disease. This will involve:

- Completing a questionnaire with the help of the research nurses about lifestyle factors such as smoking, diet, quality of life and mood state (You will not be under any obligation to share sensitive or embarrassing topics).
- Research nurses taking a sample of blood.
- Undertaking an evaluation of your current fitness levels by completing a six minute exercise test on a static bicycle trainer. For this test you will only be required to work at up to 85% of your maximal capacity and data from this will allow us to estimate what your maximal capacity would be. If however you are currently taking a Beta Blocker (heart medication such as Atenolol) you will not be asked to complete this exercise.
- A number of participants will also be asked to have a discussion with a researcher about their experiences during the trial. This will take up to one hour and will take place in the month following the last visit to the Wellcome Trust at a time and location convenient to you.

Expenses and payments

Travel costs (via public transport or car mileage – 47p per mile) and parking expenses for attending the Welcome Trust will be paid for by the researchers. Similar travel costs for those attending the exercise and education training programme will also be paid for by the researchers. The exercise and education training programmes will run at Bitterne Leisure Centre and Fleming Park leisure centre (Eastleigh) and participants are able to choose whichever location is more

convenient for them. After the above structured exercise programmes participants will have the option of continuing their exercises with health referral schemes run at local leisure centres. These are run at a reduced rate (typically half price) and the cost for these optional sessions will need to be met by the participants.

What are the possible disadvantages and risks of taking part?

You will need to attend two additional hospital appointments but there should be no risk to you in participating in the study. The advice and support you receive following your minor stroke or TIA will not be compromised in any way regardless of the group you are randomised to.

What are the possible benefits of taking part?

We cannot promise the study will help you, but the information we get from this study will help improve the treatment of people with minor stroke and TIA.

What if there is a problem?

If you have any concerns about any aspect of the way you have been approached or treated during the course of this study, please, in the first instance, discuss them with the researcher - Hayden Kirk (07799340839), who will do his best to answer your questions. If the problems are not resolved or you wish to comment formally please contact the normal National Health Service complaints mechanism – PALS (number below).

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Information and data collected about you will be anonymous and any information will be dealt with in such a way that no unauthorised person will have access to them under the Data Protection Act (1998).

Involvement of your General Practitioner (GP)

With your permission, your GP will be informed of your inclusion in the study and will be given information about the study design but will not be aware of the detail of your involvement in the study.

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

You are free to withdraw from the study at any time and without giving a reason. This will not affect your usual medical care or rights in any way. You also have the option to withdraw from the study but keep in contact with us to let us know your progress. Information collected about you may still be used.

What will happen to the results of the research study?

The results of this study may be published in a scientific journal and/or presented at a scientific conference. No individual will be identified in any report or publication. If you are interested in the outcomes of the study you can obtain a copy of the results from Hayden Kirk at the end of the study.

Who is organising and funding the research?

The study is funded by the Physiotherapy Research Foundation and the Private Physiotherapy Education Foundation and organised by the University of Southampton with the support of Southampton University Hospital NHS Trust and Southampton PCT. The study is being undertaken as part of a Doctoral degree. Those undertaking the research receive no additional payment for doing so.

Who oversees the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Southampton and South West Hampshire Research Ethics Committee and the Research & Development departments at Southampton City PCT and Southampton University Hospital Trust.

Further information and contact details

- ***For specific information about this study***

Hayden Kirk

07799340839

- ***For independent advice about participating in the study***

Research and Development dept

023808777222 x8591

- ***Who to approach if concerned about the conduct of the study***

Patient advice and liaison service

023 8079 8498

Thank you for considering taking part in this study

Appendix 5 Southampton Cardiac Rehabilitation

Phase 3 class schedule

Health check Undertaken every session prior to exercise and education component	<ul style="list-style-type: none"> • Blood Pressure • Pulse • Changes in medication • Subjective health
Exercise component One hour	<p>Warm up: 10 minutes: Includes paced walking, standing on the spot exercises and upper limb and lower limb stretches.</p> <p>Circuit: 40 minutes – Heart rate checks carried out twice during the exercises. Patients try to attain and then maintain a HR at 50–70% of their maximal heart rate, calculated using the Karvonen formula: Target Heart Rate = ((max HR – resting HR) × %Intensity) + resting HR example). Intensity is also monitored by the Borg scale with patients aiming to achieve a level between ‘somewhat hard’ to ‘hard’.</p> <p><u>Fleming Park centre</u>: Class is split in to four groups with an instructor in each group. Groups are based on experience and cardiac risk. Alternate every 2 minutes between higher intensity exercises and recovery exercises. The proportion of intense exercises increases in the experienced and low risk groups.</p> <p>Intense exercises: step up’s, walking/running, heel rises with lunge, step back’s with arm raises, side steps.</p> <p>Recovery exercises: bicep curls, lateral raises, shoulder press</p> <p><u>Bitterne Leisure centre</u>: Circuit exercises – walking / running, trampet, wall press ups, squats, shoulder press, bicep curls, side steps, lateral arm raises, upright rowing.</p> <p>Warm down: 10 minutes: Slow walking and stretches as for warm up</p>

Education component: One hour interactive presentation and discussion sessions	Medication: Common cardiac medications, what they do and how they should be taken.
	Alcohol: It's effect on the body and mind. Identifying safe levels.
	Exercise: Return to safe exercising. It's effect on the body and mind.
	Diet: Identifying healthy foods and recommended daily amounts. Their effect on the body and mind.
	The heart: How it works, common conditions and the effect of these conditions. Recovery post event.
	Wellbeing: Identifying mood and stress disorders. Return to – work, hobbies, an active sex life.
Relaxation	10 minutes: seated relaxation listening to relaxation tape.

BASELINE

PARTICIPANT QUESTIONNAIRE

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Research Number.....	
DATE	
Adapted from the National Database for Cardiac Rehabilitation	

ABOUT YOU

Gender (please tick)

Male

☐1

Female

☐2

Marital Status (please tick)

Single

☐1

Married

☐2

Permanent partnership

☐3

Divorced

☐4

Widowed

☐5

ETHNIC CLASSIFICATION

We are collecting this information to check that this research represents a fair cross section of the population. Please tick the one that describes you best, or, if none of them do number 6 any other

What is your ethnic group?

