# Investigations of physical therapy interventions to enhance movement recovery in people after stroke: Development and design of a novel intervention embedding Functional Strength Training within a motor learning context.

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## Abstract

Stroke is the largest cause of adult disability in the UK and stroke survivors commonly present with a partial or complete loss of movement. Physical therapy interventions as part of movement rehabilitation after stroke aim to facilitate a return to participation in activities of daily living. It has been proposed that the processes that underpin both movement recovery following stroke and motor learning are the same. By embedding physical therapies within a motor learning context it is possible that the effects of the therapy could be enhanced. Yet the application of motor learning principles within the field of movement rehabilitation after stroke is fragmented and supported by evidence of their application in studies with healthy volunteers. This thesis aims to carry out a systematic review of the evidence for the effectiveness of the application of motor learning principles in movement rehabilitation after stroke and to combine this with findings from a feasibility study of Functional Strength Training. These findings will be used to design a novel intervention embedding FST within a motor learning context.

Organisation and synthesis of the systematic review was guided by the development of a motor learning framework. Interpretation of the findings from the review showed some evidence in favour of the application of motor learning principles. A phase II randomised controlled trial of FST to the upper limb and lower limb in people within six months and five years after stroke showed evidence of feasibility for both interventions but indicated efficacy of the upper limb intervention only ($p=0.046$).

These findings were combined to inform the design and delivery of a novel intervention, testing for proof of concept for this intervention is now required.

This thesis suggests an alternative approach to the development of physical therapy interventions after stroke, however consensus for this needs to be achieved.

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Mares K, Cross J, Clark A, Barton G, Poland F, Watson W, McGlashan K, Myint PK and Pomeroy VM. The FeSTivaLs trial protocol: A randomized evaluation of the efficacy of functional strength training on enhancing walking and upper limb function later post stroke. International Journal of Stroke 2012.(Appendix II)

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## 1.0 Introduction

Stroke is defined as “a clinical syndrome, of presumed vascular origin, typified by rapidly developing signs of focal or global disturbance of cerebral functions lasting more than 24 hours or leading to death” (World Health Organisation, 1978 cited in Intercollegiate Stroke Working Party, 2012 p.4). Stroke is the largest cause of adult disability in the United Kingdom (National Audit Office, 2010); there are approximately 1.1 million people living in England, at any one time, who have had a stroke (Townsend et al., 2012) and. The disruption to the blood supply within the brain may occur as a result of a blockage to one of the major blood vessels, referred to as an ischaemic stroke, or as a bleed from these vessels, referred to as a haemorrhagic stroke (Department of Health, 2005).The resulting damage to the brain may lead to a number of impairments such as difficulties with communication, cognition and movement. The most common impairment affecting movement following stroke is hemiplegia, which presents as weakness or complete loss of movement on one side of the body (contralateral to the site of the stroke within the brain) (Rathore, Hinn et al. 2002).

Stroke is conventionally classified according to the site and subsequent impairment of the lesion. One such classification, commonly referred to in both clinical and research environments, is the Bamford classification (Bamford and Sandercock, 1991). Patients diagnosed with a stroke fall within one of four subtypes,

- Lacunar infarct (LACI) – patients presenting with a pure motor stroke, pure sensory stroke, sensori-motor stroke or ataxic hemiparesis.
- Total anterior circulation infarct (TACI) – Patients presenting with of higher cerebral dysfunction (e.g. dysphasia, dyscalculia, visuospatial disorder); homonymous visual field defect; and ipsilateral motor and/or sensory deficit of at least two areas of the face, arm and leg.
- Partial anterior circulation infarct (PACI) – Patients presenting with only two of the three components of the TACI syndrome.
- Posterior circulation infarct (POCI) – Patients presenting with any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or

> sensory deficit; disorder of conjugate eye movement; ataxic hemiparesis or isolated homonymous visual field defect.
>
> Bamford and Sandercock (1991)

Physical therapy interventions are believed to contribute significantly to the movement recovery of people after stroke (Intercollegiate Stroke Working Party, 2012). The aims of therapy are to capitalise on natural movement recovery, maximise the patient's return to functional activities and minimise secondary complications. Whilst there is general consensus about the overall aims of therapy the actual content has sometimes been described as a 'black box'. The patient goes into the 'box', they participate in 'therapy,' and they emerge with improved movement control (Pomeroy and Tallis, 2000). There are a number of different 'tools' within the therapist's 'toolkit' and each may be more or less effective depending on the presentation of each individual patient. To gain a better understanding of which therapeutic interventions, produce the best outcomes for the different movement impairments that can occur as a result of stroke, it is essential that we clearly define each intervention and investigate its efficacy and effectiveness. Physiological differences, underpinning recovery in the brain, also suggest that the same physical therapy intervention should be evaluated within populations of stroke survivors who are within both the acute and chronic period of recovery from stroke. Recovery within the so-called acute phase (up to six months after stroke) is underpinned by a rapid period of repair (Cramer, 2008). This is different to the processes that underpin later stages of recovery which have been likened to the usual physiological changes that occur within the brain in response to learning (Kleim and Jones, 2008).

Loss of movement following stroke may be caused by a number of factors, however, reductions in muscle strength is widely considered to be one of the main causes of a loss of performance in functional activities such as walking and reaching for objects (Bohannon, 2007, Burke, 1988, Harris and Eng, 2007). Research evidence suggests that following stroke, strengthening interventions can increase muscle strength and may improve the stroke survivor's ability to engage in functional activities (Ada et al., 2006).

Functional Strength Training (FST) is a physiotherapy intervention, (a 'tool' within the 'toolkit'), designed to increase the participant's ability to produce voluntary muscle force throughout joint range, increase their ability to modulate force in muscles/muscle groups appropriate for the activity being trained and improve functional ability (Cooke et al., 2010b, Donaldson et al., 2009a). FST can be used to improve function in both the upper and lower limb. In order to achieve this, FST uses conventional strengthening techniques such as increased repetition and integrates them into functional activities such as standing up and sitting down (Cooke et al., 2010b, Donaldson et al., 2009a). Findings of early phase trials give evidence of feasibility for FST for both the upper and lower limb in people who are within 3 months of a stroke affecting the anterior circulation of the brain (Bale and Strand, 2008, Cooke et al., 2010b, Donaldson et al., 2009a). However, it is unclear whether the results of these trials can be generalised to people who are at least six months after stroke – the so-called chronic phase. It is important therefore to determine the feasibility of this intervention within this other population of stroke survivors.

A body of work that coexists alongside the development of physical therapy interventions as part of movement rehabilitation after stroke is that of motor learning. There is a school of thought suggesting that the behavioural changes observed following movement rehabilitation is, in effect, a product of motor learning (Shmuelof et al., 2012), and certainly the concept of aligning motor learning to physiotherapy approaches within stroke rehabilitation is not new. The Movement Science approach (formerly the Motor Relearning Programme) (Carr and Shepherd, 2003) is underpinned by these principles and it is suggested that a number of current interventions, targeting movement recovery, are based on motor learning theories (Krakauer, 2006). Literature has identified motor learning principles in relation to mental practice, instructions, feedback, practice intensity, variability of practice and practice specificity (Magill, 2006). The application of these principles to physical therapy interventions after stroke has the potential to guide their delivery and arguably enhance their effects on subsequent movement recovery.

Evidence in relation to the efficacy of these motor learning principles comes from studies that have included only healthy volunteers and there is limited evidence in relation to their use in studies including stroke survivors. The ability to engage in motor learning may be impaired in stroke survivors compared to that of healthy individuals, so it may not be appropriate to apply these principles in the same way (Hosp and Luft, 2011). There is a need therefore to synthesise the evidence for the use of all the motor learning principles and their relative effectiveness in promoting movement recovery after stroke.

## 1.1 Development of thesis

A number of years ago, as a clinical physiotherapist working in the field of movement rehabilitation following acquired brain injury, I attended a Movement Science course. Although previously aware of aspects of motor learning such as feedback and practice intensity I had at that time not used them consistently within my clinical practice. This course stimulated an interest in this area which has developed with my subsequent shift away from the clinical environment and into teaching and learning and research. As I became increasingly knowledgeable about this body of literature I became more aware of the limitations of directly applying research findings from healthy volunteers to physical therapy interventions targeting movement recovery after stroke. I also perceived limitations in applying these principles to physical therapy interventions because of a lack of clarity and consensus around terminology. Despite this, it seemed that motor learning principles had the potential to guide delivery of physical therapy interventions and possibly enhance their effects on movement recovery after stroke.

My on-going interest in this field of research and applied clinical practice coincided with an opportunity to expand work on a specific physical therapy intervention – Functional Strength Training (FST). The concurrent development of both these aspects of my work has led to the development of this thesis. This body of work reports on two studies, a systematic review evaluating the effectiveness of the application of motor learning principles to enhance movement recovery after stroke; a phase II randomised controlled trial determining feasibility of FST in stroke survivors within the chronic phase of

recovery. The thesis seeks to use the findings from these studies to identify a novel intervention which will demonstrate how physical therapies can be informed by the application of motor learning principles. Such an approach could be used to enhance the delivery of movement rehabilitation after stroke.

The design of both studies within this thesis has been underpinned by the conceptual framework published in the guidance document “Developing and evaluating complex interventions” (Craig et al., 2008). This framework describes a cyclical process where complex interventions can be piloted and subsequently tested for efficacy. The following chapter will first introduce the MRC framework for evaluating complex interventions (section 2.1) and briefly discuss why its application is appropriate as a means of guiding the development of the studies in this thesis. The chapter will then go on to separately identify the background literature which has led to the development of the following two research questions.

Question 1:
What is the effectiveness of motor learning principles applied to people after stroke in order to promote motor learning?

Question 2:
Is Functional Strength Training a feasible intervention for improving upper and lower limb recovery later after stroke?

Subsequent chapters will identify the methods, results and interpretations from each of the studies. Finally, the findings from both studies will be combined to suggest a future intervention illustrating how physical therapy interventions can be developed within the context of motor learning.

# 2.0 Background

This chapter will address the background literature underpinning the development of both the systematic review and the trial of Functional Strength Training. Before reviewing the literature in these areas the first section will introduce the MRC framework for complex interventions. Evaluation of complex interventions prior to the publication of this guidance was problematic because the intervention had not been fully defined and developed (Campbell et al., 2000). It is hoped therefore that by using this guidance to direct the development of a novel intervention described in this thesis that these problems can be avoided. Complex interventions are defined as such because they can be subject to a number of variables that may not be present in other types of intervention. These may include heterogeneous populations such as stroke survivors, the evaluation of individual behavioural responses and variability and little consensus for outcome measures (Campbell et al., 2000, Craig et al., 2008). These factors are all present within the studies included in this thesis.

## 2.1 MRC Framework for complex interventions

The MRC Framework for evaluating complex interventions was initially published in 2000, this publication served as the precursor to a refined framework published in 2008 which sought to address some of the criticisms that had subsequently arose following the implementation of the original document (Campbell et al., 2000). The authors of the framework recognised the complexity inherent within some health care interventions and attempted to provide investigators with a framework that could guide the evaluation of these. Complex interventions were typically described as being an intervention with a number of interacting components however this definition did not preclude other aspects of complexity such as variability in a target population or the identification of a range of possible outcomes. The first document described a sequential series of investigations that enabled researchers to develop a complex intervention from a theoretical hypothesis through to a definitive trial and on to long term implementation (Campbell et al., 2000). In the most recent framework this series of sequential steps has been developed into a cyclical process (see diagram below).

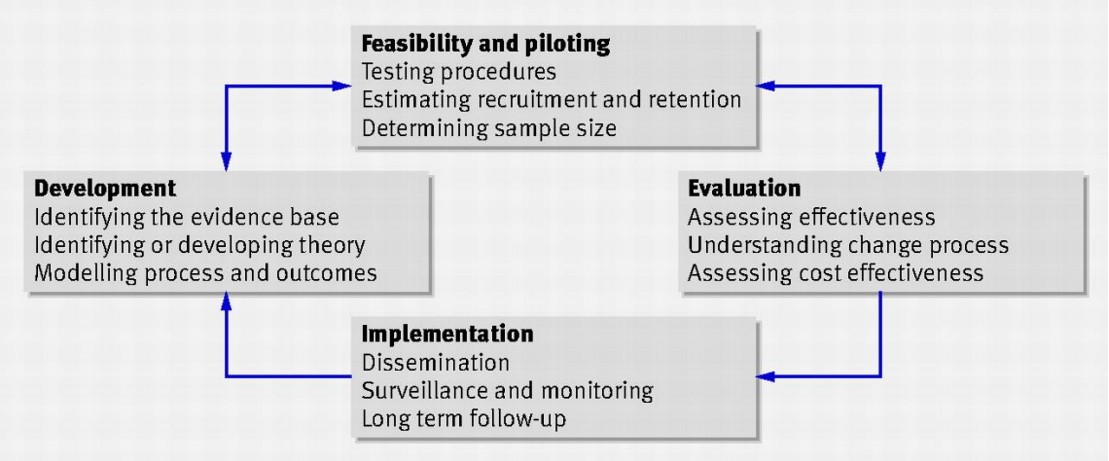


**Figure 1: Diagram describing the cyclical process for evaluating and describing complex interventions (Craig et al., 2008)**

The following paragraphs describe each of these steps (development, feasibility and piloting, evaluation and implementation) in more detail.

- Development

  Craig et al. (2008) highlighted the importance of initially developing an intervention to the point where you can reasonably expect an effect; in order to do this it is necessary to identify the evidence base. They suggested that this is achieved through a systematic review or identification of one already in existence. Other aspects of this development phase include identifying and developing the appropriate theory and modelling the process and outcomes.

- Assessing feasibility and piloting methods

  This stage is advocated in order to pre-empt issues that might arise in a definitive trial such as acceptability, likely retention and recruitment rates and sample size calculation (REF).

- Evaluation

  Evaluation of a complex intervention subsequently needs to assess effectiveness. Craig et al. (2008) acknowledged the variety of study designs to choose from but recommended that randomisation should always be considered within these as a means of preventing selection bias. This stage of the framework is also used to understand and evaluate the process in order to assess fidelity and quality of

implementation. Cost effectiveness of the intervention should also be evaluated at this stage.

- Implementation

  Implementation is achieved through publication in research journals but also provided in formats that are accessible to policy and decision makers. Successful implementation involves changing behaviour and research teams need to understand the barriers in order to overcome this.

  Monitoring of the success or not of the implementation of a complex intervention may lead to the identification of further work that needs to be carried out and thus the process may be cyclical as described in figure 1. Completion of each stage may also lead to aspects in the study design that require further refinement and thus there may be a need to revisit a previous stage in order to achieve this. This possibility is articulated by the presence of two way arrows in the diagram above.

The following sections go on to discuss the background literature supporting the two studies which were intended to inform the development of a novel intervention.

## 2.2 Motor Learning

Motor learning has been defined as:

"the acquisition of motor skills, the performance enhancement of learned or highly experienced motor skills, or the reacquisition of skills that are difficult to perform or cannot be performed because of injury, disease and the like." (Magill, 2006 p.3).

Motor learning has been assumed to take place if there has been a "relatively permanent" change in the performance of a movement in response to practice or increased experience of that movement (Magill, 2006, Shumway-Cook and Woollacott, 2007). Performance characteristics that are associated with learnt

motor skills are: consistency of performance, stability of performance in the face of disruption from internal factors (e.g. stress), sustained improvements in the performance seen over different periods of time and adaptability of performance to a variety of contexts (Magill, 2006).

Rehabilitation of movement disorders following stroke is predicated on the assumption that stroke survivors need to relearn movement so that they can regain the ability to take part in functional activities (Carr and Shepherd, 2003). In the case of stroke rehabilitation this may mean teaching task specific compensatory strategies if there has not been sufficient return of muscle control or power. Alternatively, if there has been, strategies that promote recovery of normal motor control may be used (Kitago et al., 2013).

It seems appropriate therefore to suggest that the underlying goal guiding both motor learning and movement rehabilitation following stroke is in effect the same; to produce a sustained and adaptable change in movement performance (Krakauer, 2006). Through motor learning the learner is moved from a state of little or no ability to perform, to a change in that performance through the practical application of motor learning principles. In movement rehabilitation after stroke the learner (stroke survivor) moves along the same continuum after taking part in ‘rehabilitation interventions’. Pioneering work by Carr and Shepherd has long recognised this link between movement recovery and motor learning and created the ‘Motor Relearning Programme’ (Carr and Shepherd, 1991). This has subsequently been developed into an approach now named ‘Movement Science’ (Carr and Shepherd, 2000). This project seeks to build on this work by examining the evidence for the effectiveness of the application of motor learning principles as part of movement rehabilitation after stroke.

Despite the potential to inform the delivery of physical therapies, the application of motor learning theories by therapists working in the field of movement rehabilitation, appears to be limited. In an attempt to learn whether motor learning principles were being used to underpin walking interventions DePaul et al. (2013) carried out a scoping exercise. This exercise formed part of

DePaul's thesis and is yet to be published in a peer reviewed journal. Its findings are limited by the scientific rigour that peer review provides. However, they found little evidence of adherence to motor learning principles as part of walking training interventions after stroke. More detailed examination of the literature included in this narrative review revealed that whilst studies were not describing their interventions within the context of a motor learning construct, there was evidence of the inclusion of some motor learning principles such as feedback or practice specificity. It is possible that the authors of these studies included in this review had not recognised these as motor learning principles but simply methods for delivering the intervention. The description and use of motor learning principles within experimental studies needs to be clear so that the translation of findings from research studies to the clinical environment can be facilitated (Kleynen et al., 2013).

Feedback, practice specificity and practice intensity appear to be the most commonly applied motor learning principles and have been the subject of both narrative and systematic reviews (Cooke et al., 2010a, French et al., 2010, Molier et al., 2010, Subramanian et al., 2010, and Veerbeek et al., 2011). Use of the other motor learning principles is less well documented. It is unclear why there has been a preference for the use of only one or two motor learning principles within individual studies as each has the potential to guide different aspects of the delivery of a physical therapy intervention. The development of a motor learning framework to contextualise the use of motor learning principles and their application to physical therapy interventions seems desirable. Such a framework would facilitate communication and possibly the uptake of those motor learning principles that have been less well applied. It could also provide a standardised structure to the development of motor learning theories as part of movement rehabilitation after stroke.

The following section will explore the work surrounding the development of motor learning principles in order to establish definitions and descriptions.

### 2.2.1 Overview of the development of motor learning principles

Motor learning theorists have determined two types of learning believed to underpin the changes in motor performance; these are 'implicit learning' and 'explicit learning' sometimes referred to as non-declarative or declarative (Shumway-Cook and Woollacott, 2007). In explicit learning there is a conscious intention to acquire a skill, whereas in implicit learning the act of acquiring the skill is unconscious (Shumway-Cook and Woollacott, 2007). The type of learning that underpins a change in motor performance is believed to be related to the complexity of the task that needs to be learnt (Halsband and Lange, 2006). The learning of complex tasks is therefore generally believed to occur through the process of implicit learning because the ability to consciously recall every aspect of that task is not feasible (Halsband and Lange, 2006). Tasks that are likely to be the target of movement rehabilitation after stroke, such as walking, are generally held to be complex, and therefore it is the capacity for this type of learning that has been the focus of research in participants who have been diagnosed with a stroke (Boyd et al., 2009, Boyd et al., 2007, Boyd and Winstein, 2003, Boyd and Winstein, 2004b, Gomez-Beldarrain et al., 1998, Meehan et al., 2011, Orrell et al., 2007, Pohl et al., 2006, Pohl and Winstein, 1999). This body of literature exploring whether stroke survivors can or cannot engage in implicit learning will be discussed in more detail later. This thesis is, however, based on the premise that it is this type of learning that will underpin the performance enhancement of the complex motor skills that are necessary for stroke survivors to regain the ability to take part in functional activities.

Over the last one hundred years or so the identification of motor learning principles has been guided by motor learning theorists who have developed a set of principles which serve to promote changes in movement performance (Adams, 1987). A principle is defined as:

> "a general scientific theorem or law that has special applications across a wide field"

(http://oxforddictionaries.com/definition/english/principle accessed 19.7.13)

In motor learning therefore, a motor learning principle could be interpreted as a general rule that can be applied to the field of motor learning. Thus an example of a motor learning principle might be that feedback enhances motor

learning, this interpretation appears to resound with current literature referring to the use of motor learning principles in stroke rehabilitation (Jonsdottir et al., 2007, Piron et al., 2010)

The following section will provide some background to the development of current motor learning principles by considering some of the theories that are prevalent within the published literature. Currently it seems that theorists tend to fall into two categories: those that adhere to a 'cognitive camp' and those who adhere to the 'dynamical camp' (Newell, 2003, Adams, 1987, Magill, 2006, McMorris, 2008, Shumway-Cook and Woollacott, 2007).

Within the 'cognitive camp' lie those theorists who adhere to motor learning theories evolved from the Adam's Closed Loop Theory (summarised in Adams, 1987, Magill, 2006 and Shumway-Cook and Woollacott, 2007). This motor learning theory relies on sensory feedback derived from knowledge of the results of an initial movement. The body's internal sensory mechanisms deliver information about the relative success or failure of the movement (knowledge of results), this feedback is interpreted and further movement is generated until the action is learnt. This theory emphasises the role of feedback and continued practice within motor learning. It does not however account for motor learning that has been seen to take place when there is no sensory feedback, such as in feedforward tasks like touch typing. Nor does it explain the adaptability of novel motor tasks to different contextual situations such as being able to play a piece of music on the cello when it has only been previously learnt on the violin (Shumway-Cook and Woollacott, 2007). Recognising the limitations of this theory Schmidt went on to develop the Schema Theory (Schmidt, 2003). Schmidt believed that new movements were created and learnt as 'schema'. This referred to the creation of a generalised set of rules about the movement that could be applied within different contexts, such as the ability to play the same piece of music on two different instruments, something which was not addressed within the Closed Loop Theory. Schema were created in much the same way as the closed loop theory, i.e. in response to knowledge of results and sensory feedback, however they could be adapted to enable the learner to predict what the consequences of that movement might be under different

contextual constraints. Once the ‘new movement’ had been carried out then further adjustment based on the feedback mechanisms would serve to update the schema for different contextual situations. Schmidt (2003) suggested that learning the movement schema would be enhanced by physical practice under variable conditions. In support of the schema aspect of his theory Schmidt (2003) has referenced original work by Wadman et al. (1979). This study analysed the electromyographic (EMG) trace of arm movements in seven healthy males under three conditions; the first was analysis of the movement without any interference. The second and third analyses were conducted under changes of inertial load and mechanical blocking of the movement respectively. EMG traces of the movements shown on a graph, depicting the timing of activity within the main muscle groups (triceps and biceps), showed that the activity within the muscles remained largely the same despite any interference to the movement. Schmidt (2003) suggested that this was because of the presence of the generalised motor programme or schema which was programmed to act in a pre-defined way despite disruption.

Support for the practice variability aspect of Schmidt’s theory lies within a concept referred to as ‘contextual interference’. This can be defined as:

> “the memory and performance disruption (i.e. interference) that results from performing multiple skills or variations of a skill within the context of practice” (Magill 2006, p.375).

This concept was originally introduced by Battig and William (1972) and recent interpretation of this generally refers to changes in the practice schedule of the movement (Magill and Hall, 1990). Figure one shows an example of how this can be applied; different components of a movement task that need to be learnt have been labelled A to D. In the first example the practice schedule for these components is arranged in a random fashion, this design is described as one with ‘high contextual interference’. The second example shows a practice schedule that is referred to as a blocked or massed practice schedule and is described as having low contextual interference (Shea and Morgan, 1979).

Example of a random practice schedule with high contextual interference (A,B,C and D represent different components within one task)

A C D B B D C A D A C B

Example of a massed practice schedule with low contextual interference (A,B,C and D represent different components within one task)

A A A B B B C C C D D D

Figure 2: Example of massed and random practice schedules

Schmidt (2003) contested that practice under random practice schedule conditions would lead to better retention of the movement task. In a study of healthy volunteers Shea and Morgan (1979) found statistically significantly increased retention and adaptability, as measured by reaction time, total time to complete the task (from the onset of the stimulus to task completion) and movement time, of a motor learning task following practice under random conditions compared to massed practice ($P<0.05$). This seemed to confirm Schmidt's theory that random practice schedules enhanced motor learning. However, a more recent narrative review by Magill and Hall (1990) suggested that the practice schedule should be altered according to the skill variations required within the task. They proposed that where motor learning tasks required different motor programs, then randomly scheduled practice would be best, but where motor learning tasks involved modification of the same motor program, then a mixture of massed and then random practice schedules would be more appropriate. Empirical evidence supporting this is limited.

A subsequent narrative review has also suggested that the type of practice schedule should vary according to the skill level of the learner. Brady (1998) suggested that novices and those with low skill levels would benefit more from a massed practice schedule than a random one. This hypothesis is largely based on the theoretical application of motor learning theorists; however, a study by Hebert et al. (1996) lends some support to this concept. In their study, comparing the effects of a tennis practice schedule with low or high contextual interference on low or high skilled individuals, Hebert et al. (1996) found that

low skilled students who practiced under low contextual interference scored more highly than the matched group of low skilled students who practiced under high contextual interference ($p<0.05$). Conversely however, this study did not find a statistically significant effect of practice schedule for those students who were assessed as having a high skill level ($p> 0.05$). According to the hypothesis by Brady (1998) these students should have scored more highly after practice with high contextual interference. In order to challenge the more highly skilled players, the authors of this study had included complex components of the task within their practice sessions. They suggested this complexity may have impacted on the ability of the highly skilled players to show a statistically significant improvement regardless of practice schedules. Testing of the original hypothesis for the effects of both types of practice scheduling on novice and experienced learners is therefore still needed in order to either confirm or refute Brady's theory.

The importance of feedback as a means for promoting motor learning is also inherent within Schmidt's Schema Theory (Schmidt, 2003). There are two types of feedback described within the literature, task-intrinsic feedback and augmented or extrinsic feedback (Magill, 2006). Schmidt's Schema Theory (2003) refers to feedback derived from sensory systems within the body (e.g. auditory, visual, proprioceptive or tactile) that provide information about the delivery of the movement; this is known as task-intrinsic feedback. He also refers to 'knowledge of results', which is a form of augmented or extrinsic feedback. The term knowledge of results refers to the type of feedback obtained from information of the outcome of the movement, and comes from an external source to the individual undertaking the movement. The other form of extrinsic feedback, not referred to explicitly by Schmidt (2003), is knowledge of performance and this gives information about the movement characteristics. A recent study evaluating the effect of feedback versus no feedback on a complex movement task in a group of healthy individuals, found that the group of participants who received feedback performed significantly better than those who received no feedback ($p<0.005$) (Strandbygaard et al., 2013). The effectiveness of feedback in motor learning with healthy volunteers relies on the expectation that these individuals have intact sensory, cognitive and

perceptual systems. These results may therefore not be applicable to people who have impairments within any of these.

Reflecting on his theory twenty seven years later Schmidt (2003) believed that whilst the Schema theory could offer many features to a new way of thinking it was lacking in a number of ways and he has subsequently called for a new theory to be developed. It is interesting to note, however, that despite this assertion, reference to Schmidt's work still seems to dominate motor learning texts (Magill, 2006, McMorris, 2008, Shumway-Cook and Woollacott, 2007).

An alternative 'camp' of motor learning theorists lies within those individuals who adhere to the 'dynamical approach'. In this approach motor learning evolves in a dynamic way under the cooperation and interaction of various systems. This approach evolved in response to a need to explain temporal and spatial aspects of motor learning which were not accounted for in Schmidt's theory. It refers to the evolution of movement patterns or learnt behaviours as 'attractors' rather than schema which are perceived to be a more rigid representation of a movement pattern (Newell and Vaillancourt, 2001, Newell, 1991). Practically, this theory offers the idea of stable coordination of movement through repeated practice, and the necessity of integrating many factors in order to learn movement (Newell et al., 2001, Shumway-Cook and Woollacott, 2007). It seems to differ from the Schema Theory in it's concept of the development of a more fluid motor programme (attractor), which is more responsive to adaptation, than that proposed by schema. Thus this theory appears to be an evolution of the Schema Theory rather than something that directly contradicts it. In terms of the principles of motor learning this theory continues to support the need for feedback and practice variability identified within the Schema Theory.

Theories relating to 'how do we learn?' are underpinned by theories about the stages of motor learning, and for this we are referred to the Fitts and Posner Three Stage Model and Gentile's Two Stage Model (Magill, 2006, McMorris, 2008, Shumway-Cook and Woollacott, 2007). Fitts and Posner referred to a continuum of learning whereby the learner moved from a cognitive stage,

through an associative stage and came finally to an autonomous stage (Magill, 2006). Gentile's two stage model referred more to the development of the movement goal, where the first stage was for the learner to develop a motor pattern which becomes refined through practice and interaction with the contextual aspects of the task. The later stages of the learning were then underpinned by the learner's ability to adapt the task to new contexts and to show consistency in the task performance (Magill, 2006). Arguably, common to both were the need for instructions in the earlier stages of learning, and practice of the movement throughout the learning process.

'Instructions' refer to the commands that the 'teacher' gives to the 'learner' prior to his or her practice of the motor task. Instructions can have either an internal or external focus; an external focus would be where attention is directed towards thinking about where an item is placed on a shelf, as opposed to an internal focus where the learner would be directed to think about how straight the elbow is whilst achieving that same task (Wulf, 2007). Evidence from studies evaluating either an internal or external focus of instructions on motor learning have consistently found that motor learning was better if the focus of the instructions is external (Wulf, 2007). But this evidence once again predominantly referred to learning in healthy volunteers.

Gentile's emphasis on interaction with the contextual aspects of the task is supported by another theorist and suggests a motor learning principle relating to specificity of practice. Thorndike (1914) cited by Magill (2006) proposed the 'identical elements theory' which suggested that practice of a movement should involve the same or similar elements of the movement that needed to be learnt. Practice schedules that are contextually the same or similar to the desired task would enable better learning, in that transfer of learning to the actual situation would be more accurate. The concept of specificity of practice appears to conflict with the concept of variability of practice explored during the discussion of contextual interference. In order to discuss this further it is useful to remember how successful motor learning was originally defined at the start of this chapter. Requirements for successful learning were defined as consistency of performance, stability of performance in the face of disruption from internal

factors, sustained improvements in the performance seen over different periods of time and adaptability of performance to a variety of contexts (Magill, 2006). It is likely that the motor learning principle relating to practice specificity refers to learning outcomes around consistency and sustainabilty and that that of contextual interference relates to adaptability. There seems to be a place therefore for motor learning principles referring to both concepts. The effect of practice specificity was explored by Pellecchia (2005) who compared the effects of a balance training task under task specific conditions compared to non task specific and found a significant effect in favour of the task specific training ($P<0.05$). In this study the task specific group practiced exactly the same task that was being measured as an outcome of the study. It would be difficult therefore to extrapolate conclusions about the adaptability of this task to different contexts. It may be interesting, in the future, to explore the effects of both practice variability and specificity and measure their relative affect on outcomes that represent both accuracy and adaptabiliy to see if each has a different effect depending on the outcome used.

This overview of some of the theories surrounding motor learning supports a number of motor learning principles relating to the variability of physical practice, instructions, feedback and specificity (including context of the task, the objects involved within that task and the environment). Not explicit in this overview however, is the concept that practice can also be mental as well as physical (Shumway-Cook and Woollacott, 2007). Mental practice is the cognitive act of performing or practicing a skill in the absence of actual movement (Magill, 2006, Shumway-Cook and Woollacott, 2007). A meta–analysis of the effects of mental practice in the field of sports skill acquisition has shown that mental practice alone is marginally better than performing no practice at all (effect size 0.48, SD = 0.67) (Feltz and Landers, 1983). Although the evidence suggests that mental practice is not as effective as physical practice of the task, it may be useful as a means of promoting motor learning when the capacity for physical practice is limited (Hird et al., 1991).

Thus far, this section has identified and defined a number of principles that could influence motor learning. If these principles can be applied to the

development of interventions targeted at movement recovery following stroke, then arguably the potential to improve motor recovery and promote participation in activities of daily living may be enhanced. However, the body of evidence supporting the application of these motor learning principles has been developed and evaluated predominantly within healthy individuals who have an intact central nervous system (CNS). It is possible that stroke survivors by virtue of their diagnosis may be prevented from learning in the same way. Thus it should not be assumed that evidence supporting the application of motor learning principles in healthy participants can be directly transferred to stroke survivors (Hosp and Luft, 2011).

The followig section will review the evidence investigating whether or not stroke survivors are able to engage in implicit learning.

### 2.2.2 Overview of the evidence for implicit learning following stroke

Controlled trials investigating the ability to engage in implicit learning have evaluated whether stroke survivors have been as effective at learning an implicit motor task as a control group of healthy volunteers. Studies have shown that whilst learning did occur, stroke survivors were unable to learn as well as healthy volunteers, and that this was statistically significant (Winstein et al., (1999), $P<0.001$; Pohl et al. (1999), $P<0.002$; Boyd and Winstein (2004), $P=0.003$; Boyd et al. (2007), $P<0.002$); Vidoni and Boyd (2009), $P=0.005$). In these trials participants are commonly given a motor learning task such as a serial reaction time task, in which they are asked to respond to a series of lights by pressing a corresponding button when each light is lit. The sequence in which the series of lights are illuminated is repeated and can become implicitly learnt by the participant. Learning is demonstrated by a reduction in the time taken to complete the test sequences before and after the experiment (e.g. Boyd et al., 2007). Using a similar methodology, other studies have evaluated the accuracy of reaching the target rather than the time taken (e.g. Pohl and Winstein, 1999), thus learning is demonstrated by an improvement in the accuracy of reaching the target. Arguably these aspects are only one

characteristic of movement performance and these studies have not evaluated elements such as stability and adaptability of the learnt task (Magill, 2006).

Generalisability of the findings from the studies referred to above is limited by small sample sizes (Altman, 1990). Meta-analysis of the findings from these studies would be able to provide an effect size and estimate of statistical significance, this form of summary analysis might address this limitation (Borenstein et al., 2010). Participants included in these studies were all able to follow the instructions for completion of the task inherent within the study design (Boyd et al., 2007, Boyd and Winstein, 2004a, Gomez-Beldarrain et al., 1998, Orrell et al., 2007, Pohl and Winstein, 1999, Shin et al., 2005, Vidoni and Boyd, 2009, Winstein et al., 1999). In order to do this, it implies that the participants had little or no cognitive impairment. 38% of stroke survivors have some cognitive impairment three months after stroke (Patel et al., 2002) and this is likely to impact on implicit learning (Shumway-Cook and Woollacott, 2007). Studies evaluating the capacity for implicit motor learning in stroke survivors with cognitive impairments are therefore also required.

Another limitation to these studies arises because of the decision to test implicit motor learning through reaction time tests or accuracy tests with the ipsilesional or unaffected arm. (Boyd et al., 2007, Boyd and Winstein, 2004a, Gomez-Beldarrain et al., 1998, Orrell et al., 2007, Pohl and Winstein, 1999, Shin et al., 2005, Vidoni and Boyd, 2009, Winstein et al., 1999). Following stroke the contralesional or affected arm may display movement impairments that could lead to a difficulty in carrying out a serial reaction time task. These impairments may lead to slower times on a reaction time test or inaccuracies in reaching a target. Assumptions may subsequently be made about the participant's ability to learn, when the results may have occurred because of movement difficulties experienced as a consequence of the stroke. The decision to use the ipsilesional arm during both practice and outcome assessment avoids this confounder. Whilst this would seem appropriate as a means of evaluating the behavioural ability to learn a motor task, it is not appropriate as a means of investigating CNS activity during the learning of that task by a stroke survivor. Movement in each side of the body is predominantly controlled by the

contralateral structures of the CNS. Therefore neural activity within the damaged hemisphere, occurring in response to motor learning of the impaired limb, may manifest itself differently to learning involving the unaffected limb.

There is little published work identifying CNS activity before and after an implicit motor learning task using the impaired limb following stroke (Hosp and Luft, 2011). A small study by Meehan et al. (2001) attempted to identify the underlying CNS activity in response to a learning task in a small group of participants diagnosed with stroke (n=9) compared to that of healthy volunteers (n=9). Functional Magnetic Resonance Imaging (fMRI) was conducted during early practice of the task (day 1) (baseline), practice took place over days 2-6 and then a second fMRI was taken at day 7 (retention).

Behavioural tests indicated that both groups were able to learn the tracking task used in the study and fMRI revealed that during the early phase of learning both groups showed increased activity in the fronto-parietal regions as expected (notably dorsolateral prefrontal cortex (DLPFC) and premotor cortex). Activity in the DLPFC subsequently reduced during the second imaging session (day 7 – retention) for the group of healthy volunteers, demonstrating the need for less attentional resources as the activity became more familiar (learnt). This shift away from activity in the DLPFC was not, however apparent when the participants diagnosed with stroke were scanned at retention. In contrast to the group of healthy volunteers, Meehan et al. (2011) found increased activity remained within both the dorsolateral pre frontal area and the pre motor cortex in the group of stroke survivors. This suggests that the participants diagnosed with a stroke required continued attention to the motor tasks even after behavioural assessment would suggest that the task had been learnt. This was a small study which included stroke survivors who were at least twelve months post onset, and therefore, the findings cannot be generalised to all individuals diagnosed with stroke. More research is required, but this study does suggest that there are differences in the physiological response to learning in stroke survivors that may not be apparent in healthy volunteers. The continued assumption that physiological changes underpinning learning after stroke are the same as those that occur during learning in healthy participants

may be inaccurate (Hosp and Luft, 2011). The potential for different physiological responses, together with the findings from the previously discussed behavioural studies of implicit learning, support the theory that motor learning principles may not be able to be applied to movement rehabilitation of stroke survivors in exactly the same way as for healthy volunteers.

### 2.2.3 Application of motor learning principles to movement rehabilitation after stroke

Section 2.1.1 has identified the theoretical background which supports the idenitification of motor learning principles in relation to mental practice, instructions, feedback, variability of physical practice and practice specificity. This theoretical stance has been supported by findings from studies which have applied these principles to motor learning in healthy volunteers. The findings from behavioural studies, and preliminary physiological studies, indicated that these may need to be applied differently in movement rehabilitation after stroke. The aim of this following section is to review the evidence for the application of these principles in movement rehabilitation with people who have been diagnosed with stroke.

- Mental Practice

Mental practice is the cognitive act of practicing or performing a motor skill in the absence of any physical action taking place (Barclay-Goddard et al., 2011, Garrison et al., 2010, Nilsen et al., 2010). The benefits obtained from mental practice are believed to be based on the findings that mental practice of an action activates the same CNS structures that are recruited during actual movement of the same action (Grezes and Decety, 2001). A Cochrane review of the effects of mental practice for treating upper limb deficits incurred as a result of stroke found a statistically significant effect in favour of mental practice plus physical practice versus physical practice alone (SMD 0.78, 95% CI 0.24-1.31) (Barclay-Goddard et al., 2011). Interestingly, despite a good effect size and a small confidence interval, the authors of this review concluded that there was only some limited evidence in favour of mental practice combined with physical practice than physical practice alone. This rather conservative interpretation of their results may have been as a result of the heterogeneity

that was observed within the studies included in the meta-analysis, although they had tried to control for this in the analysis through the use of a random effects model rather than a fixed effect model (Borenstein et al., 2010). This review only referred to the effects of this intervention in the affected upper limb after stroke and findings may not apply to the recovery of lower limb function, however it did suggest that mental practice may be a useful adjunct to physical practice after stroke.

The benefits of mental practice as a means of promoting motor learning in movement rehabilitation after stroke lie in the potential that it has to increase neural excitability in the motor execution areas, in a manner similar to the action actually being performed but without need for actual movement. Thus mental practice may have the potential to be useful as a means of promoting motor learning in those stroke survivors who have had little or no return of physical movement but who have capacity to perform mental practice of movement (Garrison et al., 2010, Sharma et al., 2009).

Continued use of the term mental practice in this context may lead to some confusion, as it has been described in the literature as both an intervention used as part of movement therapy (Barclay-Goddard et al., 2011) and/or a motor learning principle (Magill, 2006). Therefore throughout this thesis the motor learning principle will be described as ‘priming’ and will be defined as:

> ‘Interventions that are reported to have a motor learning effect because they increase neural excitability in the movement execution system’

The term mental practice will then be used to describe the therapeutic intervention. Precedent for the use of the term ‘priming ‘ to describe excitation within the movement execution system has already been established within the published literature, for example Stinear et al. (2007).

Defining the motor learning principle in this way facilitates the identification and inclusion of other therapies which are also believed to be efficacious predominantly because of their ability to increase excitability in the motor

execution system. This would ensure that any subsequent reviews are inclusive of all therapies which are perceived to have the same motor learning effect. Examples of these therapies include action observation (Buccino et al., 2001), passive movements (Matteis et al., 2003), transcutaneous electrical stimulation (Golaszewski et al., 1999), thermal stimulation (Gelnar et al., 1999) and mirror therapy (Michielsen et al., 2011). Synthesis of the evidence for these therapies within the context of a motor learning approach for stroke survivors has not been carried out but could provide a valuable insight into the role that they may have in promoting motor learning.

- Instructions

Instructions are given to the participant directing their attention to either an external or internal focus. Evidence from healthy volunteers has suggested that motor learning is more effective if the instructions are externally focussed (Wulf, 2007). There is limited evidence evaluating the effect of instructions in stroke survivors, although a small study by Fasoli et al (2002) suggested the same outcome. Using a repeated-measures design, participants were randomly assigned to either an AB or BA sequence. Participants were asked to carry out the same reaching tasks under a set of instructions which had either an external or internal focus. Participants diagnosed with a stroke showed a statistically significant improvement in movement time ($p=0.002$) and peak velocity or speed ($p=0.002$) under the external focus condition. The generalisability of these findings is limited by the small sample size ($n = 16$), and inclusion criteria that stipulated that the participants had to be able to reach forward and grasp objects with the affected arm and show no evidence of comprehension impairments or apraxia (Fasoli et al., 2002a). Inclusion criteria such as these have the potential to exclude those individuals who have been more severely affected by the stroke; hence it is not readily applied to a broader population of stroke survivors. DePaul (2013) found that the use of motor learning principles was not always reported accurately. In light of this a more robust review of the literature is required to ensure that evidence underpinning the application of this motor learning principle has not been missed.

- Feedback

Feedback refers to information given to an individual about their performance, and which can be used as a basis for improvement (Magill, 2006). Feedback can be derived intrinsically or extrinsically. Intrinsic feedback is feedback provided through the body's sensory systems during completion of the task. Extrinsic or augmented feedback is provided by an outside source and can therefore be manipulated in order to provide feedback relevant to knowledge of results or knowledge of performance (Subramanian et al., 2010). Synthesis of the evidence for motor learning strategies after stroke has primarily focussed on the provision of extrinsic feedback (Glanz et al., 1995, Laver et al., 2011, Molier et al., 2010, Moreland and Thomson, 1994, Moreland et al., 1998, Subramanian et al., 2010, Woodford and Price, 2007). Feedback has been provided via electromyographic (EMG) biofeedback (Basmajian et al., 1982, Bradley et al., 1998, Wolf et al., 1980), balance platforms (Sackley and Lincoln, 1997) and virtual reality environments using a variety of sensory, visual or auditory feedback methods (Adamovich et al., 2008, Boian et al., 2002, Broeren et al., 2006, Deutsch and Mirelman, 2007, Gourlay et al., 2000).

Two reviews of extrinsic feedback have concluded that it may be of general benefit as a means of facilitating movement recovery following stroke (Molier et al., 2010, Subramanian et al., 2010). This assumption was based on a narrative synthesis of the included studies as the authors determined that heterogeneity prevented any form of meta-analysis. Meta-analysis would have provided a more rigorous means of assessing the findings and implications from the studies included in these reviews (Borenstein et al., 2010). These reviews were also confined to findings from studies that included upper limb function as an outcome, thus limiting their generalisability to lower limb outcomes such as walking. Woodford and Price (2009) appears to be the only review to date which has attempted to evaluate the effects of extrinsic feedback on lower limb functions such as walking. This review was however limited to one specific intervention, that of electromyographic (EMG) biofeedback and was similarly prevented from carrying out meta-analysis by virtue of the differing outcome scales used (Woodford and Price, 2007). A systematic

review of the effects of feedback including meta-analysis is warranted in order to determine more robust findings from the published studies to date.

- Practice Intensity

Engaging in physical practice was identified as an essential motor learning principle within all the motor learning theories reviewed at the commencement of this chapter. The quantification of the amount (dose) or intensity of physical practice necessary to promote motor learning after stroke remains however, undetermined (Cooke et al., 2010a, Veerbeek et al., 2011). Following stroke it is a widely held tenet by both researchers and clinicians that more practice is likely to result in better movement outcome (Kwakkel et al., 2006). The relationship between intensity of practice and movement outcome after stroke has been evaluated through two recent systematic reviews (Cooke et al., 2010a, Veerbeek et al., 2011). Both found limited support for the hypothesis that a higher dose of exercise-based therapy enhances motor recovery after stroke. However both reviews were limited by the heterogeneity of the included trials. There remains an ongoing need for well-designed trials that evaluate prospectively the intensity or dose of the same intervention (Cooke et al., 2010a). Without this work to evaluate optimum dose of an intervention, subsequent trials may go on to incorrectly interpret a lack of efficacy. This is an interpretation which could occur because an insufficient amount/dose of the therapy was actually given. Until this work is carried out further synthesis of trials already published is unlikely to produce more definitive findings.

The author of this present thesis extended the review initiated by Emma Cooke; the published paper has been attached as an appendix to this thesis as it adds to the body of knowledge surrounding the application of motor learning principles but would not have been appropriate for inclusion in this present thesis (appendix III).

- Variability of Physical Practice

Studies of healthy volunteers have suggested that motor learning is improved when the practice schedule is variable or random (Shea and Morgan, 1979),

although this may depend on the skill level of the learner (Brady, 1998). A theoretical review by Brady (1998) suggested that those with low levels of skill may show greater improvements in motor learning from a less random or massed schedule.

There is little work evaluating the effect of practice schedules in motor learning after stroke. Deprey (1999) published a single case report where random practice of a task led both to improved performance in the task and to effective transferability of the learnt skills. This report was based on a participant diagnosed with a stroke affecting the right parietal lobe; she had neglect and sensory problems affecting her left side and was also found to have severe cognitive problems. Although the task being taught was based around independence in walking, the problems that the participant experienced were not caused by motor impairments but were rather a product of her cognitive, perceptual and sensory impairments. Therefore results of this case report may be less relevant to improving motor impairment after stroke.

Cauraugh et al. (2007) evaluated the effect of a random schedule of practice versus a massed schedule of practice in patients presenting with chronic hemiplegia. They found no evidence to suggest that one schedule was better than the other but this may have been because outcome measurement took place immediately after the training programme. One of the reported benefits of random practice schedules is improved retention of learning (consolidation) or adaptability of that learning (Shea and Morgan, 1979). A more robust way of measuring the effects of random practice schedules may have been to carry out follow up assessments some time after the intervention phase. This may have provided a means of determining whether retention was better with one approach or the other. Outcome assessments could also have included a means of measuring adaptability of the learnt task by seeing whether it transferred to alternate environments. The findings from this study may also have been confounded by the presence of active muscle stimulation which was used to augment the movement practice. The muscle stimulation may have proved so effective that any effects of the practice schedules were negated.

The evidence in favour of either a random or massed practice schedule as a means of promoting motor learning in stroke survivors is lacking. It is possible that there is other evidence evaluating this motor learning principle in stroke rehabilitation studies but that they may be 'hidden' behind key words that describe an intervention rather than the way in which that intervention was delivered. A thorough, systematic search of the stroke rehabilitation literature, using key words that would encompass these studies, is required to determine if there are other relevant studies applying the principle of practice variability.