1 White

British ☐1

Irish ☐2

Any other White background ☐3

.....

2 Mixed

White and Black Caribbean ☐4

White and Black African ☐5

White and Asian ☐6

Any other Mixed background ☐7

.....

3 Asian or Asian British

Indian ☐8

Pakistani ☐9

Bangladeshi ☐10

Any other Asian background ☐11

.....

4 Black or Black British

Caribbean ☐12

African ☐13

Any other Black background ☐14

.....

5 Chinese or other ethnic group

Chinese ☐15

6 Any other ☐16

OTHER ILLNESSES YOU HAVE BEEN TOLD YOU HAVE

Have you ever been told by a doctor that you have definitely had any of the following illnesses? Please answer every question even if they are all NO.

Angina	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Arthritis (osteo)	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Cancer	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Diabetes	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Rheumatism	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
A stroke	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Osteoporosis	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Hypertension	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Chronic bronchitis	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Emphysema	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Asthma	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Leg pain when walking due to poor blood supply -Claudication	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Back problems or chronic pain	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>
Other illnesses	NO	<input type="checkbox"/>	YES	<input type="checkbox"/>

PILLS and SMOKING

Are you currently taking these 4 medicines for your heart (please tick a yes or a no for each one)

1. Aspirin or other antiplatelet agent No ☐ Yes ☐

if you are allergic to aspirin you may be taking either:

Clopidogrel or Dipyridamole

2. Blood Pressure tablets No ☐ Yes ☐

Examples include

Ramipril (trade name Tritace)

Losartan /Candesartan (trade name Cozaar)

Irbesartan (trade name Aprovel)

Thiazides e.g. Bendroflumethiazide

3. Beta Blocker No ☐ Yes ☐

often ending in 'olol' examples include:

Atenolol (trade name Tenormin)

Bisoprolol (trade name Cardicor)

4. Cholesterol pills (Statins) No ☐ Yes ☐

Examples include: Simvastatin (trade name Zocor)

Pravastatin (trade name Lipostat)

Atorvastatin (trade name Lipitor)

SMOKING & DIET

Have you smoked in the last 4 weeks?

YES	NO
-----	----

Please indicate how frequently
you smoke a day? e.g., 1, 5, 20
(cigarettes, cigars or pipes)

--

Please *circle* how many portions of fruit
and vegetables you eat each day?

Portions per day

0, 1, 2, 3, 4, 5,

HAD Scale

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more. This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take long in your replies your immediate reaction to each item will probably be more accurate than a long thought-out response. **Tick only one box in each section**

I feel tense or 'wound up':

Most of the time
A lot of the time
Time to time, Occasionally
Not at all

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I feel as if I am slowed down:

Nearly all the time
Very often
Sometimes
Not at all

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I still enjoy the things I used to enjoy:

Definitely as much
Not quite so much
Only a little
Hardly at all

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all
Occasionally
Quite often
Very often

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly
Yes, but not too badly ..
A little but it doesn't worry me
Not at all

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I have lost interest in my appearance:

Definitely

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I don't take so much care as I should
I may not take quite as much care ..

I take just as much care as ever

I can laugh and see the funny side of things:

As much as I always could .
Not quite so much now
Definitely not so much now
Not at all

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I feel restless as if I have to be on the move:

Very much indeed ..
Quite a lot
Not very much ..
Not at all

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Worrying thoughts go through my mind:

A great deal of the time ...
A lot of the time
From time to time but not too often
Only occasionally

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I look forward with enjoyment to things:

As much as ever I did .
Rather less than I used to ..
Definitely less than I used to

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Hardly at all

I feel cheerful:

Not at all
Not often
Sometimes
Most of the time

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I get sudden feelings of panic

Very often indeed
Quite often ...
Not very often
Not at all ...

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I can sit at ease and feel relaxed:

Definitely
Usually
Not often
Not at all

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I can enjoy a good book or radio or TV programme:

Often
Sometimes
Not often
Very seldom

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

PHYSICAL ACTIVITY

- 1 Considering a 7-day period (a week), how many times on average do you do the following kinds of exercise for **more than 15 minutes** (write the appropriate number in the boxes) number of times

a. Strenuous Activity (heart beats rapidly/tiring)?

(e.g. running, jogging, vigorous long distance cycling, circuit training, aerobic dance, skipping, football, squash, basketball, roller skating, vigorous swimming)

b. Moderate Activity (not exhausting)?

(e.g. fast walking, mowing the lawn, tennis, easy cycling, badminton, easy swimming, ballroom dancing, fast or high step ups)

c. Mild Activity (minimal effort)?

(e.g. easy walking, slow dancing, standing active fishing, bowling, golf, low step-ups)

- 2 Considering a **7-day period** (a week), how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?
Please tick only one box

A Often

B Sometimes

C Never/Rarely

<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>

Please tick only one box

- 3 Do you take regular physical activity of at least 30 minutes duration on average 5 times a week?

YES

NO

This final section asks questions relating to your quality of life.

Please **circle** the number that you feel best applies to you.

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, how would you rate your health in general now?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing several flights of stairs	[1]	[2]	[3]
7. Climbing one flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking more than a mile	[1]	[2]	[3]
10. Walking several blocks	[1]	[2]	[3]
11. Walking one block	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

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

(Circle One Number on Each Line)	Yes	No
17. Cut down the amount of time you spent on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? **(Circle One Number)**

- | | |
|-------------|---|
| Not at all | 1 |
| Slightly | 2 |
| Moderately | 3 |
| Quite a bit | 4 |
| Extremely | 5 |

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

(Circle One Number)

- | | |
|-----------|---|
| None | 1 |
| Very mild | 2 |
| Mild | 3 |
| Moderate | 4 |
| Severe | 5 |

Very severe 6

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

(Circle One Number)

- | | |
|--------------|---|
| Not at all | 1 |
| A little bit | 2 |
| Moderately | 3 |
| Quite a bit | 4 |
| Extremely | 5 |

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

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)? **(Circle One Number)**

- All of the time 1
- Most of the time 2
- Some of the time 3
- A little of the time 4
- None of the time 5

How TRUE or FALSE is each of the following statements for you. **(Circle One Number on Each Line)**

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Thank you.

You have now finished the questionnaire.