- Practice Specificity

Specificity of practice refers to the similarity between the task practice conditions and the final task that needs to be learnt. It can be related to the objects involved in the task practice, the task itself and/or the environment in which the practice takes place (Magill, 2006). This concept is already widely advocated within stroke rehabilitation (Langhorne et al., 2011). Aspects of this approach have been supported by a recent Cochrane review which evaluated the effects of task specific practice on functional outcomes measured by functional activity scales. Studies were included if the intervention involved practice of functional activities of the upper and/or lower limb. The review found statistically significant treatment effects for walking distance (standardised mean difference (SMD) 54.59 95% CI 17.5-91.68), walking speed (SMD 0.29 95% CI 0.04-0.53) and sit to stand (standardised effect estimate 0.35 95% CI 0.13-0.56). Results were however equivocal for upper limb interventions (French et al., 2010). Whilst this review did find statistically significant findings for the impact of the interventions on walking distance it is worth noting the large confidence interval for this analysis, which suggests a large degree of variability in the outcomes from these studies. This review was limited by the level of heterogeneity between the studies and this may have impacted on the findings particularly for the upper limb intervention studies. Further robust trials using the same outcome measures are needed before subsequent reviews of this aspect of practice specificity (task specific practice) are warranted.

Practice specificity has not been limited to physical practice, as evidence from imaging studies also highlights the potential benefits of object specificity during

mental practice interventions such as observation to imitate. Buccino et al. (2001) found more regions of the CNS were activated during action observation of an individual reaching to grasp a cup, compared to action observation of the same individual mimicking a reach to grasp movement without the cup. Evidence of excitation in areas of the motor execution system suggests that these areas are active. Evidence of increased activity in more areas of the motor execution system is desirable in that it correlates more highly with activation that occurs in response to movement. Priming of as many areas as possible may be more beneficial in influencing motor recovery following stroke (Garrison et al., 2010, Sharma et al., 2009). The increased activity experienced in the object specific scenario suggests, therefore, that greater efficacy may result from practice that is more specific to the intended action in context as well as in terms of the actual movement.

The manipulation of the environment through virtual reality, as another means of altering practice specificity after stroke, has also been documented (Laver et al., 2011). A Cochrane review of studies evaluating the effects of virtual reality and interactive gaming on measures of upper limb, lower limb and global function after stroke concluded that virtual reality was a promising rehabilitation approach (moderate effect on arm function measures (SMD 0.53 95% CI 0.25 to 0.81 based on seven studies with 205 participants) and larger effect on Activities of Daily Living measures (SMD 0.81 95% CI 0.39 to 1.22 based on three studies with 101 participants) (Laver et al., 2011). Virtual reality interventions in this study were diverse, in that they included studies where the participant interacted with a computer generated environment in both an immersive (as part of the environment) or non-immersive (gaming technology) situation. Some interventions were therefore designed to give extrinsic feedback about the accuracy of a specific reaching movement and therefore may not be facilitating motor learning via the principle of practice specificity.

This section has highlighted some of the evidence underpinning the application of motor learning principles in movement rehabilitation after stroke. The subsequent critique has suggested the need for a more robust review of the application of ‘priming’, ‘instructions’, ‘feedback’, ‘practice variability’ and

aspects of ‘practice specificity’. Further reviews of the task specific aspect of ‘practice specificity’ and ‘practice intensity’ were not indicated.

The following section will discuss the development of a framework as indicated by the discussion in section 2.1.

### 2.2.4 Developing a motor learning framework

Section 2.1 suggested that the development of a framework could contextualise the application of motor learning principles in movement rehabilitation after stroke. Such a framework could facilitate clarity of definitions and provide a common template for use within both research and clinical practice. Within the framework, clearly defined motor learning principles could facilitate systematic synthesis of individual therapy interventions, with the same underlying theoretical construct. For example therapies described as ‘observation to imitate’ and ‘thermal stimulation’ are reported to be efficacious because they increase neural excitability in the movement execution system, thus although different, both therapies could be seen to be applying the ‘priming’ motor learning principle. Similarly, studies which have used both biofeedback and balance performance monitors are applying the ‘feedback’ motor learning principle. Thus, in the emerging field of rehabilitation science where systematic synthesis of studies is limited because of heterogeneity, a motor learning framework may provide a means of grouping these studies under a common theoretical construct. Such categorisation may serve to decrease heterogeneity and facilitate systematic synthesis in order to provide robust evidence to support movement rehabilitation interventions after stroke (Shepperd et al., 2009 and Gough et al., 2012).

Motor learning principles per se are generally applied within the context of physical practice as a means of augmenting its effects (Magill, 2006). Stroke survivors who regain little or no movement may not benefit from motor learning principles that are usually applied to physical practice. Sub categorisation of the motor learning principles, within a framework, according to whether they

rely on physical practice or not may also prove useful within the context of stroke rehabilitation.

Figure two proposes a motor learning framework which includes the motor learning principles sub categorised according to whether there is evidence of their effectiveness in the absence of physical practice. 'Priming' is the only motor learning principle within the no/little movement category. This decision was founded on the findings by Feltz and Landers (1983) who found an effect on motor learning of mental practice without physical practice. No evidence of the same effect was found for the application of the other motor learning principles and therefore they have been categorised as 'augmenting'.

The framework has been shown in the context of its application to a physical therapy intervention. This linear representation of the motor learning principles is arguably too simplistic as practice specificity is likely to influence both the priming motor learning principle as well as physical practice, however, this framework does offer a starting point in trying to achieve some definition and structure to the application of these principles to physical therapies after stroke.

Since the development of this framework DePaul et al. (2011) have published a study evaluating the effects of the 'Motor Learning Walking Program'. This program embeds a treadmill training intervention within a motor learning framework. The framework and application proposed by DePaul et al. (2011) does not refer to the motor learning principles of mental practice or instructions and is supported by evidence from studies with healthy volunteers. It therefore seems less robust than the framework used in the present thesis in terms of its application to movement rehabilitation after stroke.

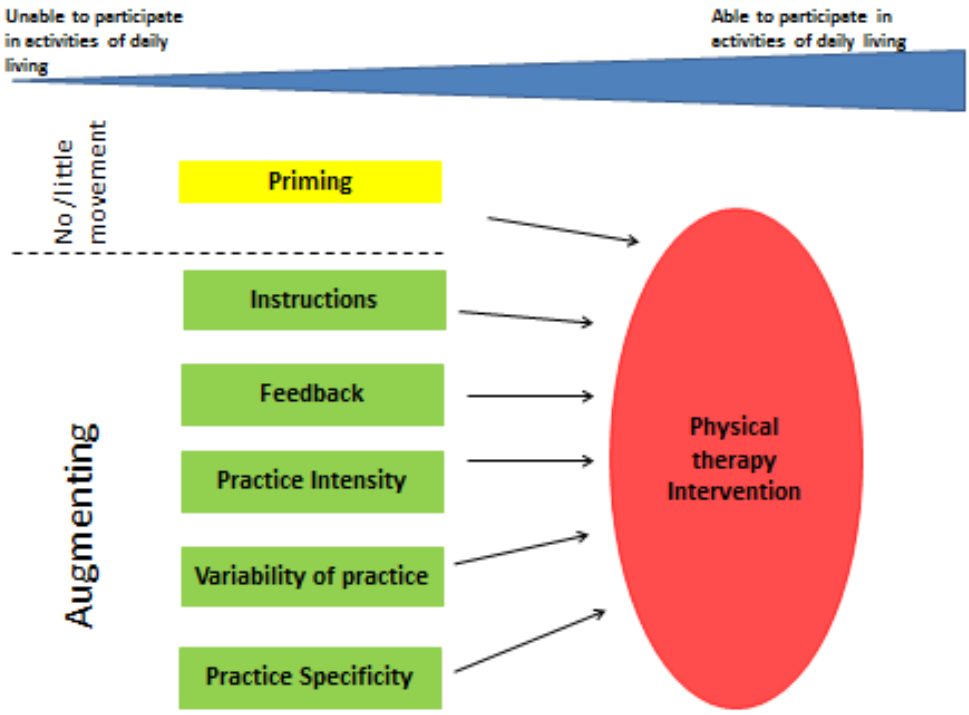


Figure 3: Motor learning framework

### 2.2.5 Summary

The use of motor learning principles within movement rehabilitation after stroke is becoming more evident, however, their application within this context has to a large extent been guided by evidence from studies in healthy volunteers. Studies investigating whether stroke survivors can engage in implicit learning, the type of learning that underpins complex motor skills, have shown that whilst they can learn, this learning is impaired compared to that of healthy participants. Thus it may not be appropriate to apply motor learning principles that have been investigated in healthy volunteers in the same way to stroke survivors. Systematic and quantitative synthesis of studies investigating how motor learning principles should be applied to motor learning after stroke is therefore required. A framework for contextualising the motor learning principles has been proposed. This facilitates clarity of definitions and provides structure to the application of these principles to interventions targeting movement recovery after stroke. Organisation of studies included in the subsequent review within

a motor learning framework may also serve to limit heterogeneity and thereby facilitate meta-analysis (Gough et al., 2012). Such a framework would allow for the grouping of disparate therapeutic interventions under motor learning themes identified by the motor learning principle that is being applied within the study. This would facilitate meta-analysis of studies comparing, for example, feedback derived through virtual reality and feedback from equipment such as balance performance monitors, as both interventions would be grouped under the 'feedback' principle.

One aim of this thesis is to develop a novel intervention by embedding a physical therapy (Functional Strength Training) within a motor learning context. The following section will explore the background literature supporting Functional Strength Training.

## 2.3 Functional Strength Training

Muscle weakness affecting one side of the body is a common symptom of stroke, with strength training interventions recommended by the National Institute for Health and Care Excellence in their recent guidelines for stroke rehabilitation (NICE guidelines, 2013).

Quantification of weakness during a static muscle contraction in both the affected upper limb and lower limb demonstrated that following stroke, muscle strength was statistically significantly impaired relative to the unaffected side ($p<0.001$) (Andrews and Bohannon, 2000). This loss of muscle strength is believed to contribute to the decreased levels of activity experienced by stroke survivors and consequently strengthening interventions have increased in popularity as part of movement rehabilitation after stroke (Ada et al., 2006). A systematic review of strengthening interventions, including non-exercise based trials using electrical stimulation and biofeedback, has revealed the potential for improvement in muscle strength in people following stroke. Muscle strength changes were measured in voluntary force production ($p=0.001$) (Ada et al., 2006) and grip strength ($p<0.001$) (Harris and Eng, 2010). Arguably, of more clinical relevance is the finding that these interventions can also effect a

statistically significant change in functional performance (p=0.002, (Ada et al., 2006) and p=0.03, (Harris and Eng, 2010), although this has only tended to occur in the manoeuvres that were being trained and thus did not transfer to other functional activities (Bohannon, 2007). This finding, together with the assertion that muscle strength is only one among many factors influencing the production of movement, has led to the conclusion that strength training interventions need to incorporate task specific elements within their programmes (Bohannon, 2007, Harris and Eng, 2010).

Functional Strength Training (FST) is an exercise-based intervention that combines conventional strength training techniques within a task specific context. The aims of FST are to improve muscle function such that the participant is able to take part in functional activities. The development of FST has emerged from early phase studies investigating both strength training interventions and task specific training. Patten et al. (2006) described a case study where one participant had received a combination strengthening and functional task practice programme called 'hybrid therapy'. The participant was 16 weeks post stroke so was arguably still within the subacute period of recovery. She received hybrid therapy for 75 minutes (35 minutes of resistance training and 40 minutes of functional practice) three times a week over six weeks aimed at improving strength and functional ability in the upper limb. The participant was reported to have been able to complete all training sessions and showed improvement in impairment and activity scores both immediately after the end of the intervention and at six months follow up. At this early stage of recovery this improvement could still be attributed to spontaneous recovery however the authors suggested that by completing this intensive post rehabilitation training that the participant had been motivated to sustain practice and continue to improve. The case study described by Patten et al. (2006) had no control phase and therefore the relative effects of the intervention as opposed to other factors such as spontaneous recovery were not detectable, however the intervention seemed well received by the participant and she tolerated the dose well. As described 'Hybrid therapy' offers both components of a functional strength training programme but each were delivered separately.

Sullivan et al. (2006) described another case study using a similar methodology but this time targeting lower limb recovery (Sullivan et al., 2006). The participant was 15 months post stroke at the time of enrolment to the study and therefore findings were at less risk of being confounded by spontaneous recovery (Cramer, 2008). The intervention offered a strengthening component through a progressive increase in limb loading during treadmill walking and increased resistance during a static cycling task, thus combining the strengthening component with task specific practice. On admission to the study the participant was relatively high functioning (52/56 on the BBS). The participant tolerated the intensity of treatment (24 sessions; 4 one hour sessions over six weeks) and showed improvement in the clinical outcome measures (gait speed increased by 18% and the distance walked in the 6 minute walk test increased by 4%). The Berg Balance Score (BBS) however decreased immediately following treatment by 3. Any score on the BBS above 45 is generally accepted to mean that the participant has no balance impairment (Berg et al., 1992, Zwick et al., 2000). A decrease by 3 in this case therefore is not likely to have any functional significance for the participant. At six months follow up the participant retained the improvements in walking speed. Although it is arguable whether these changes were also functionally significant to the participant as walking speed only increased by 0.09m/s. The intervention in this study necessitated use of equipment that would only be accessible in a clinical environment therefore delivery of this intervention would be limited to within a clinical setting. A qualitative study investigating barriers to exercise found that travel to and from the exercise location was one factor that inhibited participation in exercise programmes (Rimmer et al., 2008). The study by Sullivan et al. (2006) involved a single participant and therefore recruitment to the study was not an issue, however future studies aimed at determining feasibility and/or efficacy are likely to require a larger sample size. It may be useful therefore for future study designs to consider delivering the intervention using equipment that can be transported to home settings. This may facilitate recruitment to such a study as participants would not have to travel to take part.

Early work investigating the task specific practice component of a functional physical therapy programme was reported by Andrews (2000). The aim of this

study was to report on the findings from a case study which investigated the effects of a task specific physical therapy programme on lower limb recovery in one participant who was 38 months post stroke. The intervention took place in the participants own home. This study lacked the strengthening component and was delivered over a much greater period of time and with less frequency (twelve sessions every one to two weeks over a four month period, each session lasting between 60-75 minutes) than the previously described case studies. Following delivery of the intervention the participant showed an improvement in maximum ambulatory distance (increased by 200 feet) and the study indicated that a functional programme could be delivered successfully in a home environment.

Teixeira-Salmela et al. (1999) carried out a randomised pre-test, post-test study with thirteeen participants who were at least nine months after stroke. The study was targeted at the lower limb with six participants receiving the intervention and seven assigned to the control group. Once again the intervention was not specifically described as functional strength training but the description of the intervention suggests that both a progressive strengthening component and a functional task practice component were present. This study was delivered in an outpatient setting over ten weeks (three times a week for between 60 and 90 minutes). Following training walking speed increased by 31% ($p=0.004$) suggesting an effect of the intervention, although the absence of a power calculation for this study undermines this finding. A power calculation would indicate the sample size needed to determine whether the study had enough participants that the results once analysed could either support or refute the null hypothesis. Interpretation of the statistical significance is limited without a power calculation and it is unlikely that with such a small sample size that the findings from the study by Teixeira-Salmela et al. (1999) are robust (Altman 1990). The study authors also reported quality of life findings using the Nottingham Health profile. Improvements in this for those individuals who received the intervention also suggested that they found the intervention acceptable and perceived benefits greater than just improvements to their physical activity although this aspect of the study was also not powered therefore the same critique as described above applies.

Pilot work investigating strengthening and functional therapy programmes delivered to people later after stroke tentatively indicate that both these interventions were tolerated well by the participants. The studies described above have been predominantly carried out in people who are within the chronic phase of recovery from stroke. They suggest that people are able to tolerate an increased level of activity at later stages post stroke and that the potential for further recovery remains. The following paragraphs describe the trial-based literature that underpins functional strength training as an intervention that combines both strength training and task specific practice.

To date three randomised controlled trials have reported findings evaluating the effects of FST in participants following stroke. Findings from the trials are summarised in Table two (Bale and Strand, 2008, Cooke et al., 2010b, Donaldson et al., 2009a). The following risk of bias table shows the methodological strengths and weaknesses of the three studies according to the Cochrane method for assessing study quality (Higgins and Green, 2011).

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Bale and Strand (2008) | L | U | L | L | L | L | L |
| Donaldson et al (2009) | L | L | L | L | L | L | L |
| Cooke et al (2010) | L | L | L | L | L | L | L |

U Unclear
L Low risk
H High risk

Table 1: Table to show risk of bias from studies evaluating Functional Strength Training

The study by Bale and Strand (2008) was judged to be ‘unclear’ with respect to allocation concealment, this was because insufficient information was given within the published article to judge whether there might have been a risk of selection bias caused by biased allocation to either of the interventions (Higgins and Green, 2011). Findings from this study therefore need to be interpreted within this context and could be less rigorous than those from the other two studies. The risk of bias assessment for all other aspects of the study by Bale and Strand (2008) were judged to be low, as were all aspects of the studies by Donaldson et al. (2009a) and Cooke et al. (2010b) respectively. This assessment suggests that with respects to methodological quality the findings from both Donaldson et al. (2009a) and Cooke et al. (2010b) can be judged to be rigorous and the effects of the interventions on the study outcomes relied upon (Higgins and Green, 2011).

The trials conducted by Donaldson et al. (2009a) and Cooke et al. (2010b) compared three groups. These groups delivered conventional therapy (CPT), conventional therapy plus extra conventional therapy (CPT+CPT) and conventional therapy plus functional strength training (CPT+FST). The aim for this design was to provide an intervention group that would control for the potential confounder of dose or quantity of therapy received (CPT+CPT vs. CPT+FST). Findings summarised in Table 3 are the results from the CPT+CPT and CPT+FST groups. These results have been presented as they were the most comparable groups in terms of dose, thus findings from a comparison of these two groups were not confounded by the length of time that the intervention was received.

Bale and Strand (2008) and Cooke et al. (2010b) have targeted lower limb recovery following stroke and Donaldson et al. (2009a) targeted upper limb recovery. All three studies included stroke survivors within the so-called subacute period after stroke. Mean time from stroke onset to inclusion in the study was similar in all three studies (between 25.6 and 32.4 days). Movement recovery following stroke over this period of time is underpinned by a period of spontaneous recovery (Cramer, 2008). This process is different to the physiological changes that underpin movement recovery later after stroke

(Kleim and Jones, 2008) therefore findings from these studies cannot be directly applied to people who are within the chronic phase of recovery from stroke (six months and beyond).

Findings from the study by Bale and Strand (2008) showed a statistically significant improvement for the FST group in change in percentage body weight on both the affected and unaffected leg (although this was greater in the affected leg ($p=0.001$). There were improvements in both the control and experimental groups for isometric muscle strength of the affected knee extensors ($p=0.01$), habitual gait speed ($p>0.05$) and maximum walking speed ($p>0.05$), suggesting no difference between the effects of either the control group intervention or the experimental group intervention (FST). There was however a statistically significant effect in favour of FST on isometric muscle strength of the affected knee flexors ($p=0.02$), which was not replicated by the control group ($p=0.10$). There is some limited evidence to suggest therefore that FST may lead to both improved weightbearing and an increase in isometric muscle force of the knee flexors on the affected leg, however this is a small study and therefore there is potential for a Type II error. A type II error is the failure to reject a null hypothesis. Thus interpretation of these results might incorrectly suggest an effect for FST (Altman, 1990).

This study showed little difference between the control and experimental group interventions for activities that could arguably be perceived to be more meaningful to the participant. Measures of walking speed showed equivocal changes for both groups (Bale and Strand, 2008). In order to determine whether FST can be more effective than usual care it may be appropriate to consider alternative outcome measures that reflect functional activities which are influenced by increased weight bearing on the affected side. At present there is little evidence from this study to support the use of FST instead of usual care as an intervention that could make a change to a participant's ability to return to functional activities.

| | Control (CPT+CPT) group | | | | | Functional Strength Training (CPT+FST) group | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Participants** | **Age (years, SD[1])** | **Time since stroke (days, SD[1])** | **Side of hemiplegia** | **Intervention** | **Participants** | **Age (years, SD[1])** | **Time since stroke (days, SD[1])** | **Side of hemiplegia** | **Intervention** | **Motor related outcome measures** | **Findings** |
| Bale and Strand (2008) CPT+FST vs Training as usual for lower limb | n = 10 | 64.9 (8.8) | 32.0 (18.5) | Right 3, Left 7 | Training as usual, infleunced by Bobath concept, emphasis on decreased use of power to avoid associated reactions. | n = 8 | 60.8 (13) | 49.4 (22.1) | Right 6, Left 2 | CPT+FST to improve power of the lower limb, 50 minutes/day 5 days/week for 4 weeks | Maximum weight bearing (% body weight) | Increase in weight bearing on affected side in CPT+FST group (p=0.001). Control group p=0.153 |
| | | | | | | | | | | | Isometric muscle strength (knee ext and flex) (torque Nm) | Increase in torque on affected knee extension in both groups (p=0.01). Increase in knee torque on affected knee flexion in CPT+FST group (p=0.02). Control group p=0.10 |
| | | | | | | | | | | | Habitual Gait Speed | Improvement in both groups at p<0.05. Better in CPT+FST group |
| | | | | | | | | | | | Maximum gait speed | Improvement in both groups at p<0.05. Better in CPT+FST group |
| | | | | | | | | | | | Motor Assessment Scale | Not reported |
| Donaldson et al (2009) CPT+FST vs dose matched conventional PT upper limb | n = 10 | 73.3 (8.6) | 25.6 (15.5) | Right 6. Left 4 | Therapy with an emphasis on preparation and joint alignment via 'hands-on' sensory input. Activities like grasp and reach would use objects such as cones rather than cups. | n = 10 | 72.6 (12.5) | 21.7 (16.8) | Right 5, Left 5 | Specific functional tasks using verbal prompting rather than sensory cueing. Systematic progression through increased repetition and resistance. Up to 60 mins, 4 days a week for 6 weeks. | Action Research Arm Test | Improved score in both groups, Median change baseline to outcome - CPT+CPT 8.0 (13.2):CPT+FST 19.5 (22.0). Difference between groups p=0.23 |
| | | | | | | | | | | | Nine hole peg test (pegs per second) | Improved score in both groups, Median change baseline to outcome (IQR2) - CPT+CPT 0.05 (0.22):CPT+FST 0.11 (0.27). Difference between groups p=0.93 |
| | | | | | | | | | | | Hand grip force (N) | Improved score in both groups, Change baseline to outcome (IQR2) - Median 10.5 (40.25):CPT+FST 26.0 (44.0). Difference between groups p=0.52 |
| | | | | | | | | | | | Pinch Grip force (N) | Improved score in both groups, Median change baseline to outcome (IQR2) - CPT+CPT 9.0 (13.8):CPT+FST 19.0 (19.75). Difference groups p=0.60 |
| | | | | | | | | | | | Isometric elbow flexion force (N) | Improved score in both groups, Median change baseline to outcome (IQR2) - CPT+CPT 15.1 (25.3):CPT+FST 32.5 (55.8). Difference between groups p=0.70 |
| | | | | | | | | | | | Isometric elbow extension force (N) | Improved score in both groups, Median change baseline to outcome (IQR2) - CPT+CPT 9.0 (27.8):CPT+FST 13.5 (36.5). Difference between groups p=0.60 |
| Cooke et al (2010) CPT+FST vs dose matched conventional PT lower limb | n = 35 | 67.5 (11.3) | 32.4 (21.29) | Right 13: Left 22 | Included soft tissue mobilisation, facilitation of muscle activity, facilitation of coordinated multi joint movement, tactile and proprioceptive input, resistive exercise and functional retraining. | n = 36 | 71.2 (10.6) | 33.9 (16.5) | Right 12: Left 24 | Specific functional tasks using verbal prompting rather than sensory cueing. Systematic progression through increased repetition and resistance through goal-directed functional activity. Up to 60 mins, 4 days a week for 6 weeks. | Walking speed (m/s) | Improved score in both groups, Mean (SD[1]) - CPT+CPT 0.6 (0.5) (p=0.03):CPT+FST 0.4 (0.4)(p=0.33) |
| | | | | | | | | | | | Knee flexion torque | Greatest improvement in CPT+CPT group, Mean(SD[1]) - CPT+CPT 34.0(23.1)(p=0.16):CPT+FST 25.4(20.3)(p=0.33) |
| | | | | | | | | | | | Knee extension torque | Greatest improvement in CPT+CPT group, Mean(SD[1]) - CPT+CPT 45.3(35.9)(p=0.88):CPT+FST 35.9(28.5)(p=0.97) |
| | | | | | | | | | | | Modified Rivermead Index | Improved score in both groups. Mean (SD[1]) - CPT+CPT 36.6 (10.4)(p=0.73):CPT+FST 37.7 (8.6)(p=0.45) |
| | | | | | | | | | | | Symmetry step length % | Greater improvement in CPT+CPT group, Mean (SD[1]) - CPT+CPT 13.5 (15.8)(p=0.46):CPT+FST 51.5 (156.4)(p=0.24) |
| | | | | | | | | | | | Symmetry step time % | Greater improvement in CPT+CPT group, Mean (SD[1]) - CPT+CPT 18.8 (35.6)(p=0.48):CPT+FST 32.4 (91.5)(p=0.90) |
| | | | | | | | | | | | Walking speed of 0.8m/s | Greater improvement in CPT+CPT group, CPT+CPT 11/31 (35%)(p=0.04):CPT+FST 7/35 (20%)(p=0.42) |

**Table 2: Table to show the findings from the Functional Strength Training Studies**

Cooke et al. (2010b) found improvements in all the outcome measures for the CPT+FST group when compared to the control group in the study (CPT) but these did not reach statistical significance. Comparison of the outcomes between the CPT and CPT+CPT group showed statistically significant findings for walking speed (p=0.03). The improvements in the other outcome measures for CPT+CPT were also greater than those of the CPT+FST group, although these did not reach statistical significance. Findings from this study therefore suggest little effect of FST. Interpretation of the findings from this study need to be considered within the context of the study design, this was a phase II trial designed to evaluate feasibility of the intervention. A sample size calculated from the results of this trial estimated 660 participants would be required to determine effectiveness of the interventions. It would not be appropriate therefore to infer efficacy from a trial that included 109 participants (Cooke et al., 2010b).