TIA Trial Assessment Protocols

All assessments are to be carried out within the Wellcome Trust Clinical Research Facilities, Southampton General Hospital. A research nurse from the aforementioned facility must be present for all assessments and medical supervisory cover will be provided by Elderly Medicine Team with the Registrar contactable via blp:1586 and the Consultants via the operator (Mon – Fri, 9 – 5).

If medical cover is required contact bleep

All eighty participants will undergo a number of assessments prior to group allocation. Each participant will have been asked to avoid eating overnight (12 hours) before assessment the following morning. The first assessment will be a blood test (to test for CRP, diabetic status and cholesterol) following this participants can have a drink (tea, coffee etc) and something to eat. The participant will then be asked to complete the self assessment questionnaire. Physiological measures (blood pressure, heart rate, weight, hip / waist measurements) will then be recorded, followed by a six minute sub-maximal exercise test on the stationary exercise bicycle. The participants will then have a supervised cool down period before returning home.

Equipment required

- Tape measure
- Stop watch
- Scales
- Heart rate monitor
- BP monitor (sphygmomanometer, stethoscope + automatic)
- BNF (to check queries regarding medication)
- Fan (for bicycle test)
- Phlebotomy equipment
- Cycle Ergometer (SECA cardiostest 100)

Test Protocols

Blood tests & tubes required:

1 x blue top 2.7 mL Coag tube(Prothrombin time + fibrinogen)

1 x grey top 6 mL fluoride oxalate tube (Glucose)

1 x gold top 6 mL SST tube (CRP/cholesterol/triglyceride/HDL cholesterol)

- Complete Pathology Trial request form (TR543) and send to Path labs within 6 hrs.

Physiological Measures:

- Waist to hip circumference assessment procedures- ACSM protocol (pg 63)
 - Waist is to be measured at the narrowest part of the torso (above the umbilicus and below the xiphoid process).
 - Hip is to be measured at the maximal circumference of the hips or buttock region (above the gluteal line), whichever is the largest.
- BMI assessment procedures - ACSM protocol (pg 63)
 - Calculated by dividing the body weight in kilograms by the height in meters squared (KG/m^2)
- Blood Pressure assessment procedures - ACSM protocol (pg 40)
 - Patients must be seated for at least five minutes in a chair with their back supported and their arms bared and supported at heart level. Patients should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurement.

- Wrap cuff firmly around upper arm at heart level; align cuff with brachial artery. The bladder within the cuff should encircle at least 80% of the upper arm.
- Place stethoscope bell below the antecubital space over the brachial artery.
- Quickly inflate cuff to 20mm Hg above estimated systolic BP.
- Slowly release pressure at a rate equal to 2 – 3 mm Hg/s, noting first Korotkoff sound.
- Continue releasing pressure, noting when sound becomes muffled (4th phase diastolic BP) and when sound disappears (5th phase diastolic BP). For classification purposes, the latter is used.
- In line with D'Agostino protocol the blood pressure measurements were made on the left arm with the average of 2 clinician obtained measures constituting the examination blood pressure.

Cycle Ergometer Test

THIS TEST IS NOT TO BE UNDERTAKEN BY PARTICIPANTS WITH:

- **KNOWN HEART DISEASE AND OR TAKING MEDICATION WHICH WILL AFFECT THEIR HEART RATE. i.e. Beta Blockers (Atenolol)**
- **WITH A RESTING BP GREATER THAN 180/110**

This is a single stage test lasting six minutes based on the Astrand-Ryhming test as described in the ACSM's guidelines for Exercise Testing & Prescription (Sixth Edition) & Heyward (2006): Advanced Fitness Assessment and Exercise prescription.

During the test participants are required to cycle on an ergometer at 50rpm for 6 minutes. Resistance is set at pre-determined levels (Table 3) and the goal is to obtain heart rate (HR) values between 125 & 170 beats/min (bpm), measured during the fifth and sixth minute. During the test, measure the heart rate every minute and record the average HR during the 5th and 6th minute. If the difference between these two heart rates exceeds 5 to 6 bpm, extend the bout until a steady state HR is achieved. If the HR is less than 125bpm at the end of the exercise bout, increase the workload by 50 watts and have the participant exercise an additional 6 minutes.

The average of the two heart rates is then used to estimate $\text{VO}_{2\text{ max}}$ from a monogram (ACSM pg 73). This value is then age adjusted by multiplying the $\text{VO}_{2\text{ max}}$ value by correction values (ACSM pg74). Procedures outlined in Table 2.

References

- American College Of Sports Medicine. *ACSM's Guidelines For Exercise Testing & Prescription* (Sixth Edition) (2000). Lippincott Williams & Wilkins London
- R D'Agostino, R. Vasan, M, Pencina, P Wolf, MCobain, J Massaro W, Kannel (2008) General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study *Circulation* 117;743-753;
- Heyward, V. (2006): *Advanced Fitness Assessment and Exercise prescription*. Fifth Edition. Human Kinetics. Leeds.

Table 2. Procedures for Sub-maximal Testing of Cardiorespiratory Endurance using a Cycle Ergometer. (Adapted from ACSM's Guidelines for Exercise Testing & Prescription 2000)

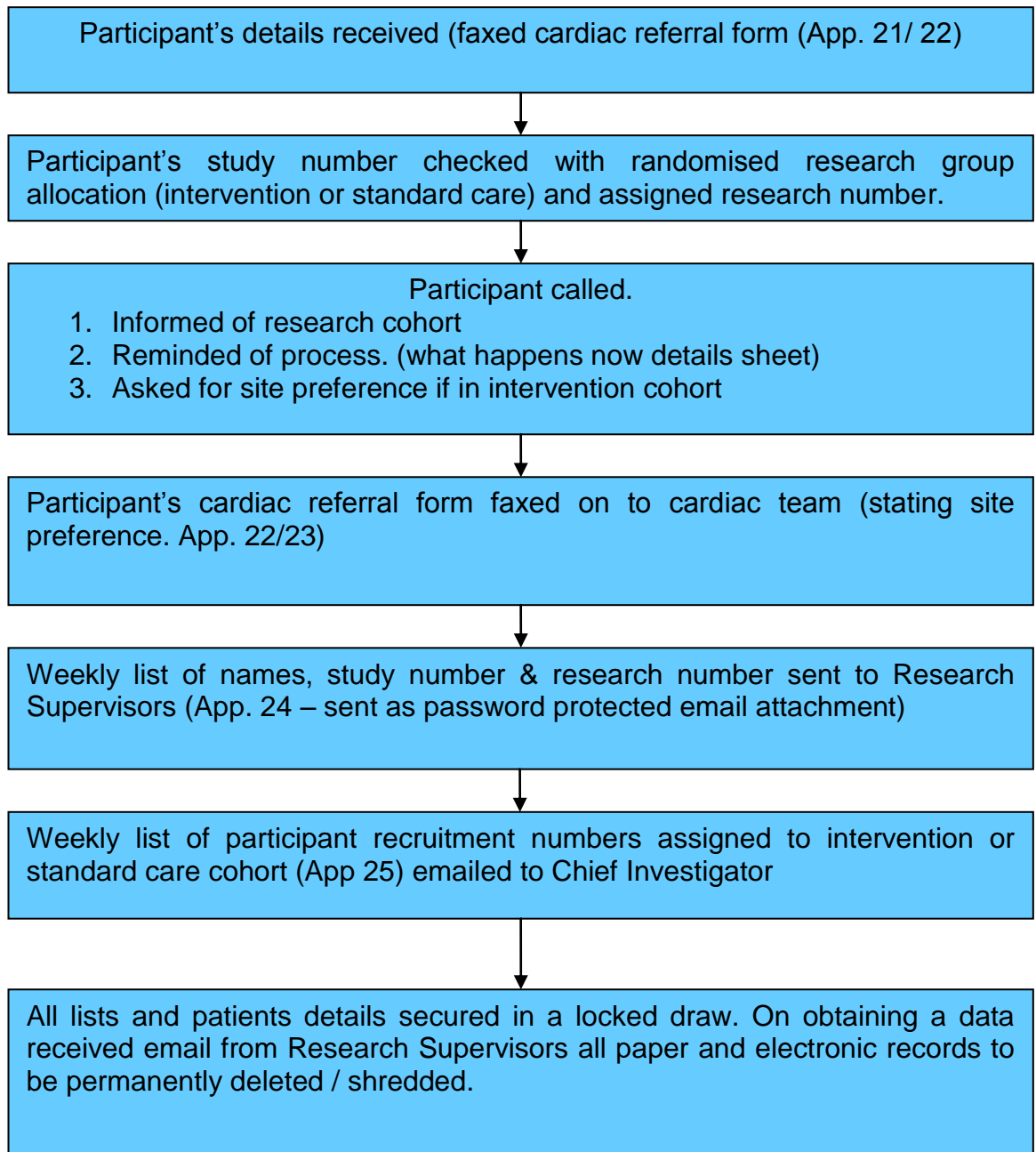
1. Two to three minute warm up to acquaint participant with the cycle ergometer and prepare him or her for the exercise intensity (< 50 Watts for warm up)
3. The participant will be positioned in an upright position, 5° bend in the knee at maximal leg extension, hands in proper position on handle bar.
4. Participants will wear a Heart Rate monitor and heart rate will be monitored continuously with average measurements taken during the 5th and 6th minute of the test.
5. Blood pressure will be monitored regularly during the test and repeated in the event of hypotensive or hypertensive response.
6. Perceived exertion will be monitored using Borg's Perceived Exertion and Pain Scale (1998). Particular attention for stopping the test should occur if the participant records scores of 15 – 17 or greater as this equates to approximately 85% of a persons maximal HR.
7. Participant appearance and symptoms will be monitored regularly.
8. The test will be terminated when the participant reaches 85% of age predicted maximal heart rate (see appendix 15), fails to conform to the exercise test protocol, experiences adverse signs or symptoms, requests to stop, or experiences an emergency situation.
9. An appropriate cool-down/recovery period should be initiated consisting of either:
 - continued pedalling at a work rate equivalent to that of the first stage of the exercise protocol or lower or;
 - a passive cool-down if the subject experiences signs of discomfort or an emergency situation occurs.
10. All physiological observations (e.g., HR, BP, signs & symptoms) will be continued for at least 4 min of recovery unless abnormal responses occur, which would warrant a longer post test surveillance period.

Table 3. Cycle Ergometer: Suggested work rates

Gender	Physical Conditioning	Work rate
Male	Unconditioned*	300 or 600 kg.m.min ⁻¹ (50 or 100 watts)
Male	Conditioned*	600 or 900 kg.m.min ⁻¹ (100 or 150 watts)
Female	Unconditioned*	300 or 450 kg.m.min ⁻¹ (50 or 75 watts)
Female	Conditioned*	450 or 600 kg.m.min ⁻¹ (75 or 100 watts)

* For older participants (50 yrs old+) always start on a workload of 50 watts. Conditioned is considered those taking moderately intensive exercise (gym, running) at least 3 x week.

Appendix 8 Randomisation process



Appendix 9 Ethical approval letter

RK/STA/hph

16 April 2009

Mr Hayden Kirk
Trainee Consultant Practitioner:
Neurological Rehabilitation (stroke)
NHS Education South Central
MP 886, Rehabilitation Research
Southampton General Hospital
Tremona Rd, Southampton
SO16 6YD


National Research Ethics Service
SOUTHAMPTON & SOUTH WEST HAMPSHIRE
RESEARCH ETHICS COMMITTEE (B)

1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
Hampshire
SO16 4RJ

Tel: 023 8036 2466
023 8036 3462
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Email: scsha.SWHRECB@nhs.net

Dear Mr Kirk

Full title of study: A feasibility study evaluating if the cardiac model of rehabilitation is more effective than standard care in reducing cerebrovascular risk factors post Transient Ischaemic Attack?
REC reference number: 09/H0504/46

Thank you for your letter of 07 April 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

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

Confirmation of ethical opinion

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

Ethical review of research sites

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

Conditions of the favourable opinion

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

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

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Other conditions specified by the REC

The Committee has noted a typographical error in both questionnaires. Replace "Cadesartartan" by "Candesartan". Revised copies should be submitted for information only.