The authors of this study proposed a number of reasons for the improvements seen in the CPT+CPT group. Arguably the one that is most important for the design of future trials of FST, is the possibility that the conventional physiotherapy, provided in the study, had incorporated a more task specific focus and was therefore too similar to the CPT+FST group (Cooke et al., 2010b). The design of this study had tried to control for this confounder by the use of treatment protocols emphasising different aspects of movement rehabilitation, however these did incorporate functional training. Clear protocols detailing the content of CPT and FST are needed in future trials of FST to ensure that the therapy received by each group is sufficiently different.

Trials of lower limb interventions may also need to consider the amount of 'extra' practice that patients receive outside of the research study. Simple transfers on and off the bed could be considered 'functional practice' and so the extra FST provided by Cooke et a.l (2010) could have been insufficient to provide further benefit.

The study of FST for the upper limb suggested more positive findings in favour of FST (Donaldson et al., 2009a). Once again the early phase study was not

powered to detect statistically significant changes in the outcome measures; however, median change scores for the FST group were much larger than those for the CPT group suggesting some effect of FST. The measures of functional ability at baseline for participants in the CPT+FST group were lower than those of the CPT+CPT group indicating that the participants in the CPT+FST group were more impaired. This difference caused the authors of this study to suggest that the change scores between the baseline and outcome measures for the CPT+FST group may have been better because these participants had more capacity for improvement (Donaldson et al., 2009a). This suggestion is at odds with studies that have found poor functional recovery on admission to stroke units to be an indicator of poor functional recovery following rehabilitation (Kwakkel et al., 1996). FST may therefore have proven highly effective in this group of participants, although this can only be speculation in light of the small sample size. As a precaution future trials of FST should consider severity of stroke as a potential confounder and control for this within the study design.

The previous sections have summarised findings from FST studies to date. The evidence suggests that FST is a feasible intervention for both the affected upper limb and affected lower limb in people after stroke but that the findings from these trials are only relevant to stroke survivors within the first three months after stroke.

Recovery in the acute phase of stroke is underpinned by a period of repair. Following the damage caused by stroke, the brain responds by clearing away debris and creating an environment for remodelling and synaptogenesis (Cramer, 2008, Kelley and Steward, 1997). This increase in activity is time dependent and decreases approximately six weeks after the onset of stroke, with most recovery from stroke reported to be within the first three months (Cramer, 2008). Recovery of functional activities over this period of time show rapid improvement (Partridge et al., 1987). The rapidity of functional gains subsequently decreases as time from onset increases, although significant changes to functional ability can still be made years after stroke onset (Murphy and Corbett, 2009, Ferrarello et al., 2011).

The processes that underpin later stage recovery from stroke are different from those occurring in the earlier stages (Kleim and Jones, 2008). Changes in functional ability later after stroke, are underpinned by the same physiological changes that occur within the healthy brain during learning (Kleim and Jones, 2008, Nudo and Milliken, 1996, Taub et al., 2002). These processes include cortical reorganisation, such as the unmasking of existing pathways (Qu et al., 1998) and sprouting of new dendrites (Allred and Jones, 2004), and they have been revealed through a variety of imaging techniques, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and transcranial magnetic stimulation (TMS) (Buma et al., 2012).

Despite the potential for on-going movement recovery later after stroke, movement impairments may persist. These impairments may lead to difficulties moving the affected arm or the affected leg which can in turn lead to poor levels of activity. Persistent inactivity may lead to physiological adaptation of the brain structures. A study involving stroke survivors within the chronic phase of recovery showed, poor motor function measured by the motor activity log paralleled decreased activation of central nervous system (CNS) structures involved in movement execution (Liepert et al., 2000). Thus, there is an opinion that physiological changes within the brain and body structures may further compound the disabling effects of the stroke (Taub, 2004). Secondary adaptation in muscle leads to length associated changes and disuse, which in turn leads to alterations in both the active and passive properties of the muscle. This causes further negative impact on movement and function (Ng and Shepherd, 2000). These adaptations are unlikely to be present to the same degree within the early phases of recovery after stroke. Thus physical therapy interventions perceived to be efficacious or feasible over this period of recovery may not be effective in the chronic phase because they may not target these time dependent changes.

There is a widely held belief that stroke survivors in the so-called chronic phase of recovery from stroke are perceived to have plateaued in terms of potential for further motor improvement (Page et al., 2004), and this belief may have led

to the assumption that rehabilitation services delivered to people later after stroke would have little impact. In a healthy population the capacity to learn, and thus the brain's capacity to physiologically adapt and change, remains throughout life (Kleim and Jones, 2008), although it decreases with age (Sawaki et al., 2003). Therefore if the process for functional recovery from stroke, and the process underpinning learning are similar, then the concept of a motor recovery plateau may be caused by something other than the stroke survivor's capacity to relearn and/or compensate for the movement impairments created as a consequence of stroke.

It has been suggested that the perception of a motor recovery plateau may be driven by the healthcare environment rather than a true occurrence (Page et al., 2004). Stroke rehabilitation is often subject to restrictions in terms of time and resources and whilst acute services in the UK have seen considerable improvement since the advent of the National Stroke Strategy, rehabilitation services have not matched this (National Audit Office, 2010). It is possible that when stroke survivors stop making significant improvements in their recovery, access to services such as physiotherapy, declines and eventually stops. Stroke survivors are told that they have plateaued and are unlikely to make further progress (McKevitt et al., 2004). Believing this to be the case and without access to health professionals, it is highly possible that stroke survivors have little motivation to continue with exercise programmes that may continue to benefit them in terms of functional outcome. Thus the perception of a motor recovery plateau is reinforced. Overcoming a lack of motivation to exercise is one barrier faced by a research team that is looking to evaluate the effects/feasibility of exercise-based physiotherapy techniques in stroke survivors. Other factors which have been identified and which would also limit engagement in physical activity include: not knowing how to exercise, having a lack of energy as well as motivation, the perception that the exercise would not improve their condition and a lack of transportation to facilities (Rimmer et al,, 2008). Physically stroke survivors, who have continued to experience impairments, may adopt a more sedentary lifestyle which is likely to impact on their overall cardiorespiratory fitness (Marsden et al., 2013). Therefore exercise programs, even those which are not specifically targeted at aerobic fitness,

need to be designed to incorporate the possibly greater potential for fatigue. Barriers to the participation in exercise groups outside of the home may also occur because of impairments related to communication difficulties. A survey found that those individuals with communication problems were more likely to need help with social participation than those individuals without a communication problem ($p<0.001$) (McKevitt et al. 2011). This survey included 1251 participants who were within one to five years after stroke The findings from the survey have particular implications for the delivery of programs to stroke survivors where the incidence of communication problems is one third (Department of Health, 2007).

The factors described above seem to have evolved as responses stroke survivors have made because of the long term impairments that are a consequence of stroke. The evaluation of exercise based physiotherapy techniques, such as Functional Strength Training, which have been developed with people in the early stage of recovery will need to consider the impact of these factors on the delivery and acceptability of the intervention, if it is to be successfully evaluated in people who are within the chronic phase of recovery from stroke.

Despite these potential barriers research programmes involving exercise have been delivered to people in the chronic stage of stroke and have proven efficacious in terms of improving functional ability (Ferrarello et al., 2011). Stroke survivors who have participated in an exercise program have identified positive reasons for taking part in both aerobic and resistance training. Most commonly, these were “desire to improve overall health, improve functional abilities, enhance confidence, reduce musculoskeletal issues, and family support.” (Jurkiewicz et al., 2011 p. 280).

Awareness of both the potential barriers and motivators to engaging in exercise programmes later after stroke may help researchers adapt the design of an intervention and its subsequent evaluation from that which has previously been tested in stroke survivors in the acute stage of recovery and within a hospital setting. Notably they may need to ensure that the exercises will aim to improve

functional ability so that participants are able to discern what the potential benefits of taking part in the study may mean to them; they may need to ensure that the intervention is delivered in such a way that the participant is able to carry out the required activities; they may need to consider how to motivate the participant throughout the course of the study and they may need to consider the context of the study so that travel costs are avoided/costed into the study and participants are socially supported where appropriate (Rimmer et al., 2008).

### 2.3.1 Overview

Muscle weakness is common after stroke and is believed to contribute to the loss of function experienced by stroke survivors although strength training interventions may be effective in increasing muscle power. These interventions are likely to be most effective at increasing the stroke survivors ability to take part in activities of daily living, if they incorporate strength training principles within a task specific context. Functional Strength Training incorporates both these elements, and early phase trials have shown that FST is a feasible intervention for improving functional recovery in both the arm and the leg early after stroke. The differences in recovery processes observed in the brain between stroke survivors in the early and later stages after stroke, and the long term effects of disuse, indicate however that the efficacy of rehabilitation interventions evaluated in people within the acute phase of recovery may not necessarily be applicable to people later after stroke. There is a need therefore to determine whether FST is a feasible intervention for both the upper and lower limb in people in the chronic phase of recovery after stroke.

The following section will consider the topic of intervention fidelity and how it might usefully inform the design and delivery of a feasibility study of FST to people later after stroke.

### 2.3.2 Intervention Fidelity

Intervention fidelity, a term which can also be used interchangeably with treatment fidelity refers to the methodological strategies used to enhance the reliability and validity of clinical interventions which are designed to effect a change in behaviour. Section 2.2 identified that people in the chronic stage of

recovery from stroke may not have engaged in exercise for a prolonged period of time. In order for a study which is designed to test the feasibility of an exercise-based intervention such as FST to succeed, it is apparent that this behaviour will have to change.

The concept of intervention fidelity appears to have been studied predominantly within psychological, social and behavioural research (Bellg et al., 2004, Gearing et al., 2011). In an early opinion paper on this topic Moncher and Prinz (1991: pp. 247) referred to treatment fidelity as being “two related, but distinct, issues”. These were:
The degree to which the experimental interventions were implemented as intended and secondly that there was sufficient differentiation between the two experimental conditions such that the findings from the study could be attributed to the independent variable.

It was reported that poor intervention fidelity could lead to unreproducible interventions, a decrease in statistical power and low uptake of potentially effective interventions (Moncher and Prinz, 1991). With this in mind a working party was subsequently created to examine the issues of intervention fidelity and to produce a set of guidelines for improving this in a particular group of studies examining the effectiveness of experimental interventions targeting change in health behaviours. The Behaviour Change Consortium (BCC) published best practice and recommendations for ensuring intervention fidelity (Bellg et al. 2004). In this the authors have addressed areas broader than the original definition of intervention fidelity posited by Moncher and Prinz (1991) and the working definition for intervention fidelity expanded to “the methodological strategies used to monitor and enhance the reliability and validity of behavioural interventions” (Borelli et al., 2005 pp852). However the underlying goal of improving study rigour remained the same.

The BCC described five areas where intervention fidelity could be addressed. These are:
- Design of study
- Training providers

- Delivery of treatment
- Receipt of treatment
- Enactment of treatment skills' (Bellg et al., 2004).

These will be described below along with barriers and facilitators to each of these with examples from studies published in the field of long term conditions. There appears to be limited work published in this field specific to exercise and stroke and therefore the literature used has been expanded to include studies which have also evaluated the use of exercise in the management of other cardiovascular diseases.

- Design of study: Methodological strategies aimed at ensuring intervention fidelity in this category are intended to ensure that the intervention has been appropriately identified (i.e. that there is sufficient theoretical and clinical underpinning), to avoid confounders such as the delivery of different 'doses' of each experimental intervention and strict adherence to the research protocol (Bellg et al., 2004).

  Defining and delivering an intervention consistently is important in research trials because of the need to be able to communicate it's content to care providers if the results suggest that the intervention is effective. This can be particularly challenging in the evaluation and subsequent dissemination of complex interventions such as those designed to manage health behaviour change which may have several components and be delivered across different care settings (Spillane et al., 2007). The development of a robust treatment manual with clearly defined interventions may go some way to addressing this.

  Monitoring adherence to a research protocol and ensuring effective delivery of interventions that are self-directed such as engagement in an exercise programme may however prove particularly challenging. In their guidelines for best practice Bellg et al (2004) listed several strategies that could be incorporated into the study design which may help address these potential issues. These included checking by

research staff to ensure adherence to the protocol and the inclusion of methods for enabling participants a means of recording their engagement in the exercise programme. A review of intervention fidelity across exercise trials in participants with diabetes found that studies ensured adherence to the intended quantity of therapy by telephone calls, and motivational techniques such as goal setting (Avery et al., 2012).

Bellg et al. (2004) also suggested that studies could prevent implementation setbacks, such as lack of research staff to deliver the intervention by ensuring a pool of trained researchers. This of course carries its own challenges in that training of any extra staff needs to be maintained and monitored to ensure adherence to a protocol. Although this is likely to increase the costs of a study Henggeler et al. (1997) argued that these were minimal when compared to the expense incurred if ineffective treatments are declared effective because of poor intervention fidelity practices.

The following area published in the guidelines specifically addresses training the intervention providers. The underlying goal for this area is also related to ensuring adherence to the research protocol.

- Training providers; strategies within this category suggest standardising training, ensuring provider skill acquisition and maintaining provider skills throughout the study.

Consistent training of the intervention providers is one method of attempting to improve adherence to a protocol. Particular barriers to this include lack of resource dedicated to this aspect of a study and poorly defined interventions. Studies may need to consider the costing implications for ensuring that intervention providers are trained and that this training is monitored and updated throughout the study. The quality of the training should be supported by treatment manuals which describe clearly defined interventions. Where this is not the case then intervention providers may misinterpret the instructions and deviate from

the protocol. Such actions would threaten the rigour of the study findings (Bellg et al., 2004).

In a study evaluating the effectiveness of a treadmill training programme with stroke survivors Resnick et al. (2011) identified that demonstrating intervention fidelity within this category was particularly challenging because of the high turnover of intervention providers. This had led to some discrepancies between the protocol and aspects of the intervention delivery. As the study progressed the research team had managed this by ensuring that there were regular reviews of treatment fidelity which enabled them to be able to reinforce prior training and pre-empt further deviations.

Borelli et al. (2005) developed a tool for assessing intervention fidelity and used this to evaluate the quality of treatment fidelity in 342 trials evaluating interventions targeted at health behaviour change. They found that only 22% of the included studies reported on the training strategies for the intervention providers. This review only reflects how well these studies have reported this aspect of intervention fidelity but does seem to indicate that further consideration may need to be given to the challenges researchers face in ensuring that intervention providers are suitably trained.

- Delivery of treatment. This category was created to address aspects such as controlling for provider differences, ensuring adherence to treatment protocol and ensuring that control and intervention are sufficiently different and that there is no overlap between these if they are delivered by the same provider (Bellg et al. 2004).

  Where one provider is providing both experimental and control interventions then there is the potential for contamination of either intervention, this may be exacerbated if the provider has a particular bias, inadvertent or otherwise (Bellg et al., 2004). In the SPHERE project which evaluated the effectiveness of secondary prevention measures

including exercise in people with heart disease this aspect of intervention fidelity was managed through quality assurance visits by the research nurses, The study team also carried out randomly selected ‘checks’ of the intervention delivery at different time points in the study (Spillane et al., 2007).

- Receipt of treatment – Bellg et al. 2004 created this category to monitor whether studies were able to demonstrate that the participant understood the intervention and whether or not they were able to carry it out.

  Where studies rely on active participant engagement with cognitive strategies it is important that the research group determine that the participant understands what is involved and is able to carry out the task. Interventions such as mental imagery may involve the generation of static images, auditory recall, complex tasks or visual patterns and it may not always be possible for individuals to carry out these activities (Pearson et al., 2013). This may be particularly challenging if researchers are seeking to be inclusive in their sampling strategy. For example, following stroke, potential participants with cognitive problems may be unable to take part, thus biasing the sample.

  Studies aiming to deliver exercise such as that conducted by Resnick et al. (2011) need to ensure that the study population is capable of carrying out the required level of intensity and will remain motivated to do so. Resnick et al. (2011) evaluated the effects of treadmill training on cardiovascular fitness in stroke survivors who were within the chronic phase of recovery from the stroke. The threshold level of intensity (40% to 50% of the maximal heart rate reserve, 20 minutes continuous exercise, three times per week for six months) set by the study authors was arguably quite challenging for the participants who, as has previously been identified, may not have engaged in physical activity for some period of time. Inclusion criteria for this study therefore focussed on a more physically able sample of stroke survivors making the findings

less generalisable to the wider population (Altman, 1990). Strategies that were then used to facilitate ongoing engagement with the exercise were to deliver the intervention in an environment where the participants were socially engaged and able to motivate one another and to use verbal encouragement by the research staff. These strategies appeared to be effective as participants completed the desired number of exercise training sessions.

- Enactment of treatment skills – this refers to the ability of the participant to be able to perform the skills/behaviours required by the research study to 'real-life' settings. An example of this described by Bellg et al. (2004) are the appropriate use of a cognitive strategy to prevent cigarette cravings. This category is distinct from adherence to the treatment protocol which would simply record whether or not the participant had engaged in the intervention not whether or not they had used it in the appropriate way.

  Interventions aimed at changing behaviours are generally deemed successful only if they can effect a change within 'real-life', therefore by addressing 'enactment of treatment skills' in the study design, study authors are prompted to assess whether participants use the experimental skills appropriately throughout the study. This is believed to give an indication of whether this will effect a change in their health behaviour once the study has stopped, a factor which can then be more accurately assessed if participants are subsequently followed up after completion of the intervention phase (Bellg et al., 2004). Adherence to exercise programmes declines following withdrawal of an exercise intervention (Jurkiewicz et al., 2011, Karingen et al., 2011). Arguably studies that address the concept of 'enactment of treatment skills' may find that long term adherence to the exercise programme following the end of the study may improve.

Intervention fidelity refers to the strategies that have been developed for ensuring that the findings from studies evaluating interventions targeting health

behaviour change are both reliable and robust (Moncher and Prinz, 1991; Bellg et al., 2004). This section has briefly reviewed some of the literature around intervention fidelity and the barriers and facilitators to its implementation. Arguably many of the aspects included in the guidelines developed by Bellg et al. (2004) could be considered to be best practice in research design and therefore should be inherent within individual study designs and protocols. However a review of intervention fidelity by Gearing et al. (2011) found that core components of fidelity such as study design, training providers and intervention receipt were still not being addressed sufficiently. Further reflection on the role of intervention fidelity strategies and their place within the design of the feasibility study described in this thesis will be discussed in chapter seven.

## 2.3 Summary

Therapies, such as Functional Strength Training, targeting late stage recovery of movement after stroke have the potential to increase an individual's ability to engage in activities of daily living. These may be more effective if they are integrated into motor learning. Within the framework of developing complex interventions this thesis seeks to describe two studies, the results of which will inform the future development of a novel intervention. The following chapter will outline the aims and objectives for this thesis.

## 3.0 Statement of Aims

There are approximately 1.1 million stroke survivors living in the United Kingdom (Townsend et al., 2012) and 76% of these people have movement impairments as a result of stroke (Intercollegiate Stroke Working Party, 2011). Physical therapy after stroke includes a number of interventions that aim to minimise the secondary effects of stroke and promote the return of movement so that the stroke survivor is able to take part in activities of daily living. This may be achieved by retraining movement so that individuals can return to activities in the same way that they had done before the stroke, or it may mean teaching compensatory strategies where this is not possible.

The field of motor learning addresses the theories and principles that are believed to underpin skill acquisition. In chapter two it was suggested that the goal for both physical therapy interventions after stroke and motor learning are the same i.e. a change in movement performance. There is potential therefore to develop an intervention which combines both bodies of work, such an intervention may lead to enhanced movement recovery and a better return to activities of daily living.

The application of motor learning principles to date has been largely based on the findings from studies in healthy volunteers, a systematic review of their application within movement recovery after stroke will provide evidence of their use with stroke survivors and therefore may be able to suggest more relevant methods of applying these.

Muscle strength is widely considered to be one of the main causes of loss of performance in functional activities; interventions targeting this impairment are arguably therefore of great importance. Functional Strength Training is designed to increase muscle strength and increase participation in activities of daily living in stroke survivors. The work to develop this intervention was however restricted to people within the early phase of recovery from stroke. Physiological differences in response to early and late stage recovery from stroke mean that an intervention which is feasible in one group of stroke

survivors may not be in the other. A feasibility study investigating the effects of Functional Strength Training in stroke survivors within the so-called chronic phase of recovery from stroke is therefore indicated.

Subsequent development of a novel intervention from the results of both studies will show how Functional Strength Training can be delivered within a motor learning context. This could serve as an exemplar to inform the development of physical therapy interventions in the future.

## 3.1 Aims:

The aims of this thesis are to:

- Aim 1: To systematically identify the relevant literature for inclusion in a literature review according to a motor learning framework.
- Aim 2: To seek to quantify the findings from the review through meta-analysis where appropriate.

    Objective 1: Establish the evidence for the effectiveness of the application of motor learning principles to promote motor learning after stroke.

- Aim 3: To carry out a phase II randomised controlled trial to determine feasibility of a physical therapy intervention – Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke.

    Objective 2: Establish feasibility of Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke by determining likely rates of recruitment.

    Objective 3: Establish feasibility of Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke by testing procedures for acceptability including the choice of outcome measures and the pragmatics of delivering the interventions.

Objective 4: Provide information for calculating a sample size for evaluation trials.

- Aim 4: To present a novel intervention combining the results of the studies conducted fulfilling aims one and two in order to suggest how a motor learning framework could inform the delivery of physical therapy interventions as part of movement rehabilitation after stroke.

This thesis will therefore aim to address the following research questions:

**Question 1:**
What is the effectiveness of motor learning principles applied to people after stroke in order to promote motor learning?

Study 1: To systematically review the relevant literature and carry out meta-analysis in order to provide evidence for the use of motor learning principles in stroke rehabilitation.

**Question 2:**
Is Functional Strength Training a feasible intervention for improving upper and lower limb recovery later after stroke?

Study 2: Functional Strength Training to improve upper limb function and walking in people between six months and five years after stroke: A phase II trial.

**Question 3:**
Based on the findings from study one and study two how should physical therapy intervention be developed in the future within the context of a motor learning framework?