Approved documents

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

<i>Document</i>	<i>Version</i>	<i>Date</i>
Trial Assessment Protocols	1	13 February 2009
Physician Checklis - Protocols	1	13 February 2009
Stroke Physician checklist for consideration of study eligibility	1	13 February 2009
GP Information Letter	1	13 February 2009
Participant Assessment Letter	1	13 February 2009
Questionnaire: Data Collection Sheet	1	13 February 2009
Summary/Synopsis	1	13 February 2009
Covering Letter		26 February 2009
Letter from Funder		11 December 2008
Adverse & Serious Adverse Events - Protocol	1	13 February 2009
Letter from Sponsor		21 July 2008
Protocol	1	13 February 2009
Investigator CV: Dr P Kersten		16 February 2009
Letter from Sally Roberts		15 February 2009
Investigator CV: Mr H Kirk		25 February 2009
Response to Request for Further Information		07 April 2009
Participant Consent Form	2	07 April 2009
Participant Information Sheet	2	07 April 2009
GP/Consultant Information Sheets	2	07 April 2009
Letter of invitation to participant	2	07 April 2009
Questionnaire: End Point including Pills, Smoking and Diet, HAD Scale, Physical Activity, Quality of Life	2	07 April 2009
Questionnaire: Baseline Participant including About You, Ethnic Classification, Other Illnesses You Have been Told You have, Pills, Smoking and Diet, HAD Scale, Physical Activity, Quality of Life	2	07 April 2009
Application		07 April 2009

Statement of compliance

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

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views

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known please use the feedback form available on the website.

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

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

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

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H0504/46

Please quote this number on all correspondence

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

Yours sincerely

✉ **Professor R King**
Alternate Vice-Chair

Email: scsha.SWHRECB@nhs.net

Enclosures: "After ethical review – guidance for researchers" SL- AR2 for other studies]

Copy to: Mrs Christine McGrath
Southampton University Hospitals NHS Trust

Appendix 10 Substantial amendments

Three substantial amendments were submitted to Southampton & South West Hampshire Research Ethics Committee (B). They were:

18th May 2009: Reason for submission: Preparation for the study highlighted that a small number of patients in the study may be taking medication to regulate their heart beat (Beta Blockers such as Atenolol). This oversight was due to this type of medication not being regularly prescribed for patients with a stroke or TIA, however some patients may have had pre-existing heart condition for which Beta Blockers were prescribed.

The exercise capacity test (on a static bicycle) was one of the secondary outcomes and requires participants to work towards 85% of their maximal heart rate. As participants taking Beta Blockers have their heart rate artificially lowered medical opinion was sought and it was agreed that it would not be appropriate for such participants to undertake this test. The research team did however want to still include this patient group in the study so as to maintain the studies inclusive representation of patients affected by a TIA / minor stroke.

Documents submitted:

Outcome: Ethical approval granted 27/05/2009

<i>Document</i>	<i>Version</i>	<i>Date</i>
Participant Information Sheet	3	18/05/2009
Assessment Operating Procedure	2	18/05/2009
Trail Protocol	2	18/05/2009

24 July 2009: Reason for submission: Changes in patient assessment procedures at Southampton General Hospital meant that patients would need to be recruited from a number of different setting and by the specialist nurse as well as the doctors. Asked for approval to recruit patients from patients the Acute Stroke Unit, Acute Medical Unit as well as those attending the TIA clinic.

Documents submitted: Outcome: Ethical approval granted: 29/07/2009

<i>Document</i>	<i>Version</i>	<i>Date</i>
Trail Protocol	2	18/05/2009

9 December 2009: Reason for submission: We wanted to amend the recruitment personnel and sites within the local region. In order to ensure the study recruits sufficient participants who provide a correct representation of the TIA / minor stroke population we wanted to expand the recruiting sites and amend the recruitment personnel to include a CLRN stroke research nurse and a pre-reg MSc student (Kaye Hillsdon) to assist with the qualitative data gathering and analysis. The two proposed sites and rationale were:

- Winchester & Eastleigh Healthcare Trust - as participants' will be able to access the intervention site at Eastleigh
- Lymington New Forest Hospital - since this trial commenced (July 2009) a change of practice means some New Forest patients who are suspected of having have a TIA are now being assessed at Lymington Hospital. In the past those who lived near Southampton would previously have been seen at SUHT.

Documents submitted: Outcome: Ethical approval granted: 16/12/2009

<i>Document</i>	<i>Version</i>	<i>Date</i>
Trail Protocol	3	18/05/2009

Appendix 11 Interview guide

- 1) Could you tell me about your TIA / minor stroke?
 - 2) Could you tell me about the care you received after your TIA / minor stroke?
 - 3) What are your views on any advice you were given about reducing the risk of stroke in the future?
 - 4) Could you tell me about any lifestyle changes you have made since having had your TIA / minor stroke?
 - 5) Do you have any thoughts about what might have caused you to have a TIA / minor stroke?
 - 6) In the ideal world what support would you like to see provided for people following a TIA or minor stroke in the future?
-

Appendix 12 Trial Funding

Funder One	Funder Two
Physiotherapy Research Foundation	Private Physiotherapy Education Foundation
Funding: £20,711	Funding: £4,202

Category	Year 1 costs	Year 2 costs
STAFF SALARIES		
Rehab Phase 3 support	£1,081	£1,081
Wellcome Trust Research Nurse	£2698	£2698
TRAVEL & SUBSITENCE		
Participant Hospital car park –	£320	£320
Participant mileage	£511	£511
Advisory group patient representation honorarium and travel costs –	£297	£297
Participant/Interviewer travel: qualitative study	£200	£200
OTHER		
Wellcome Trust Facility Charge	£1,360	£1,360
Controlled Trials Limited Registration	£176	£0
Pathology Analysis (160 samples)	£900	£900
Total Cholesterol	£900	£900
High Density Lipoprotein	£900	£900
Triglyceride	£900	£900
Fibrinogen	£1000	£1000
hsCRP		
Qualitative Data Transcription	£876	£876
Digital recorder	£250	£0
CSP Congress Presentation	£0	£600
TOTAL = £24913	£12,370	£12,543

Appendix 13 Recruitment Audit

Recruitment for the trial was substantially below the anticipated ratio outlined in section 4.3.3. An audit was therefore undertaken to assess the possible reasons for this. Over the same two week period in February 2009 and 2010 a prospective audit of patients seen in TIA clinics (table 12) shows that only 28% and 26% (n=7, n=6) of the patients seen in clinic had a definitive diagnosis of a cerebrovascular event. The audit also shows that a substantial proportion of the remaining patients 52% (n=13) and 48% (n=11) were diagnosed as having non cerebrovascular events with the remaining described as having possible cerebrovascular events.