# 4.0 What is the effectiveness of the application of motor learning principles applied to people after stroke in order to promote motor learning? A systematic review of the evidence (Question 1)

## 4.1 Introduction

Chapter two identified the following motor learning principles, priming, instructions, feedback, practice intensity, variability of physical practice and practice specificity. If these principles are applied to movement rehabilitation after stroke, they may have the potential to enhance physical recovery and promote the stroke survivor's return to functional activity. However, motor learning in people following stroke has been shown to be impaired compared to healthy volunteers and thus it may not be possible to generalise findings from studies regarding motor learning principles with these participants to stroke survivors. Synthesis and quantification of the evidence for the application of these motor learning principles to people after stroke is lacking. The aim of this study is:

- Aim 1: To systematically identify the relevant literature for inclusion in a literature review according to a motor learning framework.
- Aim 2: To seek to quantify the findings from the review through meta-analysis where appropriate.

> Objective 1: Establish the evidence for the effectiveness of the application of motor learning principles to promote motor learning after stroke.

The following section will describe the design and subsequent methodology of a systematic review in order to answer the following research question:

What is the effectiveness of motor learning principles applied to people after stroke in order to promote motor learning?

## 4.2 Design

A systematic review provides a means by which evidence can be systematically identified and synthesised in order to provide an answer to a research question or to identify gaps within the current knowledge base (Higgins and Green, 2011). As previously discussed, synthesis of the evidence identifying how motor learning principles should be applied to stroke survivors in order to promote motor learning and return to functional activity is lacking. A systematic review would therefore seem the most appropriate means of addressing this gap and providing an answer to the above research question. Due to the strict set of guidelines that are laid down Cochrane reviews are reported to be methodologically more robust and at less risk of bias than non-Cochrane reviews (Moher et al., 2007), therefore design of this review will be informed by the Cochrane methodology.

## 4.3 Eligibility criteria

The Cochrane methodology follows a process where criteria for the inclusion and exclusion of studies are pre specified. The intention behind this is to limit bias and ensure that the review process has been carried out rigorously (Higgins and Green, 2011). Where protocols stipulating the inclusion and exclusion criteria are not published before the review, then there is the potential for review authors to bias the findings (Moher et al., 2007). Eligibility criteria are guided by the research question and therefore for this study the following criteria have been defined:

Participants:

- Adults aged over eighteen years

  75% of stroke survivors are over the age of 35 (Intercollegiate Stroke Working Party, 2012). This criteria will ensure that the findings from this review are able to be generalised to a large proportion of stroke survivors. Physiologically there are also differences in the response to central nervous system damage in children compared to adults, which may prevent the application of motor learning principles in the same for both populations of stroke survivors (Johnston, 2004).

- Diagnosed with stroke of either ischaemic or haemorrhagic origin, with no restriction from time since onset.

  In order to be as inclusive as possible the diagnosis of stroke included within the review was not restricted to either ischaemic or haemorrhagic origin. All periods of time since stroke were included, although as recovery processes early after stroke are different to those later after stroke (Kleim and Jones, 2008) it is possible that this distinction will need to be reflected on at some stage within the study findings.
- Participants presenting with a motor impairment of either the affected upper limb or the affected lower limb

  The aim of the review is to consider the efficacy of motor learning strategies on movement recovery; therefore participants within the studies being considered for inclusion had to be diagnosed with a motor impairment as a consequence of stroke. Both upper and lower limb impairments were included as previous reviews have tended to focus on upper limb recovery (Molier et al., 2010, Moreland and Thomson, 1994, Subramanian et al., 2010).

Interventions:

- Randomised controlled trials (RCT)

  RCT are reported to be the 'gold standard' for measuring the efficacy of an intervention (Sim and Wright, 2000). Therefore synthesis of the evidence derived from an RCT is arguably more robust than that derived from a study of potentially lesser quality.
- Control and intervention groups needed to be identical except for the application of a motor learning principle. The findings from earlier reviews of the effects of intensity or dose of therapy have been limited by the inclusion of studies that have compared two different interventions at different doses (Kwakkel et al., 1997, Kwakkel et al., 2004). Consequently changes in the outcome measures within each of these studies could not be attributed to the different amounts of therapy that the participants had received. To avoid the potential confounder of comparing two different interventions this criteria will ensure that the only

dependent variable (i.e. one likely to affect outcome) will be the effects of the motor learning principle.

- No presence of electro-stimulation, robotics, orthotics or equipment that will supplement/support movement. Adjuncts to movement may confound the effects of the motor learning principle such as that experienced by Cauraugh et al. (2007).
- Application of a motor learning principle

  Systematic reviews of complex interventions, such as the application of motor learning principles, are confounded by inherent difficulties. Interventions may have the same underlying aim but be described differently or inadequately within the published literature (Shepperd et al., 2009). One solution to this is categorisation, this helps limit heterogeneity by identifying the common aim within studies describing different interventions (Gough et al., 2012, Shepperd et al., 2009). The content of these categories were guided by the background chapter (chapter two) and the subsequent development of a motor learning framework displayed in figure two (section 2.1.4).

  Motor learning principles were categorised as either needing 'no/little movement' or 'augmenting' if they are usually applied to physical practice as described in the framework in section 2.1.4. Motor learning principles will include priming, instructions, feedback, variability of practice and practice specificity. It did not include practice intensity as the background chapter identified a recent, robust synthesis of this body of work (Cooke et al., 2010a, Veerbeek et al., 2011). It also did not include task specific practice as one component of practice specificity for the same reasons (French et al., 2010).

  Motor learning principles were therefore categorised as:

  **Needing little or no return of movement**

  – Priming - Interventions that are reported to be efficacious because they increase neural excitability in the movement execution system.

**Augmenting**

- Instructions – Commands given by the 'teacher' and can have either an internal or external focus.
- Feedback – information given to a learner which can be used as a basis for performance improvement.
- Variability of practice – Refers to the arrangement of the practice schedules which can be arranged in either a massed or random way.
- Practice specificity – refers to the similarity between the task practice conditions and the final task that needs to be learnt.

Outcomes:

- Outcome measures in the impairment, activity or participation domains of the International Classification of Functioning, Disability and Health (ICF) (World Health Organisation, 2001), measuring movement or movement related outcomes.

  The focus of this review is on movement recovery therefore outcomes evaluating changes to cognitive, perceptual or sensory function were not included.

## 4.4 Search Strategy

In order to be as systematic and unbiased as possible it is important to design a search strategy that will identify as many relevant published studies appropriate to the research question as possible (Gough et al., 2012). Designing the search strategy includes identification of the appropriate databases as well as suitable key words with which to search. The search strategy needs to be sufficiently systematic for the prevention of bias, hence a robust search strategy should mean that another reviewer could complete the same process and get the same results (Gough et al., 2012). Developing the search strategy has been described as an evolving process and so a scoping exercise of the available literature was first carried out (Higgins and Green, 2011). Higgins and Green (2011) recommend the need to strike a balance between a search strategy that is sensitive enough to identify all the relevant published work but that is precise enough to avoid the need to read through

studies that are not. To assist with the identification of the search strategy two probe papers that were relevant to the research question were identified. If these papers were not found through a database search then that search strategy was discarded. Various permutations of key words identified by their relevance to the research question were used and a search strategy was subsequently developed. It became apparent as the process progressed that the key words used would need to incorporate a broad spectrum of movement therapy studies occurring during rehabilitation after stroke. This was because any attempt to define the search more precisely caused the loss of one or either of the probe papers.

The following key words were subsequently developed:

stroke, rehabilitation, motor, learn, feedback

An example of the search strategy used in MEDLINE is shown in table three. It is important to note that searches designed for one database do not 'translate' to another (Higgins and Green, 2011), therefore use of facilities such as 'MetaLib' which will search for key words across multiple databases were not appropriate. The search strategy was designed to be as inclusive as possible hence the use of the Boolean term 'OR' in step 9 of the search.

| |
|---|
| 1. exp Stroke/ |
| 2. rehabilitation/ or early ambulation/ or exercise therapy/ |
| 3. $rehabilitation.mp. |
| 4. Motor Skills/ |
| 5. motor.mp. |
| 6. learn$.mp. |
| 7. Feedback, Psychological/ |
| 8. Biofeedback, Psychology/ |
| 9. 2 or 3 or 4 or 5 or 6 or 7 or 8 |
| 10. 1 and 9 |

**Table 3: The electronic search used in MEDLINE**

The following databases were searched from inception to December 2011: MEDLINE, EMBASE, AMED and CINAHL. Both EMBASE and MEDLINE index biomedical literature from peer-reviewed journals. EMBASE claims to contain all literature indexed by MEDLINE and over five million records more. However both databases were included following findings from a study by Minozzi et al. (2000) which suggested that differences in indexing by the respective databases may lead to a failure to identify relevant literature if only one database is searched. AMED and CINAHL both index literature specific to professions allied to medicine and nursing, and therefore may contain a significant amount of literature relevant to physical therapy interventions. Reference lists of included studies were also searched.

## 4.5 Study Selection Process

The Cochrane methodology for systematic reviews stipulates that at least two researchers should be involved in decisions relating to the inclusion or exclusion of studies. This ensures that the findings from the review are more rigorous as it addresses the potential for bias on behalf of either researcher. Reviews conducted by one researcher are open to criticism if there is a suspicion that a study may have been excluded erroneously because of a perceived bias on behalf of the author (Higgins and Green, 2011). The findings of a systematic review are generally considered to be robust because they can offer a summary analysis of all the relevant evidence for a given intervention (Gough et al., 2012). Excluding a study inappropriately may subsequently impact on the interpretation of the findings from a review (Higgins and Green, 2011), for example the exclusion of a well-designed study showing a good effect of an intervention may lead to a summary analysis showing little or no effect. If clinical decisions are informed by such a review then there is the potential to cease delivery of an intervention that may be beneficial.

The search strategy produces a list of possible studies; inclusion and exclusion criteria are subsequently applied to study titles, abstracts and then full papers until studies that will be included in the review are identified (Higgins and Green, 2011).

In this review inclusion/exclusion criteria were applied to titles by the author only. This was a pragmatic decision which arose because of time constraints and the quantity of literature that was identified through the search strategy (see figure three). The author was very aware of the potential for bias at this stage of the study and attempted to be as rigorous as possible in her application of the inclusion criteria. The risk of bias however remained and the interpretation of this study may have been affected by inadvertently excluding a study that could have impacted on the subsequent findings. The implications of this have been explored in more detail later.

The number of studies identified within each year from 1999-2011 have been presented in the form of a bar chart below (figure 7).

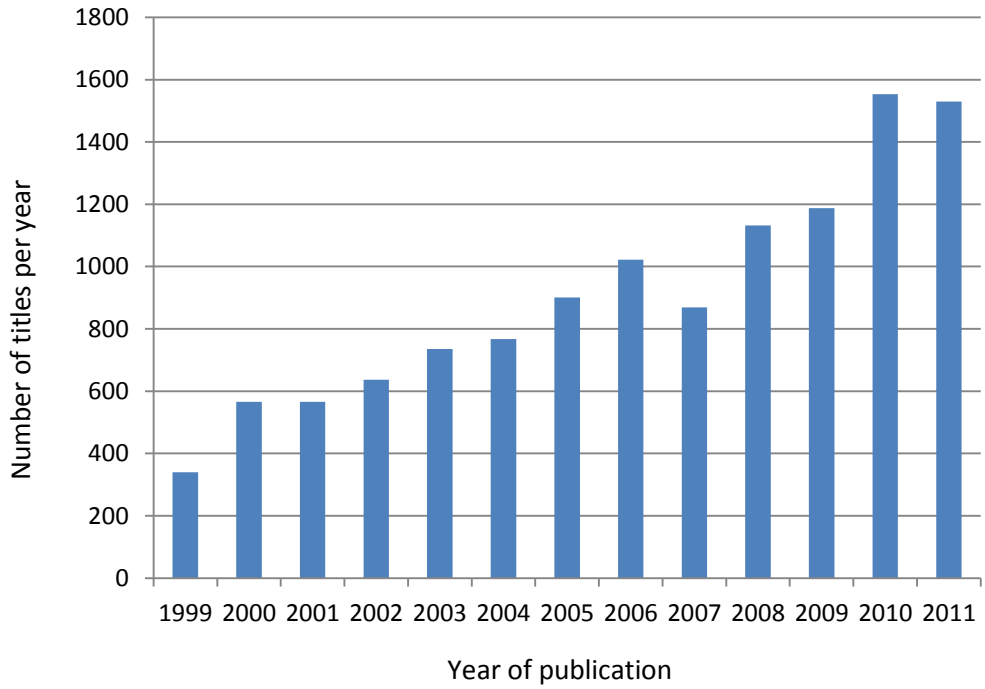


Figure 4: Bar chart to show numbers of titles identified per year for 1999-2011

As the search strategy used keywords referring to general concepts such as ‘motor’ and ‘rehabilitation’ then this bar chart shows the rising popularity of rehabilitation literature over this period of time as well as the quantity of literature that was identified.

All other stages of the study selection process were carried out by two researchers. The second researcher was a clinical colleague who had an interest in both the field of research and the methodology used. This person was not involved in the design of either the inclusion or the exclusion criteria so had no preconception of what they thought should be included or excluded. Their decisions were based solely on whether the papers fulfilled the inclusion criteria at each stage of the process and thus they were less likely to make biased decisions when applying these. If either researcher was unclear about the inclusion or exclusion of a paper then the default at each stage was to judge inclusion as 'maybe'. In the case of dispute between the two reviewers, the opinion of a third reviewer was sought before a final decision was taken.

## 4.6 Data Extraction

A copy of the data extraction form is included as appendix IV. The process of data extraction involves collating study characteristics and results relevant to the review question (Centre for Reviews and Dissemination, 2008). The data extraction form was based on examples obtained through the Cochrane Handbook for Systematic Reviews (Higgins and Green, 2011). The purpose of a systematic review is to collate all the relevant evidence for a given research question and to try and infer relationships between the given variables (Higgins et al., 2011). Sufficient data must be gathered to enable this to take place. It is also important to collect data related to the risk of bias of the included trials. If a causal relationship is to be inferred from the collection of data from numerous trials then the methodological quality of those trials has to be sufficient to ensure that those inferences are reliable (Higgins et al., 2011). This quality can be determined through the use of a numerical scale such as the PEDro scale (Verhagen et al., 1998), however these tools have been criticised for implying that the 'weighting' of different items related to quality are the same or have not been well justified (Higgins et al., 2011). Subsequently the Cochrane collaboration has developed a 'risk of bias' tool which evaluates items as either having a high, low or unclear risk of bias (Higgins et al., 2011). The criteria for judging risk of bias are listed in appendix V. The risk of bias tool assesses the risk of selection bias, performance bias, attrition bias, and detection bias. The

implications for these biases on study rigour have been discussed in chapter five. Selection bias is assessed by evaluating both the method for random sequence generation and allocation concealment. Studies are judged to be at low risk if they refer to random methods of allocation and have used adequate methods for concealing group allocation from study participants and personnel. Performance bias is assessed through the presence of blinding of participants and personnel to knowledge of the allocated intervention. Studies are judged to be at low risk if both participants and personnel are blinded to group allocation. In this category interpretation of the risk of bias assessment tool allows for the review author to take the decision as to whether or not blinding of participants or personnel would affect the outcome of that study. Blinding of both participants and personnel may be difficult to achieve in studies where there is an intervention which requires either the active engagement of the participant or the use of a device to elicit either a sensory or motor response in the participant. Even where there is the presence of a placebo, informed consent demands that the participant is fully informed of all the trial interventions, thus the participant will likely be aware of whether they are feeling/seeing something or not (MHRA, 2013). The decision was taken therefore to judge this item as high risk for all included studies.

Detection bias is assessed by determining whether outcome assessors are aware of group allocation, studies are judged to be at low risk if they are blinded to this. Attrition bias is assessed through examination of the outcome data reported in the trial. Studies are judged to be at low risk if there is no missing outcome data or they have reported and accounted for missing data within the analysis (Higgins et al., 2011).

The sections of the form referring to ‘selective reporting’ and ‘other bias’ were not used. Selective reporting refers to the potential for reporting bias due to selective outcome reporting, i.e. authors may only have reported results from the outcomes measures that showed an effect of the intervention. This can only be assessed accurately if the study protocol is present (Higgins and Green, 2011). Only two studies within the present review had published protocols that would have facilitated an accurate assessment of this criteria. Interpretation of

the risk of bias therefore needs to be made within this context. Issues that have arisen that might have been included in 'other bias' will be discussed separately if it is felt that they impacted significantly on the interpretation and synthesis of this review.

The results from these assessments will be presented in table form with an explanation of the implications for each of the findings.

## 4.7 Synthesis of data

The process of synthesis aims to transform the data from individual studies into a "connected whole" (Gough et al, 2012 p. 180) with the potential to produce new knowledge and inform practice (Gough et al., 2012). In order to do this the studies were synthesised in two categories according to the motor learning framework identified in section 2.1.4. Studies applying the priming motor learning principle were synthesised within the category of 'no/little movement' and the application of all other motor learning principles took place within the 'augmenting' category. Each was then sub categorised according to whether the intervention was targeting the upper limb or the lower limb.

## 4.8 Analysis of data

Analysis of the findings from this review was conducted using Review Manager, Version 5 (REVMAN). Section 3.1. stated that one objective of the systematic review was to seek to quantify the findings, thus where this was possible, meta-analysis of the results within the motor learning framework was undertaken in order to provide some quantification of the effect sizes of the studies. The purpose of a meta-analysis is to reflect the strength of the relationship between two variables by calculating the effect size (Borenstein et al., 2010). The data in each of the studies is likely to be presented using means and standard deviations, therefore the effect size was reported as the standardised mean difference (Borenstein et al., 2010). The inclusion criteria for this review led to the inclusion of studies that showed heterogeneity in respect of factors such as time since stroke, therefore the effect size was calculated using a random effects model in order to allow for this heterogeneity (Borenstein et al., 2010).

Where there was insufficient data for meta-analysis, i.e. only one study using any given outcome measure, data from the original study was presented. The alternative was to calculate an effect size for the individual study findings. Effect sizes make inferences about the effect of an intervention and are based on the differences between the mean outcome value of both the control and experimental groups divided by the standard deviation of the spread of all the outcome values across both groups. Thus they are reported to be a true measure of the effect of an intervention, whereas calculations identifying statistical significance make inferences about whether the outcome could have happened by chance (Coe, 2002). These calculations can be influenced by sample size and it is possible to have a statistically significant finding from a study which has a large sample size even though the effect of the intervention may be small (Altman, 1990). In light of this, calculation of effect sizes for individual studies seems intuitive; however the method for calculating an effect size requires the standard deviation of the spread of all the values across both control and experimental groups (Coe, 2002). Authors reporting the outcomes of their studies tend to provide a mean and standard deviation for each group and not for the whole sample. Standard deviations imputed into effect size calculations are therefore based on the standard deviation of one group or an average of the two groups. This can lead to inaccurate calculations of the effect size and may lead to a misleading interpretation of the findings (Coe, 2002). In order to avoid this, in the instance of only one study reporting an outcome measure, this review presented data derived from the original study.

## 4.9 Interpretation of findings

Figure four shows the PRISMA flow chart for this systematic review. This search strategy identified a large number of studies which should have ensured that the review process was sensitive enough to identify all relevant papers (Higgins and Green, 2011). Managing this quantity of data did however have implications for the organisation of this review, in that only one person was able to include/exclude studies at title stage. This may have led to appropriate studies being excluded, something which may have impacted on the rigour of the findings from this study. The results of this study therefore need to be

interpreted in light of this. The impact of this has been discussed in more detail later.

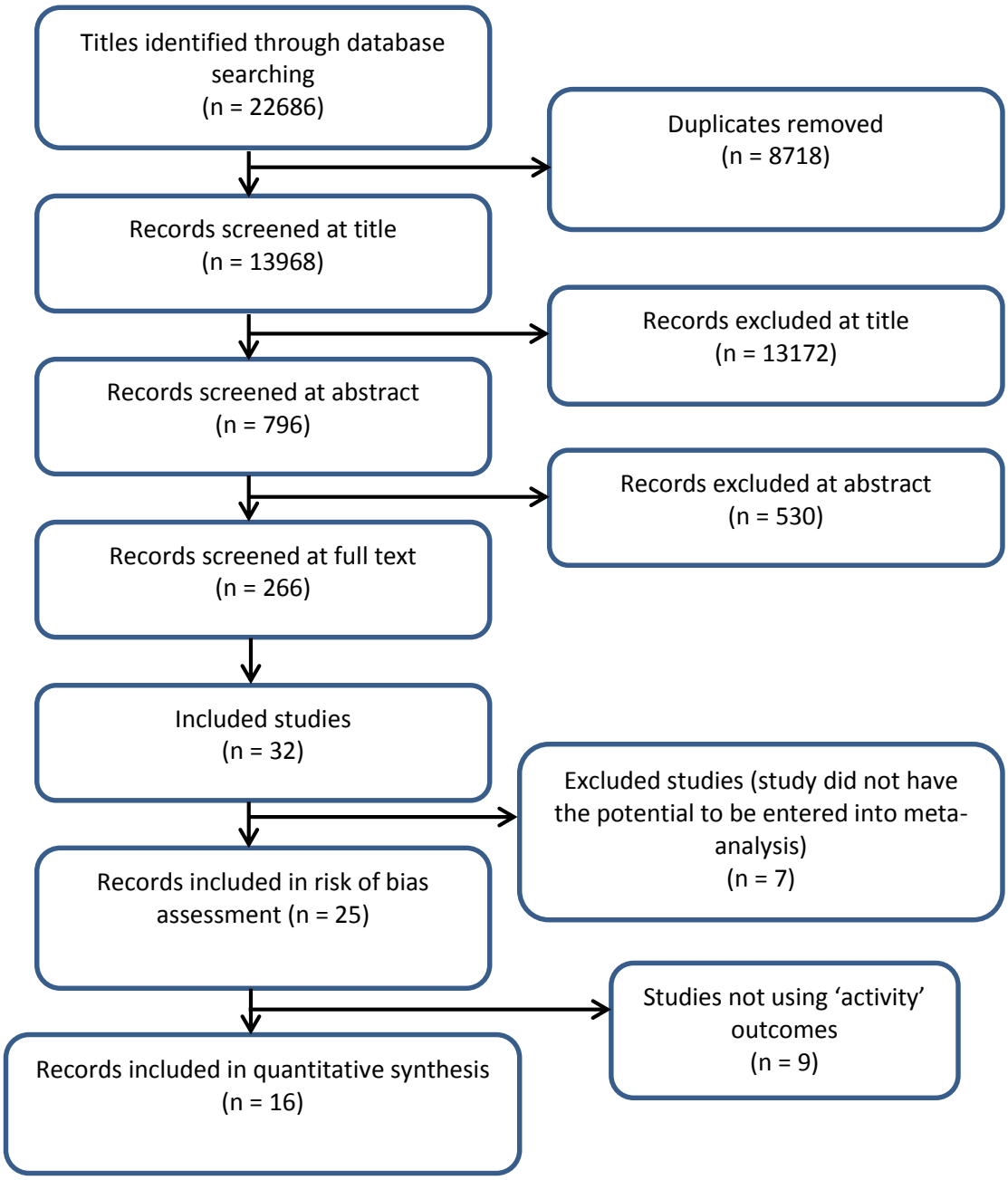


Figure 5: PRISMA flow chart for systematic review of motor learning strategies

Thirty two studies were included in the review, authors were contacted where outcome data was presented in the form of graphs and would not have the potential to be entered into meta-analysis. As quantification of the findings from this review was one of the objectives listed in section 3.1 then studies that could not meet this criteria were excluded at this stage. Two authors responded to the request for numerical data, however seven did not. These studies were therefore excluded from further analysis within this review and are listed in table four.

| Study | Reason for exclusion |
|---|---|
| Basmajian et al (1982) | Unable to enter outcome data in meta-analysis |
| Bradley et al (1998) | Unable to enter outcome data in meta-analysis |
| Engardt and Knutsson (1994) | Unable to enter outcome data in meta-analysis |
| Geiger et al (2001) | Unable to enter outcome data in meta-analysis |
| Inglis et al (1984) | Unable to enter outcome data in meta-analysis |
| Saposnik (2010) | Unable to enter outcome data in meta-analysis |
| Shiavi et al (1979) | Unable to enter outcome data in meta-analysis |

Table 4: Excluded studies

Following removal of the excluded studies 25 trials remained within the review. These studies were all included in the risk of bias assessment, however, only sixteen were subsequently included in the meta-analysis. The reasons for this decision have been discussed later in this chapter. A description of each of the twenty five studies have been included as appendix XVI.

Tables five and six display the study characteristics for all the studies included in the risk of bias assessment. Table five shows all the studies evaluating the application of the ‘priming’ motor learning principle, which have been categorised as needing little or no return of movement. Table six shows the studies evaluating the other motor learning principles, which have subsequently been categorised as ‘augmenting’.

Studies within both categories included participants who were relatively similar for age but showed a great degree of variability in terms of time since stroke onset, ranging from 0.28 months (Carmeli et al., 2011) after stroke to 73.2 months (Yang et al., 2008).

Studies included in this review have evaluated the application of priming, feedback and practice specificity motor learning principles. There were no studies evaluating the application of instructions or variability of practice.

The implications for these findings have been discussed later in this chapter.

| Study | Motor Learning Principle | Number of participants | | Affected side - right | | No. of men | | Age mean (SD[3]) | | Time since stroke onset/months (SD[3]) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Int[1] | Ctrl[2] | Int[1] | Ctrl[2] | Int[1] | Ctrl[2] | Int[1] | Ctrl[2] | Int[1] | Ctrl[2] |
| Chen 2005 | Priming | 15 | 14 | 5 | 6 | 6 | 10 | 58.5(12.9) | 59.6(12.0) | 0.47(0.22) | 0.41(0.22) |
| Chen 2011 | Priming | 17 | 16 | 6 | 7 | 13 | 9 | 58.0 (11.5) | 62.3 (11.3) | 0.36(9.5-12.0) | 0.36(9.3-14.0) |
| Ertelt 2007 | Priming | 8 | 8 | 2 | 2 | 5 | 6 | 57.1(8.7) | 55.4(10.8) | 48.42(41.39) | 23.83(11.87) |
| Ietswaart 2011 | Priming | 39 | 31 | 17 | 16 | 23 | 22 | 69.3(10.8) | 68.6(16.3) | 2.70(1.80) | 3.0(2.08) |
| Lee 2011 | Priming | 13 | 11 | | | 6 | 4 | 60.7(7.5) | 61.9(11.3) | > 6 months | |
| Malouin 2008 | Priming | 5 | 3 | 5 | 2 | 3 | 3 | 61.3(7.2) | 61.0(8.5) | 28.8(21.6) | 42(34.8) |
| Ng 2007 | Priming | 21 | 20 | 7 | 10 | 16 | 17 | 58.4(7.1) | 57.1(7.8) | > 12 months | |
| Ng 2009 | Priming | 27 | 25 | 10 | 12 | 24 | 20 | 56.5(8.2) | 56.9(8.6) | 58.8(46.8) | 51.6(45.6) |
| Page 2000 | Priming | 8 | 8 | | | 16 men | | 63.4(4.0) | | mean 21.6 months | |
| Page 2001 | Priming | 8 | 5 | 2 | 2 | 6 | 4 | 64.4(9.7) | 65.0(7.0) | 5.88(3.44) | 7.6(3.21) |
| Page 2009 | Priming | 5 | 5 | 4 | 3 | 3 | 4 | 58.4(9.8) | 6.4(9.0) | 26.4(13.6) | 30.6(11.4) |
| Sutbeyaz 2007 | Priming | 20 | 20 | 6 | 7 | 10 | 13 | 62.7(9.7) | 64.7(7.7) | 3.5(1.3) | 3.9(1.9) |
| Wu 2010 | Priming | 12 | 11 | 5 | 4 | 4 | 5 | 59.9(11.4) | 54.3(10.3) | 10.0(7.3) | 7.2(5.4) |
| Yavuzer 2008 | Priming | 20 | 20 | 7 | 8 | 9 | 10 | 63.2(9.2) | 63.3(9.5) | 5.4(2.9) | 5.5(2.5) |

**Table 5: Characteristics of 'priming' studies needing no or little return of movement**

1. Int - intervention
2. Ctrl - control
3. SD – standard deviation

| Study | Motor Learning Principle | Number of participants | | Affected side - right | | No. of men | | Age mean (SD[3]) | | Time since stroke/months (SD[3]) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Int[1] | Ctrl[2] | Int[1] | Ctrl[2] | Int[1] | Ctrl[2] | Int[1] | Ctrl[2] | Int[1] | Ctrl[2] |
| Aruin 2003 | Feedback | 8 | 8 | | | 11 | | 65.3 (3.4) | | 0.59(0.06) | |
| Carmeli 2011 | Feedback | 16 | 15 | 10 | 5 | 11 | 11 | 57.8 (8.9) | 62.5 (5.0) | 0.28 (0.25) | 0.37(0.27) |
| Crow 1989 | Feedback | 20 | 20 | 8 | 6 | 14 | 11 | 67.4(10.4) | 68.1(9.5) | 2-8 weeks post stroke | |
| da Silva 2011 | Practice specificity | 8 | 8 | 7 | 5 | 5 | 4 | 63.7(11.8) | 58.8(11.4) | 0.38(0.17) | 0.50(0.16) |
| Engardt 1994 b | Feedback | 16 | 14 | 6 | 8 | 12 | 4 | 67 (6.05) | 65 (8.46) | 33.2(6.6) | 34.3(5.8) |
| Mirelman 2010 | Feedback | 9 | 9 | no individual data but paper states that groups were matched | | | | | | >2 years | |
| Sackley 1997 | Feedback | 12 | 13 | 4 | 8 | 10 | 10 | 60.8(12.3) | 67.9(9.2) | 4.64(3.65) | 4.34(4.45) |
| Schauer 2003 | Feedback | 11 | 12 | 4 | 7 | | | 59.0(12.0) | 61.0(12.0) | 1.74 | 2.2 |
| Sungkarat 2011 | Feedback | 17 | 18 | 10 | 11 | 12 | 12 | 52.1(7.2) | 53.8(11.2) | 3.94(4.79) | 4.7(5.8) |
| Walker 2000 | Feedback | 16 | 16 | 7 | 7 | 12 | 8 | 65.4(13.8) | 62.4(13.3) | 1.34(0.64) | 1.15(0.73) |
| Yang 2008 | Practice specificity | 11 | 9 | 6 | 3 | 5 | 5 | 55.4(12.1) | 60.9(9.3) | 71.16(50.04) | 73.2(123.84) |

**Table 6: Characteristics of included studies in 'augmenting' category**

1. Int - intervention
2. Ctrl - control
3. SD – standard deviation

## 4.10 Risk of bias assessment

A risk of bias assessment was carried out on each of the studies included in this review and the results of this are displayed in table seven.

- Random Sequence generation:
  17 (68%) studies were assessed as low risk, 8 (32%) were assessed as unclear and there were no studies at high risk.
- Allocation Concealment:
  11 (44%) studies were assessed as low risk, 14 (56%) were assessed as unclear and there were no studies at high risk.
- Blinding of participants and personnel:
  25 (100%) studies were assessed as high risk. As previously discussed it is difficult to blind participants to interventions which require active engagement in rehabilitation, therapies therefore whilst the studies were all assessed as high risk it was not felt that these results would adversely affect the interpretation of the findings from these trials.
- Blinding of outcome assessment:
  16 (64%) studies were assessed as low risk, 8 (32%) were assessed as unclear and 1 (4%) study was at high risk.
  The only study that was judged to be at high risk was that of Walker et al (2000) who explicitly stated that the outcome assessor in their trial was aware of group allocation. The study authors perceived this to be acceptable because the outcome measures used were standardised, this they stated would prevent the assessor from entering inaccurate data. Clearly, despite the use of standardised measures there is still room for an individual who is aware of group allocation to knowingly enter incorrect data in order to bias the findings from the study in favour of one intervention or the other, therefore this study was judged to be at high risk of bias in this review.
- Incomplete outcome data:
  25 (100%) studies were assessed as low risk.

In summary only one study was found to have a high risk of bias in any of the categories described by the risk of bias assessment tool (Walker et al., 2000).

All studies were judged to have a low risk of bias for ‘blinding of participants and personnel’ and ‘incomplete outcome data’ suggesting that the studies were not at risk of either performance bias or attrition bias. Between 32% and 56% of studies were judged to be ‘unclear’ for random sequence generation, allocation concealment and blinding of outcome assessment. This suggests that this information was either unavailable or that there was uncertainty of the risk of bias for these studies within these categories (Higgins and Green, 2011). 40% (10) of studies were at low risk of bias for all categories. The implications of these findings have been discussed narratively together with the results of the meta-analysis.

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data |
|---|---|---|---|---|---|
| Aruin 2003 | U | U | H | U | L |
| Carmeli 2011 | L | U | H | L | L |
| Chen 2005 | L | L | H | L | L |
| Chen 2011 | L | L | H | L | L |
| Crow 1989 | L | L | H | L | L |
| Da Silva 2011 | U | U | H | L | L |
| Engardt 1994 | U | U | H | U | L |
| Ertelt 2007 | U | U | H | U | L |
| Ietswaart 2011 | L | L | H | L | L |
| Lee 2011 | L | U | H | U | L |
| Malouin 2008 | L | U | H | L | L |
| Mirelman 2010 | U | U | H | U | L |
| Ng 2007 | L | L | H | L | L |
| Ng 2009 | L | L | H | L | L |
| Page 2000 | U | U | H | U | L |
| Page 2001 | L | L | H | U | L |
| Page 2009 | L | U | H | L | L |
| Sackley 1997 | L | U | H | L | L |
| Schauer 2003 | U | U | H | U | L |
| Sungkarat 2011 | L | L | H | L | L |
| Sutbeyaz 2007 | L | L | H | L | L |
| Walker 2000 | L | U | H | H | L |
| Wu 2010 | U | U | H | L | L |
| Yang 2008 | L | L | H | L | L |
| Yavuzer 2008 | L | L | H | L | L |

U Unclear
L Low risk
H High risk

Table 7: Risk of bias assessment for all included studies

## 4.11 Quantitative Synthesis

Tables eight through to twelve summarise the individual results for each of the included studies. The intention was to carry out meta-analysis within these categories; however this synthesis of the study results revealed considerable heterogeneity in the outcome measures used (see tables thirteen and fourteen). Attempts at summary analysis using studies that have evaluated outcome with measures falling within the impairment domain of the ICF with those in the activity domain could lead to an accusation of comparing apples with oranges (Borenstein et al., 2010, Gough et al., 2012). By definition these domains measure different aspects of health and therefore the meta-analysis would not be comparing like with like. In order to avoid this outcome measures were mapped to their corresponding ICF domain.

Table thirteen shows the range of measures that fall within the impairment domain across all the studies and table fourteen shows those that fall within the activity domain. Measures that have recorded global bodily function (i.e. not specific to the upper limb or lower limb), are listed here under the term Functional Measures.

Lower Limb

| Study | Outcomes | Results at primary end point<br>Experimental median (IQR)[1] | Control median (IQR)[1] | between group change scores |
|---|---|---|---|---|
| Chen 2011 | Fugl Meyer LL | 14.0(10.5-15.5) | 6(3.0-9.8) | p<0.001* |
| | Motor Assessment Score | 16.0(12.5-18.5) | 10.5(5.3-14.0) | p=0.010 |
| | Postural assessment for stroke trunk control | 5.0(3.5-7.0) | 5.0(2.5-7.8) | p>0.05 |
| | Berg Balance Scale | 28.0(20.5-33.5) | 15.5(9.3-23.5) | p=0.007* |
| | Functional Ambulation Categories | 2.0(2.0-2.0) | 1(1.0-1.0) | p<0.001* |
| | MRC Lower Extremity | 6.0(4.0-7.0) | 3(1.3-4.0) | p<0.001* |
| | | **mean (SD)[2]** | **mean (SD)[2]** | |
| Lee 2011 | Speed cm/s | 55.6(17.7) | 51.5(19.7) | p>0.05 |
| | Cadence step/min | 84.9(15.9) | 74.3(20.3) | p>0.05 |
| | step length cm | 41.9(9.0) | 42.8(8.7) | p>0.05 |
| | stride length cm | 77.2(13.5) | 81.5(11.9) | p>0.05 |
| | single limb support | 25.4(6.3) | 24.9(6.4) | p>0.05 |
| | double limb support | 38.0(9.3) | 40.4(10.2) | p>0.05 |
| Malouin 2008 | Limb loading Rising | 43.3(8.9) | 43.4(4.0) | p<0.03* |
| | Limb loading Sitting | 35.7(4.2) | 41.9(1.9) | p<0.03* |
| Ng 2007 | Composite spasticity scale | 11.0(1.4) | 11.2(1.7) | p>0.05 |
| | isometric ankle dorsi-flexion | 16.9(4.8) | 14.7(6.2) | p>0.05 |
| | isometric ankle plantar flexion | 23.8(8.5) | 20.3(16.0) | p>0.05 |
| | Gait velocity cm/s | 68.2(34.5) | 57.7(29.8) | p<0.01* |
| Ng 2009 | Gait velocity cm/s | 66.6(32.5) | 60.6(29.7) | p<0.01* |
| | 6 Minute Walk Test | 242.0(104.0) | 206.7(97.2) | p>0.01 |
| | Timed Up and Go | 18.7(9.7) | 26.2(21.7) | p<0.01* |
| Sutbeyaz 2007 | Brunnstroms stages of motor recovery | 3.5(0.8) | 3.0(0.7) | analysis based on mean change score over three time periods |
| | Modified Ashworth Scale | 2.0(2.3) | 2.2(0.7) | |
| | Motor Functional Independence Measure | 65.9(4.8) | 61.7(14.6) | |
| | Functional Ambulation Categories | 2.8(0.6) | 2.9(0.7) | |

**Table 8: Reported outcomes for included studies evaluating interventions categorised as no/little movement**

1. IQR – interquartile range
2. SD - standard deviation
* - statistically significant result

Upper Limb

| Study | Outcomes | Results at primary end point: Experimental mean (SD)[1] | Control mean (SD)[1] | between group change scores |
|---|---|---|---|---|
| Chen 2005 | Brunnstrom stage | 0.4(0.2) | 0.2(0.1) | p=0.005* |
| | Modified Motor assessment scale | 4.0(0.9) | 2.4(0.8) | p=0.001* |
| | Grasping | 0.8(1.2) | 0.2(0.4) | p=0.19 |
| | wrist flexion | 5.4(5.4) | 1.6(3.0) | p=0.07 |
| | wrist extension | 3.4(3.1) | 0.7(1.5) | p=0.01* |
| Ertelt 2007 | Frenchay Arm Test | 4.4(0.5) | 2.1(1.0) | p=0.0005* |
| | Wolf Motor Function Test | 7.0(6.9) | 17.0(19.0) | p=0.0525 |
| Ietswaart 2011 | Action Research Arm Test | 31.5(20.7) | 32.9(20.8) | p=0.77 |
| | grip force % of unaffected arm | 38.2(36.1) | 34.6(34.9) | p=0.60 |
| | Timed manual dexterity | 104.4(55.9) | 95.7(57.6) | p=0.98 |
| | Barthel | 16.2(4.1) | 16.8(3.8) | p=0.38 |
| | Modified Functional Limitation Profile | 50.3(18.8) | 55.4(15.8) | p=0.98 |
| Page 2000 | Fugl Meyer Upper Limb | 30.0(4.1) | 26.9(5.4) | p<0.05* |
| Page 2001 | Fugl Meyer Upper Limb | 43.0(10.1) | 32.4(14.9) | No value |
| | Action Research Arm Test | 40.4(13.4) | 25.0(11.7) | No value |
| Page 2009 | Action Research Arm Test | 42.6(1.2) | 43.5(1.5) | analysis based on change score from follow up to baseline |
| | Fugl Meyer Upper Limb | 46.4(0.9) | 48.8)1.31) | |
| Wu 2010 | UE subscale STREAM[2] | 10.0(5.3) | 7.3(5.6) | p<0.01* |
| | Action Research Arm Test | 24.8(20.8) | 14.7(18.8) | p<0.05* |
| | Modified Ashworth Scale Elbow | 1.7(0.9) | 1.9(1.0) | p>0.05 |
| | Modified Ashworth Scale Wrist | 1.8(1.1) | 2.0(1.3) | p>0.05 |
| | LL subscale STREAM | 11.0(5.3) | 9.7(5.0) | p>0.05 |
| | Barthel | 17.4(2.6) | 16.4(2.4) | p>0.05 |
| Yavuzer 2008 | Brunnstrom stages hand | 3.5(1.3) | 2.7(1.0) | analysis based on change score from follow up to baseline |
| | Modified Ashworth Scale | 1.3(0.5) | 1.6(0.6) | |
| | Self care Functional Independence Measure | 28.9(10.0) | 22.2(6.3) | |
| | Brunnstrom Upper Extremity | 3.7(1.2) | 2.8(0.9) | |

**Table 9: Reported outcomes for studies evaluating interventions categorised as little/no movement**

1. IQR – interquartile range
2. STREAM – Stroke Rehabilitation Assessment of Movement

* - statistically significant result

Lower Limb

| Study | Outcomes | Results at primary end point Experimental mean (SD)[1] | Within group change score | Control mean (SD)[1] | Between group change score |
|---|---|---|---|---|---|
| Aruin 2003 | Step width | 0.2(0.0) | | 0.1(0.0) | <0.05* |
| Engardt 1994 b | Body weight distribution (BWD) standing up % | 47.8(6.7) | | 44.2(6.6) | |
| | BWD sitting down % | 47.9(5.3) | | 43.5(7.6) | Analysis is based on follow up results |
| | Time to stand | 3.1(1.0) | | 3.2(0.8) | |
| | Time to sit | 3.5(0.9) | | 2.8(0.6) | |
| Mirelman 2010 | self selected walking speed m/s | 0.80 | p=0.003 | 0.7 | P>0.05 |
| | Hip range | 32.7(11.3) | P>0.05 | 32.3(13.6) | P>0.05* |
| | knee stance range | 17.3(3.4) | p=0.05 | 13.4(4.5) | P>0.05 |
| | knee swing range | 38.1(10.7) | p=0.05 | 32.5(17.0) | P>0.05 |
| | ankle range | 20.9(8.1) | p=0.05 | 18.3(7.1) | p=0.05* |
| | Onset of push off - time | No data | | | |
| | Onset of push off - power | No data | | | |
| Sackley 1997 | Rivermead Motor Function Assessment | 17.0(2.9) | | 12.7(4.5) | p<0.05* |
| | Balance coefficient | 0.0(0.0) | | 0.1(0.0) | p<0.05* |
| | Sway coefficient | 0.0(0.0) | | 0.0(0.2) | NS |
| Schauer 2003 | Gait velocity m/s | 0.8(0.3) | | 0.8(0.4) | p=0.008* |
| | stride length cm | 1.0(0.3) | | 1.0(0.3) | p=0.009* |
| | Gait cadence | 47.2(7.8) | | 48.5(7.8) | p=0.045* |
| | Symmetry deviation | 7.1(6.0) | | 8.4(9.7) | p=0.008* |
| | Heel on toe off distance | 87.6(23.6) | | 89.2(19.0) | p=0.006* |

No analysis for between groups

**Table 10: Reported outcomes for studies evaluating interventions categorised as augmenting (authors Aruin to Schauer)**

1. SD- standard deviation
* - statistically significant result

Lower Limb

| Study | Outcomes | Results at primary end point Experimental mean (SD)[1] | Control Mean (SD)[1] | Between group change score |
|---|---|---|---|---|
| Sungkarat 2011 | Gait speed cm/s | 35.9(13.6) | 26.3(8.5) | p=0.02* |
| | step length asymmetry ratio | 0.4(0.1) | 0.8(0.3) | p=0.03* |
| | single support time asymmetry ratio | 0.4(0.0) | 0.5(0.0) | p=0.03* |
| | Berg Balance Scale | 45.6(4.3) | 41.8(7.3) | p=0.001* |
| | Timed Up and Go | 22.3(10.4) | 27.2(10.9) | p=0.04* |
| | Loading on paretic leg during stance % body weight | 45.5(4.8) | 39.8(9.7) | p=0.004* |
| Walker 2000 | postural sway eyes open | 0.2(0.1) | 0.3(0.3) | |
| | postural sway eyes closed | 0.6(0.4) | 0.5(0.5) | analysis is based on mean |
| | Berg Balance Scale | 46.6(6.0) | 48.8(6.2) | scores achieved over three |
| | Gait speed (m/s) | 0.6(0.3) | 0.9(0.7) | time periods |
| | Timed Up and Go | 33.4(20.3) | 21.3(12.8) | |
| Yang 2007 | Walking speed m/s | 0.9(0.3) | 0.7(0.6) | p=0.03* |
| | Community Walk test | 17.0(18.4) | 20.6(20.0) | p=0.04* |
| | Walking ability questionnaire | 58.4(9.3) | 58.7(12.8) | p=0.19 |
| | Activity specific balance confidence | 87.4(6.8) | 72.3(16.9) | p=0.31 |

**Table 11: Reported outcomes for studies reporting interventions categorised as augmenting (authors Sungkarat to Yang)**

1. SD- standard deviation
* - statistically significant result

| | Study | Outcomes | Results at primary end point | | |
|---|---|---|---|---|---|
| | | | Experimental mean (SD)[1] | Control mean (SD) | between group change scores |
| Upper Limb | Carmeli 2011 | Box and Block | 32.0(11.6) | 31.4(16.1) | p=0.015* |
| | | Fugl Meyer Upper Limb | 56.6(6.6) | 52.4(8.1) | p=0.0417* |
| | | Tracking speed | 2.8(1.3) | 1.4(0.4) | p=0.00049* |
| | | Tracking width | 3.5(1.3) | 6.7(1.6) | p=0.000002* |
| | Crow 1989 | Action Research Arm Test | 21.3(22.8) | 12.5(21.7) | p=0.05* |
| | | Fugl Meyer Upper Limb | 34.5(22.0) | 22.9(21.1) | p=0.02* |
| | da Silva 2011 | Barthel | 94.9(8.9) | 88.0(17.8) | p>0.05 |
| | | Motricity Index | 73.6(16.1) | 60.2(20.0) | p>0.05 |
| | | Fugl Meyer Upper Limb | 84.6(18.4) | 66.9(22.9) | p>0.05 |
| | | Chedoke Arm and Hand Activity Inventory | 90.2(17.0) | 70.6(70.6) | comparison of normalised improvement between groups P = 0.025 |

**Table 12: Reported outcomes for interventions categorised as augmenting**

1. SD- standard deviation
* - standard deviation

| | Needing little or no movement | | Augmenting | |
|---|---|---|---|---|
| | **Upper Limb** | **Lower Limb** | **Upper Limb** | **Lower Limb** |
| **Impairment** | Grasping | Speed cm/s | Nine hole peg test | Ankle range |
| | Wrist flexion | Cadence step/min | Fugl Meyer Upper Limb | Balance coefficient |
| | Wrist extension | Step length cm | Grip and pinch | Body weight distribution standing up |
| | Modified Ashworth Scale | Stride length cm | Modified Ashworth scale | BWD sitting down |
| | Modified Ashworth Scale | Single limb support | Tracking speed | Heel on toe off distance |
| | Grip force % of unaffected arm | Double limb support | Tracking width | Hip range |
| | Timed manual dexterity | Composite spasticity scale | | Knee stance range |
| | Fugl Meyer Upper Limb | Isometric ankle dorsiflexion | | Knee swing range |
| | Upper Extremity subscale STREAM | Isometric ankle plantarflexion | | Limb loading |
| | Brunnstroms stages of motor recovery | Lower Limb subscale STREAM | | Loading on paretic leg during stance |
| | | Brunnstroms stages of motor recovery | | Modified Ashworth scale |
| | | | | Onset of push off – power and time |
| | | | | Postural sway eyes closed |
| | | | | Postural sway eyes open |
| | | | | Single support time asymmetry ratio |
| | | | | Step length asymmetry ratio |
| | | | | Sway coefficient |
| | | | | Symmetry deviation |
| | | | | Time to sit |
| | | | | Time to stand |

Table 13; Outcome measures within the impairment domain of the ICF

| | Needing little or no movement | | Augmenting | |
|---|---|---|---|---|
| | **Upper Limb** | **Lower Limb** | **Upper Limb** | **Lower Limb** |
| **Activity** | Action Research Arm Test | Functional Ambulation Categories | Action Research Arm Test | Berg Balance Scale |
| | Frenchay Arm Test | 6 Minute Walk Test | Arm Motor Ability Test | Timed Up and Go |
| | Wolf Motor Function Test | Timed Up and Go | Box and Block | Walking speed |
| **Functional Measures** | Barthel | | Rivermead Motor Function Assessment | |
| | Motor and Self-care items of Functional Independence Measure | | Stroke Impact Score | |
| | Modified Functional Limitation Profile | | Community Walk Test | |
| | Modified Motor assessment scale | | | |

Table 14: Outcome measures within the activity domain of the ICF and global measures of function

Heterogeneity of measures within the impairment domain of the ICF limits the ability to carry out a coherent, quantitative summary analysis of the findings from the studies included in this review. There were however fewer measures across all the studies which fell within the activity domain. Outcome measures that fall within the activity domain of the ICF are likely to be more meaningful to participants than those that fall within the impairment domain (World Health Organisation, 2001). Evidence for the effectiveness of an applied motor learning principle which has been evaluated using activity domain measures may therefore be more relevant to the functional recovery of a participant. Findings from this review were also intended to inform the future delivery of Functional Strength Training as an exemplar of how motor learning principles can be applied to physical therapy interventions. The phase II trial of Functional Strength Training interventions evaluated outcome using only measures that fell within the activity domain, therefore parity across both studies would be facilitated if summary analysis of the review did the same. The decision was taken to carry out a quantitative summary analysis using the measures that fall within the activity domain, this resulted in sixteen studies (those using activity domain outcome measures), being included (see figure four for PRISMA diagram).