TIA Clinic Audit

Patients seen in TIA clinic	February 2009	February 2010
Number of patients seen in clinic	25	23
Patients with a diagnosis of TIA	5	4
Patients with a possible diagnosis of TIA	3	5
Patients with a diagnosis of stroke	2	2
Patients with a possible diagnosis of stroke	2	1
Non cerebrovascular event	13	11

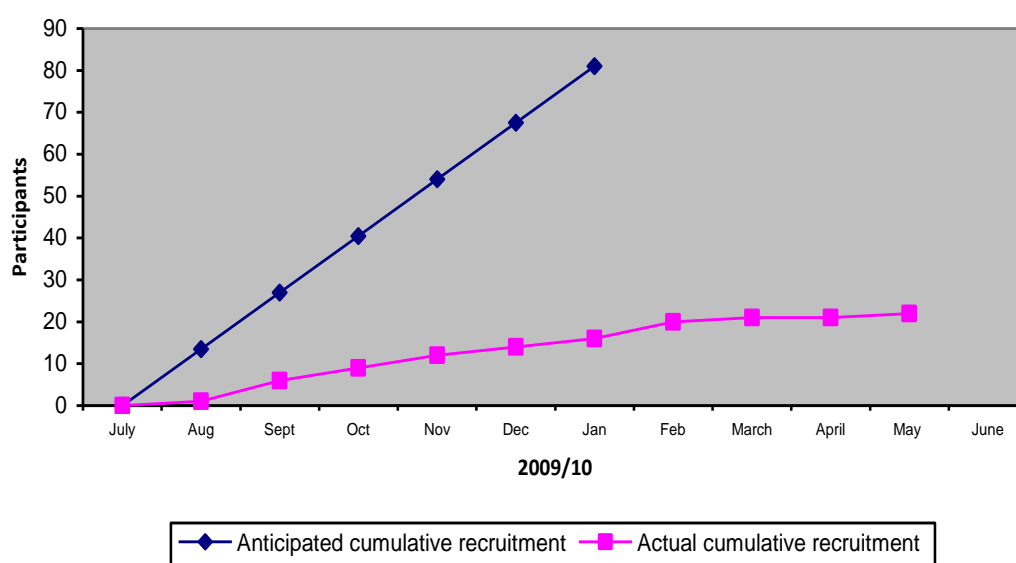
A subsequent one week audit (Table 13) conducted by the TIA clinic nurse specialist re-confirmed what was seen in the retrospective notes audit. This showed that there were a high number (62%, n=8) of patients seen who were not believed to have had a cerebrovascular event and of those who did have a confirmed event 80% (n=4) did not meet the trial entry requirements.

The rate of recruitment was originally anticipated to average 13.5 participants per month. Graphs 1 and 2 illustrate the difference between the anticipated and actual cumulative and monthly recruitment rates which were on average just 16% (2.2 participants per month) of the original anticipated rate.

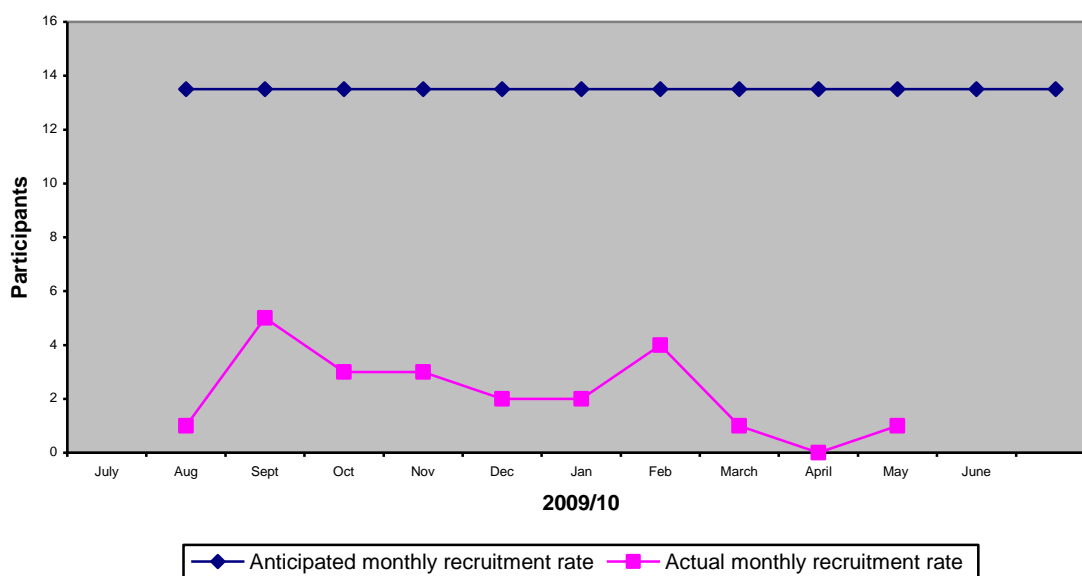
Study suitability Audit: 18 - 24th May 2010

Total number of patients	Suitable		Not suitable				
	Interested	Not interested	Not TIA / Stroke	Poor mobility	Poor cognitive function	Not medically suitable	Other
13	1	0	8	2	2	0	0

Cumulative recruitment rate



Monthly recruitment rate



Appendix 14 Co-morbidity benchmarking

Ex4TIA trial and Cardiac Rehabilitation Co-morbidities

Co-morbidities	Ex4TA (n=24) % of patients	Cardiac Rehabilitation* (n=64,074) % of patients
Angina	8	29
Arthritis (osteo)	16	16
Cancer	4	6
Diabetes	8	22
Rheumatism	0	4
Osteoporosis	0	3
Hypertension	29	49
Chronic Bronchitis	4	2
Emphysema	0	2
Asthma	16	10
Claudication	13	5
Chronic back pain	13	11
Other illness	16	30

*Lewin 2011; National Audit of Cardiac Rehabilitation 2009-10

EX 4 TIA Study

Rehabilitation Research Dept. Mailpoint 886
Southampton University Hospital Trust
Tremona Road
Southampton
SO16 6YD
Email: hjsk1k06@soton.ac.uk

Adverse Event: Reasonable, Reasoned & Thorough review

Issue Arising: When conducting the Astrand Rhythmic static bike test to obtain a submaximal estimation of the participants exercise capacity (V02 max) both participants to date have had an adverse event for which it is possible there is a causation link.