### 4.11.1 Meta-analysis and summary results

The following tables show the different interventions included in this synthesis and their place within the motor learning framework proposed in chapter two.

**Lower Limb**

| | Motor Learning Principle (MLP) | Method of applying MLP | Study |
|---|---|---|---|
| **No/little movement:** | Priming | Motor Imagery | Lee et al (2011) |
| | | Transcutaneous electrical nerve stimulation (TENS) | Ng and Hui Chan (2007 and 2009) |
| | | Mirror therapy | Sutbeyaz et al (2007) |
| **Augmenting:** | Practice specificity | Virtual reality | Yang et al (2008) |
| | Feedback | Music | Schauer and Mauritz (2003) |
| | Feedback | Insole shoe wedge | Sungkarat et al (2011) |
| | Feedback | Biofeedback device | Walker et al (2000) |

Table 15: Summary of methods for applying motor learning principles to lower limb movement impairment

**Upper Limb**

| | Motor Learning Principle (MLP) | Method of applying MLP | Study |
|---|---|---|---|
| **No or little movement:** | Priming | Combined approach of motor imagery interventions | Ietswaart et al (2011) |
| | Priming | Motor imagery | Page (2001) |
| | Priming | Mental practice | Page (2009) |
| | Priming | Thermal stimulation | Wu et al (2010) |
| **Augmenting:** | Practice specificity | Virtual reality | Da Silva Cameirao et al (2011) |
| | Feedback | Glove | Carmeli et al (2010) |
| | Feedback | Electromyographic (EMG) | Crow et al (1989) |

Table 16: Summary of methods for applying motor learning principles to upper limb movement impairment

#### *4.11.1.1 Lower limb studies in no/little movement category*

Studies included within this category all applied the priming motor learning principle. Application of this principle was achieved through motor imagery (Lee et al., 2011), mirror therapy (Sutbeyaz et al., 2007) and transcutaneous electrical stimulation (Ng and Hui-Chan, 2007, Ng and Hui-Chan, 2009). This was set at a sensory threshold and therefore met the inclusion criteria because it did not provide movement or movement support. All three studies included in this meta-analysis included participants who were within the chronic phase of recovery from stroke (greater than six months (Lee et al., 2011); mean time from stroke 5.3 years and 4.6 years Ng and Hui-Chan (2007 and 2009).

Meta-analysis was only possible for the findings from studies including walking speed as an outcome measure, this has been reported in table seventeen. To enable comparison all measurements were converted to metres per second. The results of the other outcome measures have been reported separately (table eighteen).

Meta-analysis of the separate study findings measuring a change in walking speed showed no effect of the intervention, although it was arguably close to statistical significance for a hypothesis tested at a significance level of 5%. (p=0.57).

Other activity related outcome measures that have been used to evaluate the effects of the application of the priming motor learning principle to promote movement recovery in the lower limb were the Functional Ambulation Categories (FAC), the Six Minute Walk Test (6MWT) and the Timed Up and Go (TUG) (see table eighteen).

Sutbeyaz et al (2007) applied this principle by evaluating mirror therapy combined with a conventional stroke rehabilitation programme versus a control group who were offered a sham therapy combined with the same conventional programme. All participants were within the first 3-6 months after stroke (mean 3.7 months). Analysis of the findings from their study did not find a statistically significant effect for the experimental intervention (p=0.610). Analysis of the

study outcomes was based on a mean change score which was calculated over three time periods (pre-treatment, post treatment and follow up). Results of this study therefore do not show changes in response to the intervention as this was withdrawn between the post treatment and follow up measurement points.

Ng and Hui-Chan (2009) included the 6MWT and TUG as part of their assessment battery as well as timed walking speed. They found statistically significant results for the improvement in the TUG ($P<0.01$) but not the 6MWT ($p>0.01$). Although both are a measure of mobility these two outcomes quantify different aspects of this function. The TUG includes rising from a chair and turning (Rockwood et al., 2000), whereas the 6MWT measures sustained walking ability (Butland et al., 1982). Differences in the effects of the same intervention on these outcome measures are therefore possible.

Meta-analysis finds no evidence for the effects of applying a priming motor learning principle on walking speed ($P=0.57$) (Lee et al., 2011, Ng and Hui-Chan, 2007, Ng and Hui-Chan, 2009) and summary analysis of the findings from the other studies in relation to the 6 minute walk test and the Functional Ambulation categories supports this interpretation. There is the possibility however, that there was some effect of the experimental intervention on mobility measured by the Timed Up and Go.

| | Experimental | | | Control | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Mean** | **SD[1]** | **Total** | **Mean** | **SD[1]** | **Total** | **SMD[2] (random)** | **25% CI[3]** | **75% CI[3]** | **Weight** | **P** |
| Lee 2011 | 0.56 | 0.18 | 13 | 0.52 | 0.2 | 11 | 0.20 | -0.60 | 1.01 | 20.4 | |
| Ng 2007 | 0.68 | 0.35 | 21 | 0.58 | 0.3 | 20 | 0.30 | -0.32 | 0.92 | 34.9 | |
| Ng 2009 | 0.67 | 0.33 | 27 | 0.7 | 0.33 | 25 | -0.09 | -0.63 | 0.45 | 44.7 | |
| **Total** | | | 61 | | | 56 | 0.11 | -0.26 | 0.47 | 100 | 0.57 |

**Table 17: Summary results for walking speed in no/little movement category**

| **Study** | **Outcomes** | **Experimental** | **Control** | |
|---|---|---|---|---|
| | | **Mean (SD)[1]** | **Mean (SD)[1]** | **between group change scores** |
| Sutbeyaz 2007 | Functional Ambulation Categories | 65.9(4.8) | 61.7(14.6) | P=0.610 |
| Ng 2009 | 6 minute walk test | 242.0(104.0) | 206.7(97.2) | p>0.01 |
| Ng 2009 | Timed Up and Go | 18.7(9.7) | 26.2(21.7) | p<0.01* |

**Table 18: Individual study findings for other lower limb outcome measures in no/little movement category**

1. SD- standard deviation
2. SMD – standardised mean difference
3. CI- confidence interval
4. * - statistically significant

#### *4.11.1.2 Upper limb studies in no/little movement category*

Studies included in this category evaluated the effects of the priming motor learning principle by a combined approach of motor imagery interventions (Ietswaart et al., 2011), motor imagery (Page, 2001), mental practice (Page et al., 2009) and action observation (Ertelt et al., 2007).

Meta-analysis of the results from these studies was only possible for the Action Research Arm Test (table nineteen). This did not find an effect of the intervention at outcome (p=0.11).

Table twenty shows the individual study findings from Ertelt et al (2007). This study evaluated the effects of a priming motor learning principle delivered via 'action observation'. Effects of the intervention were measured using the Frenchay Arm test (FAT) and the Wolf Motor Function Test (WMFT) The study authors found statistically significant results in favour of the experimental intervention when measuring change using the FAT (P=0.0005) but not the WMFT (P=0.0525), although arguably this is very close to statistical significance. The WMFT (Wolf et al., 2001) is reported to be a more robust measure of upper limb function in that it tests the ability to carry out more functional activities of the arm and measures more aspects of upper limb function including reaching, grip and prehensile movements. The FAT, whilst designed as an evaluative tool is brief and measures performance on five upper limb activities only (Heller et al., 1987). It has subsequently been described as being a better screening tool than an evaluative measure (Finch et al., 2002). The findings from the WMFT may therefore be more reliable as an indication of the effects of the experimental intervention in this study. This was a small study (n=16), which included only those participants within the chronic phase of recovery from stroke (mean 36.13 months) and therefore findings from this study may not be applicable to the wider population of stroke survivors. The small sample size may also have impacted on the study's power to determine statistical significance. Underpowered studies are at risk of wrongly interpreting a false negative (Button et al., 2013).

| | Experimental | | | Control | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Mean** | **SD[1]** | **Total** | **Mean** | **SD[1]** | **Total** | **SMD[2] (random)** | **25% CI[3]** | **75% CI[3]** | **Weight** | **P** |
| **Action Research Arm Test** | | | | | | | | | | | |
| Ietswaart 2011 | 31.51 | 20.68 | 39 | 32.87 | 20.76 | 31 | -0.06 | -0.54 | 0.41 | 35.0 | |
| Page 2001 | 40.4 | 13.4 | 8 | 25 | 11.7 | 5 | 1.12 | -0.11 | 2.35 | 25.0 | |
| Page 2009 | 42.6 | 1.2 | 5 | 36.4 | 1.1 | 5 | 4.86 | 1.86 | 7.87 | 9.4 | |
| Wu 2010 | 24.8 | 20.8 | 12 | 14.7 | 18.8 | 11 | 0.49 | -0.34 | 1.32 | 7.87 | |
| **Total** | | | 64 | | | 52 | 0.86 | -0.20 | 1.93 | 100 | 0.11 |

**Table 19: Summary results for the Action Research Arm Test in no/little movement category**

| **Study** | **Outcomes** | **Experimental** | **Control** | |
|---|---|---|---|---|
| | | **Mean (SD)[1]** | **Mean (SD)[1]** | **between group change scores** |
| Ertelt 2007 | Frenchay Arm Test | 4.4(0.5) | 2.1(1.0) | p=0.0005* |
| Ertelt 2007 | Wolf Motor Function Test | 7.0(6.9) | 17.0(19.0) | p=0.0525 |

**Table 20: Individual study findings for other upper limb outcome measures in no/little movement category**

1. SD- standard deviation
2. SMD – standardised mean difference
3. CI- confidence interval
4. * - statistically significant

#### *4.11.1.3 Lower limb studies in augmenting category*

Table 21 shows the meta-analysis of the studies that included interventions targeted at lower limb recovery following stroke which, for the purposes of this review, have been categorised as augmenting. Meta-analysis was possible for the Berg balance scale (BBS), the Timed up and go (TUG) and timed walking speed.

Motor learning principles applied in this category included feedback which was achieved through musical motor feedback (Schauer and Mauritz, 2003), an insole shoe wedge which provided auditory feedback (Sungkarat et al., 2011) and visual feedback from a biofeedback device called the Balance Master (Walker et al., 2000). The effects of practice specificity were also evaluated through the medium of virtual reality (Yang et al., 2008).

Participants included in the respective studies ranged in time from stroke onset. Schauer and Mauritz (2003) and Walker et al., both included participants within the first three months after stroke; Sungkarat et al (2011) included participants within the first six months and Yang et al (2008) included those within the chronic phase of recovery (mean times of 71.16 months and 73.2 months).

All studies within this category contributed to the meta-analysis of the findings in relation to walking speed. The results of this found no statistically significant effect of the interventions (p=0.73).

The meta-analysis for the BBS and the TUG included two studies by Sungkarat et al (2011) and Walker et al (2000) respectively. Both studies evaluated the effects of feedback. No effect was found for the intervention following meta-analysis of both results from the BBS and the TUG (p=0.77 and 0.84 respectively).

In summary therefore, there appears to have been no statistically significant effect for interventions categorised as augmenting on lower limb recovery after

stroke when measured using walking speed (m/s) (p=0.73) , the Timed Up and Go (p=0.84) and the Berg Balance Scale (p= 0.77).

| | Experimental | | | Control | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Mean** | **SD[1]** | **Total** | **Mean** | **SD[1]** | **Total** | **SMD[2] (random)** | **25% CI[3]** | **75% CI[3]** | **Weight** | **P** |
| **Berg Balance Scale** | | | | | | | | | | | |
| Sungkarat 2011 | 45.64 | 4.3 | 17 | 41.76 | 7.3 | 18 | 0.63 | -0.05 | 1.31 | 50.3 | |
| Walker 2000 | 46.6 | 6 | 16 | 48.8 | 6.2 | 16 | -2.2 | -0.35 | 0.35 | 49.7 | |
| **Total** | | | 33 | | | 34 | 0.14 | -0.82 | 1.10 | 100 | 0.77 |
| **Timed Up and Go** | | | | | | | | | | | |
| Sungkarat 2011 | 22.26 | 10.4 | 17 | 27.17 | 10.9 | 18 | -0.45 | -1.12 | 0.22 | 50.6 | |
| Walker 2000 | 33.4 | 20.3 | 16 | 21.3 | 12.8 | 16 | 0.70 | -0.02 | 1.41 | 49.4 | |
| **Total** | | | 33 | | | 34 | 0.12 | -1.01 | 1.24 | 100 | 0.84 |
| **Timed Walking Speed m/s** | | | | | | | | | | | |
| Schauer 2003 | 0.81 | 0.29 | 11 | 0.8 | 0.35 | 12 | 0.03 | -0.79 | 0.85 | 23.8 | |
| Sungkarat 2011 | 0.35 | 0.14 | 17 | 0.26 | 0.09 | 18 | 0.75 | 0.06 | 1.44 | 27.3 | |
| Walker 2000 | 0.57 | 0.34 | 16 | 0.89 | 0.65 | 16 | -0.60 | -1.31 | 0.11 | 26.7 | |
| Yang 2008 | 0.85 | 0.31 | 11 | 0.73 | 0.63 | 9 | 0.24 | -0.65 | 1.12 | 22.2 | |
| **Total** | | | 55 | | | 55 | -0.78 | -1.9 | 0.45 | 100 | 0.73 |

**Table 21: Summary results for the Berg Balance Scale, the Timed Up and Go and Timed Walking Speed in augmenting category**

1. SD- standard deviation
2. SMD – standardised mean difference
3. CI- confidence interval
4. * - statistically significant

#### *4.11.1.4 Upper limb studies in augmenting category*

Meta-analysis for upper limb studies defined within the category of augmenting was not possible because of the heterogeneity of outcome measures used. Individual results of the activity based outcomes were therefore presented for each of the studies (table 22). Motor learning principles included in these studies and which have been categorised as augmenting are feedback (Carmeli et al., 2011, Crow et al., 1989) and practice specificity (da Silva Cameirao et al., 2011).

Both studies by Carmeli et al (2010) and Crow et al (1989) evaluated the effects of feedback; in the study by Carmeli et al (2010) this was provided by a custom designed glove and in the study by Crow et al (1989) by EMG biofeedback. Participants within both studies were within the first three months after stroke.

Carmeli et al (2010) found statistically significant results for the Box and Block (BBT) (p= 0.015). The study by Crow et al (1989) also found statistically significant results in favour of the intervention measured by the Action Research Arm Test (ARAT) (p= 0.04). These findings concur with those from a previous narrative review of the role of feedback in promoting motor learning in the upper limb following stroke (Subramanian et al., 2010).

The final study included in this analysis of upper limb augmenting studies was that of da Silva Cameirao et al (2011). This study evaluated the application of practice specificity by changing the context in which practice of an upper limb movement task took place. This was achieved through the use of a virtual reality (VR) environment and the effects were measured using the Chedoke-McMaster Stroke Assessment. Participants included in this study were within the first three months after stroke. This study attempted to control for both the movement practice that was part of the experimental intervention and the gaming experience that was inherent within the VR task. As such it had two control groups and so the results of both groups were pooled to provide data for the analysis. Statistically significant results were found in favour of the intervention (p= 0.025).

Synthesis of the findings for this category of motor learning was only supported by the interpretation of individual study findings and without benefit of meta-analysis. All studies within this category showed a statistically significant effect of the interventions and therefore there is some evidence to support the use of motor learning principles which augment the effects of physical practice.

| Study | Outcomes | Experimental Mean (SD)[1] | Control Mean (SD)[1] | between group change scores |
|---|---|---|---|---|
| Carmeli 2011 | Box and Block | 32.0(11.6) | 31.4(16.1) | p=0.015* |
| Crow 1989 | Action Research Arm Test | 21.3(22.8) | 12.5(21.7) | p=0.05* |
| da Silva 2011 | Chedoke Arm and Hand Activity Inventory | 90.2(17.0) | 70.6(70.6) | P=0.025* |

Table 22: Individual study findings for upper limb outcome measures in augmenting category

1. SD- standard deviation
2. SMD – standardised mean difference
3. CI- confidence interval
4. * - statistically significant

## 4.12 Discussion

The purpose of a systematic review is to identify the evidence base for any given intervention by synthesising the findings from individual studies in order to establish a body of evidence. Individual studies evaluating many different interventions provide little evidence for changing practice because of the risks inherent in applying the findings from studies with relatively small sample sizes (Button et al., 2013). By defining interventions within a framework which has identified an underlying principle common to them all, it is possible to bring together a body of evidence which may provide an answer to the research question or identify relevant gaps (Higgins and Green, 2011). The aim of this review was to establish the evidence for the effectiveness of the application of motor learning principles to promote motor learning after stroke. The following sections have presented a summary discussion and critique of this review in the context of the objectives that were defined in chapter three.

- **Objective 1: To systematically identify the relevant literature for inclusion in a literature review according to a motor learning framework.**

The design of this systematic review was guided by the identification of motor learning principles and the subsequent development of a motor learning framework described in chapter two. The framework was developed following a review of the theoretical literature underpinning motor learning and provided definitions for each of the motor learning principles. Previous reviews of motor learning principles in movement rehabilitation after stroke may have failed to include all appropriate studies, because the application of these principles was not made explicit within the studies themselves. This may have occurred because of a lack of clarity around what constitutes a motor learning principle (DePaul, 2013). The development of definitions and a subsequent framework for motor learning within this thesis was intended to assist in identifying motor learning principles by defining the underlying theoretical construct for therapeutic interventions. Thus studies evaluating the effects of biofeedback by EMG and use of a device such as a Balance Performance Monitor could both be defined as applying the motor learning principle of feedback. This strategy

may have facilitated the identification of studies that might not have otherwise been identified.

The use of the term ‘priming’ to describe a motor learning principle facilitated the identification of studies which evaluated therapies such as ‘action observation’, ‘thermal stimulation’ and ‘mental imagery’. The decision to rename the motor learning principle ‘mental practice ‘ to ‘priming’ was made because of the potential for confusion which arose around the use of ‘mental practice’ as both a therapeutic intervention and the motor learning principle. Mental practice is believed to have a motor learning effect because of its action on the movement execution system in the brain (Grezes and Decety, 2001). Stinear and colleagues (2007) have used the term ‘priming’ to describe this action and therefore precedent for its use in this context had already been developed. The term ‘priming’ was therefore adopted to describe the motor learning principle. However, consensus around definition and descriptions in the terminology used within the context of motor learning has been cited as one reason for a lack of uptake of motor learning in movement rehabilitation after stroke (Kleynen et al., 2013). Discussion around the use of this term needs to be carried out in order to achieve a consensus of opinion around its use within the context of motor learning.

As the systematic review progressed it became apparent that the motor learning framework developed in chapter two was not appropriate. Drawbacks in the framework’s design emerged because of the synthesis of the motor learning principles within the two categories of ‘no/little movement’ and ‘augmenting’. Development of motor learning principles has been based on the assumption that physical practice of the motor task that needs to be learnt is possible (Magill, 2006, Shumway-Cook and Woollacott, 2007). This is not always the case following stroke, therefore the framework developed in this thesis categorised motor learning principles according to whether there was evidence of their effectiveness in the absence of movement recovery or not. Only the ‘priming’ motor learning principle was categorised as ‘needing little or no movement’. This decision was supported by Feltz and Landers (1983) who showed mental practice was effective in promoting motor learning even when

this technique had not been accompanied by physical practice of the task. All other motor learning principles were categorised within the ‘augmenting’ category. Such categorisation of motor learning principles was subsequently judged to be inappropriate as motor learning principles related to instructions, practice specificity and practice intensity could be applied even when there is no movement recovery, i.e. they could be used to influence the delivery of therapies such as mental imagery.

Synthesis of these motor learning principles within one category was also felt to be inappropriate. Whilst categorisation is one means of coping with heterogeneity in a meta-analysis (Shepperd et al., 2009), in this instance, this led to over-generalisation of the effects of each motor learning principle.

In light of these reflections a revised framework has been designed and this will be presented and taken forward to inform the design of the novel intervention described in chapter six.

Studies using electrostimulation or orthotics to either support or provide movement were excluded from this review. This decision had been determined by the findings from Cauraugh et al. (2007), where the effectiveness of the motor learning principle (variability of practice) may have been confounded by the presence of electrostimulation. Robotics and other external devices are however becoming established methods for delivering movement therapy after stroke (Langhorne et al., 2011) and so the decision to exclude them may have been inappropriate. The place for these interventions and the presence of electrostimulation and orthotics within a motor learning framework needs to be considered more carefully in future reviews.

The systematic identification of literature relies on a robust search strategy (Centre for Reviews and Dissemination, 2008, Gough et al., 2012, Higgins and Green, 2011). In the present review, to ensure probe papers were not missed during the search process key words were kept deliberately inclusive. These incorporated a broad spectrum of movement therapy studies which facilitated the inclusion of studies even when the study authors might not have identified

the intervention within the context of motor learning. Previous reviews in this field have tended to rely on the use of key words that have been focussed on the motor learning principle: for example Subramanian et al. (2010) used the following key words in their systematic review of extrinsic feedback:

> ‘cerebrovascular accident’, ‘stroke’, ‘upper limb’, ‘motor learning’, ‘implicit and explicit feedback’, ‘extrinsic feedback’, ‘rehabilitation’, ‘treatment’, and ‘brain damage’.

Exact details of this search have not been given so it is not possible to draw any definitive conclusions about its rigour, however it was this author’s experience that early studies failed to use terms such as ‘feedback’ or ‘learning’ to describe the interventions. These studies may not have been identified as eligible for inclusion within the previous systematic reviews. The use of key words in the present study may have led to a more robust systematic review by including more studies that were appropriate to the research question.

The design and subsequent use of the key words in the present review led to an initial identification of over 20 000 titles. Exclusion of studies at this stage was carried out only by the author of this thesis. Despite best attempts, it is possible that the author may have biased this review by inappropriately excluding a study at the titles stage. Cochrane methodology suggests that the inclusion and exclusion of studies should be carried out by at least two people, because this minimises the impact of bias on behalf of one or other of the reviewers. (Higgins and Green, 2011). The second researcher was not available for the inclusion/exclusion process at the title stage because she was a full-time clinician with little time at that point in the study to give to such a quantity of work. Future reviews could avoid this scenario by widening the review team so that workload would be more manageable.

The search strategy employed in this review focussed on published studies that had been indexed in relevant databases. It is possible that despite best attempts at employing a rigorous search strategy, relevant studies may have been missed because of publication bias. It has been shown that studies with statistically significant results are more likely to be published than those with equivocal findings (adjusted odds ratio 2.32; 95% CI 1.25-4.28) (Easterbrook

et al., 1991). To avoid excluding such studies from a systematic review Higgins and Green (2011) recommend searching so-called ‘grey literature’. The present study may be at risk of excluding appropriate studies, as searching databases of grey literature were not included in the search strategy. By searching other databases it is likely that the number of studies initially included in the present review would however have been greater. Section 4.4 discussed the need to design a search strategy that was sufficiently sensitive to identify all relevant papers but precise enough to avoid reading through those that weren’t. Despite the potential for missing relevant studies this author would not advocate increasing the number of databases, unless there is a way of increasing the specificity of the search strategy.