AE summary: Participant 003: Remained hypertensive for 3 hrs post exercise (ex duration approx 1 min)

Participant 006: Developed an irregular pulse post exercise (ex duration approx 8 min)

Current situation:

- National strategy post TIA₍₁₎: *people who have had a stroke or TIA also need information and advice, particularly on smoking cessation, diet, exercise, alcohol, driving and what to do in the event of a recurrent TIA or stroke.*
- Appendix 2: Physician Check list - SIGN Protocols₍₂₎
- Appendix 11: Ex4TIA Trial Assessment Protocols

THIS TEST IS NOT TO BE UNDERTAKEN BY PARTICIPANTS WITH:

- KNOWN HEART DISEASE AND OR TAKING MEDICATION WHICH WILL AFFECT THEIR HEART RATE. i.e. Beta Blockers (Atenolol)

- WITH A RESTING BP GREATER THAN 180/110

Possible causality: In effect we are inadvertently conducting a stress test on patients who are at risk (25% – 60% ⁽³⁾) of undiagnosed cardiac disease. During the test BP is monitored pre and post test and every 2 minutes during the test. HR is monitored pre and post and continuously during the test on a three lead ECG. Participants have a final BP check approximately 20 mins post test before being discharged home.

Consequences: On both occasions cardiovascular problems have been identified and managed by the research staff and Stroke cover team. However the question remains as to whether conducting the cycle test is safe & do we have the capability and systems in place to manage any cardiac symptoms that become apparent?

Literature guidance:

- It is probably a reasonable statement to say that the general advice to TIA patients to take regular exercise at a moderate level. This is in line with the AHA Stroke Council's Ad Hoc Committee on Guidelines for the Management of Transient Ischaemic Attack₍₄₎ which recommends the 'performance of regular physical activity, i.e., 30 to 60 minutes of exercise at least three or four times a week.'
- Whether stroke patients should be investigated for asymptomatic CAD remains a matter of debate₍₃₎ although a full cardiac review is not standard practice in the UK. The moderate level (<75% HR max) of exertion during cardiac rehab is known to be low risk₍₅₎ and by following the SIGN

cardiac guidelines this risk can be further minimised. However exercising participants up to 85% of their HR max may pose a slightly greater risk and the abstract from the 'Coronary Risk Evaluation in Patients With Transient Ischemic Attack and Ischaemic Stroke'^{l(6)} gives some indication of this risk.

There is limited data on this but Macko et al⁵⁵ small study of exercise testing for stroke patients showed most patients (30 of 31) tolerated testing, achieving 84_10% of maximal age-predicted heart rate. In the absence of more systematic data on stress testing, cardiac complications during stroke rehabilitation provide an estimate of potential risks of testing. In a review of 1029 patients treated in an academic rehabilitation facility after stroke, Roth et al⁵⁶ reported that there were no MIs, 2.9% had angina; 3.2%, atrial arrhythmias; 2%, hypotension; 2%, CHF; and 0.5%, acute respiratory failure.⁵⁶ These data suggest that overall, exertion after stroke (at least that involved in rehabilitation) and exertion entailed in stress testing are associated with a low risk of serious cardiovascular complications. The enhanced monitoring involved in stress testing and the selection of patients without established CHD history provide a further measure of safety for the application of stress testing.

The questions remaining seems to be whether or not more ECG monitoring (particularly ST depression) is required during the cycle test or whether a previous baseline ECG with no abnormalities is sufficient to minimise risk and give baseline guidance should a subsequent medical review be required.

Suggestions:

WTCRF: Suggest taking a baseline ECG with a review by the medical cover team to assess for any unreported irregularities before the bike test.

HK: If a baseline ECG is taken and clear in TIA clinic (re: ST depression) can that constitute a reasonable indication of suitability for the trial & bicycle protocol.

Dr P Crawford: Expressed her opinion that both Adverse Events and the medical follow up had been appropriate and that they are happy to continue providing medical cover in this respect. Noted that both of these incidents may have been one offs but it was important to review the process to ensure patient safety. On discussion of the points raised above, Dr Crawford felt that in accordance with the current guidelines, as long as the participant was not presenting with any clinical cardiac symptoms on the day and the SIGN guidance had been met then it would be reasonable to conduct the sub-maximal exercise test. With regard to the SIGN guidelines every patient seen in the TIA clinic (or A&E / AMU) should have had an ECG. If the notes do not report any adverse findings resulting from the ECG then it can be assumed that there are no contraindications to exercise. If there is not an ECG and clinic notes in the participants file then an ECG should be conducted in the WTCRF and the medical cover team contacted to report on the ECG.

Conclusion: It would appear that Dr Crawford's recommendations cover both the WTCRF's and Hayden Kirk's suggestions. It would therefore seem reasonable to continue with the current format of assessments but to ensure that a recent (post TIA) ECG recording is available. If this is not the case then a new ECG should be taken and cleared by the medical cover team before undertaking the cycle test. Subsequent cycle tests to be carefully monitored for further Adverse Events.

References:

1. DH (2007) National Stroke Strategy. QM 6, rationale 16. Crown Copyright 2007
2. SIGN 2002 Exercise Training Guidelines: See appendix 2 below
3. Touze' E., et al (2005) Risk of Myocardial Infarction and Vascular Death After Transient Ischemic Attack and Ischemic Stroke A Systematic Review and Meta-Analysis *Stroke*. 36:2748- 2755
4. Albers GW, Hart RG, Lutsep HL, et al. (1999) AHA Scientific Statement. Supplement to the guidelines for the management of transient ischemic attacks: a statement from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. *Stroke*;30:2502–2511.
5. VANGVANICH P, PAUL-LABRADOR M & MERZ C (1996). Safety of medically supervised exercise in a cardiac rehabilitation centre. *Am J Cardiology*, 77, 1383-5.
6. Coronary Risk Evaluation in Patients With Transient Ischemic Attack and Ischemic Stroke: A Scientific Statement for Healthcare Professionals From the Stroke Council *Circulation* 2003;108;1278-1290

SIGN Exercise Training Guidelines 2002

The following guidance from SIGN is to be used if there is concern about a patients' cardiac status and suitability for undertaking the cardiac rehabilitation programme.

For most patients clinical risk stratification based on history, examination and resting ECG combined with a functional capacity test should be sufficient. High risk patients may be defined as those who have:

- Experienced an MI complicated by heart failure, cardiogenic shock and/or complex ventricular rhythms.
- Angina or breathlessness occurring at a low level of exercise. (Please see Canadian score for Angina, patients must score 3 or below to be eligible for trial).
- ST segment depression > 1mm on resting ECG
- Undergone exercise testing with marked ST depression of \geq of 2 mm or angina <5 METS

Exercise testing and Echocardiography are recommended to assess residual ischemia and ventricular function respectively but are not a necessary part of cardiac rehabilitation except for high intensity exercise or in high risk patients.

Appendix 16 Participant Newsletter

CONTACT NUMBERS:

RESEARCH

- Hayden Kirk
- 07793 40339

RESEARCH SPONSORS:

PHYSIOTHERAPY RESEARCH FOUNDATION

PRIVATE PHYSIOTHERAPY EDUCATION FOUNDATION

Ex 4 TIA

Exercise for TIA & Stroke Study


VOLUME 1 ISSUE 2 DECEMBER 2010

Christmas Update

It is hard to believe but it is a year since the last newsletter was sent out. The aim of this newsletter is to update all of you who have taken part in the Ex4TIA study on the progress to date.

As most of you will now be aware the 'trial' part of the study is now complete with our last participant seeing Susan for final testing on the 24th November. This was our 24th and final participant and we are happy to say that everyone of you who started the trial returned for final data collection (a rarity in clinical trials!).

As you know from last year's newsletter we have struggled with recruitment and didn't reach our planned target of 72 participants. Achieving these targets is always very difficult in research and this is particularly so when the intervention (cardiac rehabilitation classes) is so time and energy consuming. However we should have sufficient data to be able to get an idea of whether or not these classes are as beneficial for stroke and TIA patients as they are for cardiac patients. The statistical analysis will take place after Christmas and we hope to have a complete set of data by Easter. From there we will look to submit the results for publication in a medical journal, as this is the means by which the medical community share information and build up a body of evidence which influences future health service design.



We are not alone!

At last week's National Stroke Forum it was apparent that we are not the only ones interested in investigating new ways for reducing risk factors after a stroke or TIA. This is good news, as the more research that is completed in this area the stronger the evidence for change will be. If you would like to see the results from these trials please type the below web links into your internet web browser.

<http://cre.sagepub.com/cgi/reprint/22/2/125.pdf>

<http://cre.sagepub.com/content/early/2010/07/15/0269215510367970>

UNIVERSITY OF Southampton
School of Health Sciences

Southampton City NHS Primary Care Trust

Southampton NHS University Hospitals NHS Trust

VOLUME 1 ISSUE 2

PAGE 2

Telling your story



In addition to giving blood, being measured and filling in questionnaires, many of you patiently told Kaye or Hayden about your experiences of having a TIA or stroke and any subsequent follow ups. Twenty two of you successfully completed these interviews and we stopped at that point as we had reached what is termed data saturation, which basically means that no new themes (topics) were coming up and so no further data was required. This has provided a fascinating insight into patient perspectives of health and medical care and Kaye is currently in the process of writing this up for a research article which should be published next year. When this is published we will post you all a copy of the article.

Thank you's

As the main part of the trial has finished we would like to acknowledge the hard work team members have put in. This includes (in no particular order) Ange Keens, Dr Crawford and the other stroke medical team members who you all reported gave you excellent care after your TIA/Stroke. The Southampton Cardiac Rehabilitation team that patiently and carefully put so many of you through your paces. Susan at the Welcome Trust who not only did an excellent job when testing you, but was also so very helpful with everyone. And last but by no means least, Dr Paula Kersten. Many of you will not have met Dr Kersten, but she is a researcher at Southampton University who has been instrumental in overseeing this research and is leaving us to become Associate Professor at Auckland University. We wish her well.

Finally and most importantly !

We would like to thank all of you for your time and effort and would like to wish you a Merry Christmas and happy New Year.

Hayden Kirk & Kaye Hillsdon



GLOSSARY

Cerebrovascular Disease: Disorders affecting the blood vessels that supply the brain that may result in a TIA or stroke.

Cardiac rehabilitation: Is the process by which patients with cardiac disease, in partnership with a multidisciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychosocial health (SIGN, 2002). Programmes that provide both exercise and psychological / educational support are termed comprehensive cardiac rehabilitation. These contrast with other forms of cardiac rehabilitation which provide only exercise or psychological / educational input.

CHD: Coronary heart disease (CHD) is the narrowing or blockage of the coronary arteries by atheroma, leading to angina, coronary thrombosis or heart attack, heart failure, and/or sudden death.

Ex4TIA: (Exercise for Transient Ischemic Attack). The acronym for the randomised controlled trial discussed within this thesis.

Stroke: A stroke occurs when a blood vessel that carries oxygen and nutrients to the brain is either blocked by a clot (ischemic) or bursts (haemorrhagic). When that happens, part of the brain cannot get the blood (and oxygen) it needs, so it starts to die. If a stroke occurs and blood flow can't reach the region that controls a particular body function, that part of the body won't work as it should.

Minor stroke: Using the National Institutes of Health Stroke Survey (NIHSS) which is a 15-item (3 subsets) neurological examination stroke scale used to evaluate the effect of a stroke, it is possible to define a patient as having had a stroke rather than a TIA but with minimal neurological deficits (NIHSS score < 3).

TIA: Transient Ischemic Attack: Brief episode in which the brain gets insufficient blood supply; symptoms depend on the site of the blockage. Symptoms resolve within 24hrs (> 24hrs classified as a stroke).

HRQoL: Health Related Quality of Life: Quality of life outcomes are a measure of the difference between the hopes and expectations of an individual and the individuals present experience, and health related quality of life is concerned with those factors that fall within the influence of health systems (Fayers and Machin, 2007).

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Programs: 2007 Update: A Scientific Statement From the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*, 115, 2675-2682.

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