This review was limited to those studies that were designed as randomised controlled trials (RCT). This follows general Cochrane methodology and is deemed to be one way of increasing the reliability and validity of the findings from a systematic review because of the rigour that is assigned to this type of research methodology (Centre for Reviews and Dissemination, 2008). It is of course to be expected that when searching as extensively as necessary for a systematic review that much literature will be discovered that, although not suitable for inclusion in the systematic review still forms part of the body of evidence for this topic. In this case many such studies were identified and have been reviewed in section 2.1.3.

It has been suggested that a well designed RCT with complete blinding and appropriate analysis is likely to provide the “best possible evidence of effectiveness” (McKee et al., 1999 pp.314) however there may be occasions when randomisation is neither appropriate nor feasible (Black, 1996). Randomised controlled trials have been considered to be more robust because of the theory that alternative study designs such as cohort or case-control have led to overestimates in the effect size of an intervention. However a comparison of the findings of RCT and observational studies evaluating the same clinical subjects found that this wasn’t the case (Concato et al., 2000). Although this comparison was limited to a relatively small number of studies its findings support those from an earlier review of eight comparisons made between

randomised and non randomised studies which also found no evidence that either method consistently lead to larger estimates of effect size (McKee et al., 1999).

Systematic reviews of RCT exclude studies using alternative study designs. RCT are however one method of evaluating healthcare interventions, study authors may have opted for alternative study designs when faced with particular research questions (Black 1996). For example studies using case-control series may be able to provide more information about the individual participant characteristics of people who respond to an experimental intervention. Including a timing element i.e. specifying the time point at which an intervention is delivered within this design would also be able to provide information about when, or at what stage in their recovery, a participant might respond (Bowling, 2000). Similarly dose-finding studies may have been able to provide information about the likely intensity that would be required for the experimental intervention to have an effect. It should be noted however that two reviews examining the intensity or dose of exercise therapies aimed at improving walking in people after stroke found a limited number of dose finding trials, suggesting that this type of study design is not readily used in rehabilitation therapies and therefore may not provide sufficient data for a systematic review (Cooke et al., 2010a, Veerbeek et al., 2011). This was discussed in more detail in section 2.1.3. Reviews including qualitative data either from mixed methods trials or qualitative studies may have been able to provide information about aspects of the intervention such as acceptability, context and variations in the effectiveness of the experimental intervention (Lewin et al., 2009). By including only RCT in the present systematic review it is possible that other relevant evidence may have been excluded. Whilst this work was reviewed in section 2.1.3 of the thesis its inclusion within the formal review may have been useful for the reasons discussed in the preceding paragraph. Future synthesis of this work may be able to include alternative forms of methodology although this will inherently limit the ability to synthesise findings from the literature via meta-analysis.

Generalisability of the findings from this review is limited by the characteristics of the study participants, notably the time since onset of stroke. This ranged from very early after stroke (2-8 weeks post onset) to very late (>73.2 months). As has been previously discussed within the early chapters of this thesis the physiological processes underpinning recovery and learning over these two time periods are different (Kleim and Jones, 2008) and therefore the effectiveness of interventions within one period may not be generalisable to the other. Future reviews should consider stratifying subsequent findings according to time since stroke to avoid this confounder.

- **Objective 2: To seek to quantify the findings from the review through meta-analysis.**

Twenty five studies were initially included in this review; this resulted in a total of 47 outcome measures within the impairment domain of the ICF, 12 within the activity domain and 7 classified as 'functional measures'. A systematic review of outcome measures in acute stroke trials found that in 51 trials there were 14 different measures of impairment, 11 different measures of activity, 1 measure of "quality of life," and 8 miscellaneous other measures (Duncan et al., 2000). The degree of heterogeneity seen in the present review is therefore not unusual. In an attempt to minimise heterogeneity studies were only included in the meta-analysis of the present review if they had measured outcome within the activity domain of the ICF. Despite this there was insufficient data to perform any meta-analysis on the upper limb interventions categorised as augmenting. Meta-analysis arguably provides a robust means of quantifying the effect of an intervention and therefore seems desirable (Borenstein et al., 2010). Future reviews could consider ways in which impairment domain measures could be grouped together, assuming it is possible to define an aspect of measurement that is common to them all. Synthesis of future reviews would be strengthened however if consensus around the use of fewer outcome measures could be achieved. Table 23 provides a summary of the results from the systematic review.

| | Outcome Measure | No/Little Movement | Outcome Measure | Augmenting |
|---|---|---|---|---|
| Upper limb | **Action Research Arm Test**<br>P=0.11<br>Not statistically significant effect | Meta analysis: Ietswaart et al. (2011), Page et al. (2002), Page et al. (2009) and Wu et al. (2010) | **Action Research Arm Test**<br><br>P=0.05<br><br>Statistically significant | Single study findings: Crow et al. (1989) |
| | **Frenchay Arm Test**<br>P=0.0005<br>Statistically significant effect | Single study findings: Ertelt et al. (2007) | **Box and Block**<br><br>P=0.015<br><br>Statistically significant | Single study findings: Carmeli et al. (2011) |
| | **Wolf Motor Function Test**<br>P=0.0525<br>Not statistically significant effect | Single study findings: Ertelt et al. (2007) | **Chedoke Arm and hand Inventory**<br>P=0.025<br>Statistically significant | Single study findings: Da Silva Cameirao et al. (2011). |
| Lower Limb | **Walking Speed**<br>P=0.057<br>Not statistically significant | Meta analysis: Lee et al. (2011), Ng and Huichan (2007:2009) | **Berg Balance Scale**<br>P=0.77<br>Not statistically significant | Meta analysis: Sungkarat et al. (2011), Walker et al. (2000). |
| | **Functional Ambulation Categories**<br>P=0.610<br>Not statistically significant | Single study findings: Sutbeyaz et al. (2009). | **Timed Up and Go**<br>P=0.84<br>Not statistically significant | Meta analysis: Sungkarat et al. (2011), Walker et al. (2000). |
| | **6 minute walk test**<br>P>0.01<br>Not statistically significant | Single study findings: Ng and Huichan (2009) | **Timed Walking Speed**<br>P=0.73<br>Not statistically significant | Meta analysis: Sungkarat et al. (2011), Yang et al. (2008), Schauer and Mauritz (2003) Walker et al. (2000). |
| | **Timed Up and Go**<br>P<0.01<br>statistically significant | Single study findings: Ng and Huichan (2009) | | |

Table 23: Summary table of the results from the systematic review

Findings from the meta-analysis are discussed below within the categories in which they were analysed:

**No/little movement lower limb:**

- No statistically significant effects in favour of the experimental intervention for timed walking speed (p=0.57). Meta-analysis of findings from Lee et al. (2011) and Ng and HuiChan (2007 and 2009).

- No statistically significant difference between the experimental and control groups for the Functional Ambulation Categories (p=0.610). Individual study findings from Sutbeyaz et al. (2007)

- No statistically significant difference between the experimental and control groups for the Six Minute Walk Test (p>0.01). Individual study findings from Ng and Hui Chan (2009).

- Statistically significant difference between the experimental and control groups for the Timed Up and Go (p<0.01). Individual study findings from Ng and Hui Chan (2009).

Findings from the quantitative analysis of the lower limb studies evaluating interventions within the little/no movement category suggested some evidence for the effects of the application of the priming motor learning principle on mobility when measured by the timed up and go (TUG) (Ng and Hui-Chan, 2009). This study applied this principle through the use of transcutaneous electrical nerve stimulation set to provide a sensory stimulus. Risk of bias assessment for this study was at low risk for all categories, which suggests that the relationship between the experimental intervention and the improvement in the TUG is reliable (Higgins and Green, 2011). Generalising these findings to all stroke survivors is however limited, as this study only included those participants within the chronic phase of recovery from stroke.

**No/little movement upper limb**

- No statistically significant effects in favour of the experimental intervention for the Action Research Arm Test (p=0.11). Meta-analysis of findings from Ietswaart et al. (2011), Wu et al. (2010), Page et al. (2009) and Page (2001).

- No statistically significant difference between the experimental and control groups for the Wolf Motor Function Test (p=0.0525). Individual study findings from Ertelt et a.l (2007).

- Statistically significant difference between the experimental and control groups for the Frenchay Arm Test (p=0.0005). Individual study findings from Ertelt et a.l (2007).

Summary analysis of the studies targeting upper limb interventions in the liitle/no movement category found some evidence to support the application of the priming motor learning principle. This result was from only one study (Ertert et al, 2007) which applied this principle using a therapy called ‘action observation’. The only outcome measure to show statistically significant effects of the intervention was the Frenchay Arm Test (FAT). The study by Ertelt et al. (2007) was assessed as being at unclear risk of bias for random sequence generation, allocation concealment and blinding of outcome assessment, therefore these results may not be reliable (Higgins and Green, 2011).

The design of the motor learning framework in this present review has led to the analysis of studies only evaluating the application of the priming motor learning principle, even though this was within the broader category of little/no movement. The inclusion of therapeutic interventions such as thermal stimulation and transcutaneous electrical nerve stimulation within a common category has not been carried out before thus there is no previous evidence with which to compare the findings from this present review. If a consensus around the name and definition of this motor learning principle can be achieved then further synthesis including future studies that could be defined as applying the priming motor learning principle would increase the body of evidence for

this intervention. Synthesis within this context is likely to lead to the inclusion of a greater number of studies than systematic reviews of the individual therapies. Meta-analysis of the subsequent findings could therefore produce results that could be interpreted with more confidence if the studies were of good quality (Higgins and Green, 2011). Such an interpretation may therefore make decisions about the effectiveness of this motor learning principle more robust.

It is possible that in creating the 'priming' intervention the heterogeneity inherent within studies essentially evaluating different therapeutic interventions may have impacted on the meta-analysis. In order to address this, quantification of the heterogeneity could have been carried out and then this taken into account within the subsequent summary analysis (Borenstein et al., 2010). Future reviews of this body of work will need to consider this within the analysis plan of the protocol.

**Augmenting lower limb**

- No statistically significant effects in favour of the experimental intervention for the Berg Balance Scale (p=0.77). Meta-analysis of findings from Sungkarat et al. (2011) and Walker et al. (2000).

- No statistically significant effects in favour of the experimental intervention for the Timed Up and Go (p=0.84). Meta-analysis of findings from Sungkarat et al. (2011) and Walker et al. (2000).

- No statistically significant effects in favour of the intervention for timed walking speed (p=0.73). Meta-analysis of findings from Sungkarat et al. (2011), Yang et al. (2008), Walker et al. (2000) and Schauer and Mauritz (2003).

Motor learning principles applied in these studies were practice specificity and feedback.

Walker et al. (2000) was the only study to be at high risk of bias in any category within the risk of bias assessment. The authors of this study stipulated that bias was not present because the outcome assessors used standardised outcome measures. Whilst no weighting of the importance of any of the categories is given, lack of blinding of their outcome assessor creates the potential to falsify the study results. The inclusion of studies with a high risk of bias may lead to an unreliable interpretation of the overall findings of a review because the summary analysis has been founded on studies that were of poor methodological quality (Higgins and Green, 2011). The impact of this study on the summary analysis is unclear as risk of bias assessment has only been presented visually. An alternative means of managing the impact that these studies have on the synthesis of studies within a systematic review is via meta-regression (Higgins and Green, 2011). Meta-regression can be incorporated into the meta-analysis and therefore provide a statistical means of reflecting the impact that these studies may have on the effect size (Higgins and Green, 2011). Future reviews could consider this within the analysis plan in their protocol

Analysed within the 'augmenting' category, studies included in the meta-analysis of the Berg Balance Scale and the Timed Up and Go applied the feedback principle. Sungkarat et al. (2011) used an insole shoe wedge and Walker et al (2000) used a biofeedback device known as a Balance Master. Previous reviews of the effects of feedback in the lower limb have been limited to the application of feedback delivered via EMG and meta-analysis was not possible (Woodford and Price, 2007). This present review does not however support the general consensus that seems to be present within the literature, which is that feedback, particularly extrinsic feedback, is a useful adjunct to movement therapy after stroke. However, these reviews were based on the use of this principle to support upper limb movement recovery only and thus may not be applied to the recovery of lower limb movement (Subramanian et al., 2010 and Molier et al., 2010).

Use of the augmenting category meant that the effects of practice specificity were combined with that of feedback and therefore it was not possible from this

present review to discern any specific effects of these motor learning principles. As stated previously the categorisation used in the present review may not be appropriate and future reviews of the application of each motor learning principle might be more useful.

**Augmenting upper limb**

- Statistically significant difference between the experimental and control groups for the Box and Block Test (p=0.015). Individual study findings from Carmeli et al. (2011).

- Statistically significant difference between the experimental and control groups for the Action Research Arm Test (p=0.05). Individual study findings from Crow et al. (1989).

- Statistically significant difference between the experimental and control groups for the Chedoke Arm and Hand Activity Inventory (p=0.025). Individual study findings from da Silva et al. (2011).

Evidence in support of upper limb augmenting studies came from Crow et al. (1989), Carmeli et al. (2010) and da Silva Cameirao et al. (2011). Each study used a different outcome measure and all found statistically significant changes in upper limb activity measured by the Box and Block (p=0.015), the ARAT (p=0.05) and the Chedoke Arm and Hand Activity (p=0.025).

Motor learning principles applied in this category were feedback and practice specificity. Feedback was applied through the use of a custom designed glove (Carmeli et al., 2011) and EMG biofeedback (Crow et al., 1989). These findings agree with both narrative reviews of the provision of extrinsic feedback (Subramanian et al., 2010 and Molier et al., 2010). Both reviews were prevented from meta-analysis due to the number of different outcome measures that had been used. These findings and those of the present study continue to support the need for a consensus on the use of common outcome measures as previously mentioned.

Da Silva et al. (2011) evaluated the effects of practice specificity through a virtual reality environment. A review of the use of virtual reality has identified its potential for use in movement rehabilitation after stroke (moderate effect on arm function measures (SMD 0.53 95% CI 0.25-0.81), however this review did not discriminate between the underlying principles behind its use in the individual studies. Identifying this therapy within a motor learning framework would facilitate this.

Carmeli et al. (2010) was at unclear risk of bias for allocation concealment and da Silva Cameirao et al. (2011) was assessed as unclear for both random sequence generation and allocation concealment. Although the impact of this risk of bias assessment is inherently 'unclear' these were small studies (n=31 and n=16 respectively) and therefore the probability of these studies showing an effect that can be generalised to the wider stroke population is limited (Button et al., 2013). The study by Crow et al. (2010) was at low risk of bias suggesting that the findings from this study may be more reliable.

Identification of motor learning principles within the category of augmenting was limited to just two applications (feedback and practice specificity). There were no studies included in this review that evaluated the effects of the application of instructions or variability of practice. The absence of studies evaluating the application of these principles may be explained by the inclusion of randomised controlled trials only. The background chapter identified one study by Fasoli et al. (2002) which was designed using a repeated measures case series which evaluated the effects of 'instructions' and a single case study by Deprey (1999) evaluating the effect of 'variability of practice'. Neither study would have been included in this review by virtue of their design. RCT are reported to be the gold standard (Sim, 2000) therefore the systematic synthesis of studies with this design are arguably most robust. There is an argument however that the design of a trial should be governed by the research question, consequently an RCT may not always be the most appropriate methodology (Sackett and Wennberg, 1997). The decision to exclude studies that are not RCT may bias the findings from a systematic review because it will not reflect

all the evidence within that field of research. Future reviews may wish to consider including other study designs, although this could impact on the ability to conduct meta-analysis.

## 4.13 Summary

Thus far this study has systematically reviewed the relevant literature and carried out both a risk of bias assessment and summary analysis of the findings from studies evaluating interventions defined as either priming or augmenting within a motor learning framework.

Twenty five studies were included and underwent a risk of bias assessment. Only ten (40%) studies were at low risk for all categories in the risk of bias assessment suggesting the potential for bias within the majority of studies included in this review.

Owing to the heterogeneity of outcome measures used within the included studies, summary analysis of only those studies using outcomes within the activity domain of the ICF was carried out.

Sixteen studies were subsequently included in the quantitative analysis of this review. Meta-analysis of the lower limb interventions categorised as little/no movement found no evidence for an effect of the intervention on walking speed. Findings from one study showed a statistically significant effect using the Timed Up and Go. The effectiveness of upper limb interventions within the same category were also not supported by meta-analysis of the findings of the Action Research Arm test, nor single study findings for the Wolf Motor Function test. Single study findings from the Frenchay Arm test were however, statistically significant for this category. Meta-analysis of the augmenting lower limb studies found no statistically significant effect for any outcome but individual study results for augmenting upper limb studies found statistically significant results for the Box and Block test, the Action research Arm test and the Chedoke Arm and Hand Inventory.

Interpretation of this review can only be made within the context of the definitions of the motor learning principles and the framework that has been used. Future work evaluating the evidence for each of the motor learning principles may be more appropriate as a means of informing future practice.

In order to address second and third aims of this study, the following chapter will describe the design, methodology and results of the phase II trial investigating the effects of functional strength training on walking and upper limb function.

# 5.0 Functional Strength Training to improve upper limb function and walking in people between six months and five years after stroke: A phase II trial (Question 2)

## 5.1 Introduction

Chapter three summarised findings from Functional Strength Training (FST) studies to date. The evidence suggests that FST is a feasible intervention for both the affected upper and lower limb in people after stroke but that the findings from these trials can only be applied to stroke survivors within the first three months after stroke.

Designs of future trials need to incorporate clear protocols for the study interventions to ensure that they are sufficiently different and randomisation will need to consider the impact of stroke severity as a potential confounder to ensure that groups are evenly matched for this factor. The aim of this study was:

- To carry out a phase II randomised controlled trial to determine feasibility of a physical therapy intervention – Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke.

    Objective 2: Establish feasibility of Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke by determining likely rates of recruitment.

    Objective 3: Establish feasibility of Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke by testing procedures for acceptability including the choice of outcome measures and the pragmatics of delivering the interventions.

    Objective 4: Provide information for calculating a sample size for evaluation trials.

The following sections describe the design, methods, results and interpretation of a phase II observer blinded randomised controlled trial to address the following research question.

Is Functional Strength Training a feasible intervention for improving upper and lower limb recovery later after stroke?

## 5.2. Design

Research in health care is intended to answer the question of what the future practice for patients should be (Sim and Wright, 2000). The drive to achieve evidence based practice defined as:

> "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al., 1996) (p. 71)

implies the need to engage with research in order to facilitate evidence based practice.

Quantitative methodologies assume a positivist approach towards the gathering of knowledge where theories are developed through a process of inductive reasoning (Bird, 1999). A hypothesis is deduced from these theories and this is tested against pre-determined criteria. Analysis of the results subsequently enables the researcher to either accept or refute this theory (Sim and Wright, 2000).

Guidance from the Medical Research Council (MRC) (Craig et al. 2008) describes four key elements to the development of an evaluation process, these are: Development, Feasibility, Evaluation and Implementation. Development is defined as:

1. Identifying the evidence base
2. Identifying developing theory
3. Modeling process and outcomes

Chapter two identified both the theoretical construct for the development of Functional Strength Training as an intervention for improving movement after stroke (a strength training intervention incorporating task specific practice) and the current evidence base for this intervention in people who are within 3 months of stroke (Bale and Strand, 2008, Cooke et al., 2010b, Donaldson et al., 2009a). These studies have provided information on the process for conducting future studies and identified potential outcome measures for evaluating efficacy in people early after stroke. Physiological differences in the recovery processes between people in the early stages of recovery and those in the later stages of recovery from stroke are underpinned by different processes (Kleim and Jones, 2008). Thus the feasibility of FST, established by the earlier trials, cannot be transferred to stroke survivors in the later stage of recovery. The subsequent step in the evaluation process for Functional Strength Training in people later after stroke is therefore 'Feasibility', this refers to the testing of procedures for acceptability, determining likely rates of recruitment and suggesting sample sizes for evaluation trials, this is carried out through a phase II trial (Craig et al., 2008). In essence the purpose of a phase II trial is arguably to decide whether there is merit in continuing to a phase II trial of the same intervention (Stallard, 2012).

The research design needs to be guided by the type of question that is being asked (Sackett and Wennberg, 1997, Sim and Wright, 2000). The research question suggests a relationship between FST and functional recovery of the upper and lower limb in people later after stroke. Thus the variables that need to be investigated are FST and functional recovery in the upper and lower limb.

Experimental study designs such as controlled trials are a way of evaluating the effectiveness of an intervention in a given population. They allow the researcher the opportunity to investigate the effects of an intervention against a comparator (Altman, 1990). Without the presence of a control group it becomes more difficult to attribute any changes in the outcome measures to the intervention. The typical design of a trial investigating the feasibility of FST relative to functional recovery of the upper and lower limb should have three groups: upper limb, lower limb and a control or comparator. Each group would

need to offer the same amount of therapy time so that any results would not be attributed to a dose response relationship and be sufficiently different to FST to avoid comparing 'like for like'. A three group design such as this would have carried considerable resource implications for the researcher, as it would have meant the provision of therapy to all three groups; previous trials of FST have been able to include a control group which has been provided for from within 'usual provision' and has therefore not had to be supplied by the research team (Cooke et al., 2010b, Donaldson et al., 2009a). The researcher was also concerned about the ability to recruit sufficient numbers of participants to such a three group design, a belief that was underpinned by current recruitment problems to other trials that were being conducted at the time. It was decided therefore to design this study with two intervention groups (FST – upper limb and FST- lower limb), both groups would be matched for dose or amount of therapy and each could act as control for the other (see figure 4 for trial flow chart).

There is some experimental evidence to suggest that strengthening the upper limb may have an effect on the lower limb, an effect possibly mediated by the presence of neuronal coupling between the upper and lower limbs during tasks such as walking (Dietz, 2002, Zehr et al., 2007). This effect was evidenced by an increase in EMG activity when the arms were used to passively move the legs through a cycling action (Huang and Ferris, 2004). Despite this, there are also some circumstances where the cross training effect was not evident; for example no cross training effect was seen if the lower limbs remained stationery during the same upper limb cycling action (Balter and Zehr, 2007). In light of a lack of clarity around the potential for a cross training effect between the upper and lower limbs, and the presence of clinical research that found that stroke survivors who received upper limb therapy showed statistically significant improvements in upper limb function without improvements in the lower limb and vice versa (Kwakkel et al., 1999), the two group design described above was considered feasible.

The design of a clinical trial needs to account for potential sources of bias because the effects of bias may lead to either false positive or false negative

results (Sim, 2000). Selection bias may occur where trial designs do not include a robust method of randomisation; random allocation to the intervention groups ensures that all participants are given equal chance of receiving one or other intervention (Altman, 1990). Randomisation has also been shown to improve the accuracy of the treatment effect, for example, Schultz et al (1995) found that non-randomised studies overestimated a treatment effect by 41%. This feasibility study of FST in people later after stroke was therefore designed to include randomisation.

Finally, study design can also account for 'observer bias', i.e. the bias that arises when either participants or relevant study personnel know the group allocation (Sim, 2000). To avoid this source of bias individuals are 'blinded' to group allocation; trials are said to be 'double-blinded' when both participants and study personnel responsible for outcome measurement are unaware of group allocation and single-blinded when only one of these two groups of people are unaware. In this present study it would not be possible to 'blind' the participants to group allocation as they will be aware of whether they are receiving either the upper or lower limb intervention; therefore this study included single blinding of the outcome assessor.

In summary the design of this study was determined by the previous work investigating Functional Strength Training and where this information fits within the framework provided by the Medical Research Council (Craig et al., 2008). It was also informed by the need to ensure a robust design which will avoid, where possible, sources of bias that may influence the treatment effect (Sim, 2000). Therefore in order to determine the feasibility of Functional Strength Training for improving walking and upper limb function in people later after stroke this study was designed as a phase II observer blind randomised controlled trial with two intervention groups (FSTUL and FSTLL), each acting as the control for the other (see figure five for flow chart showing trial design).

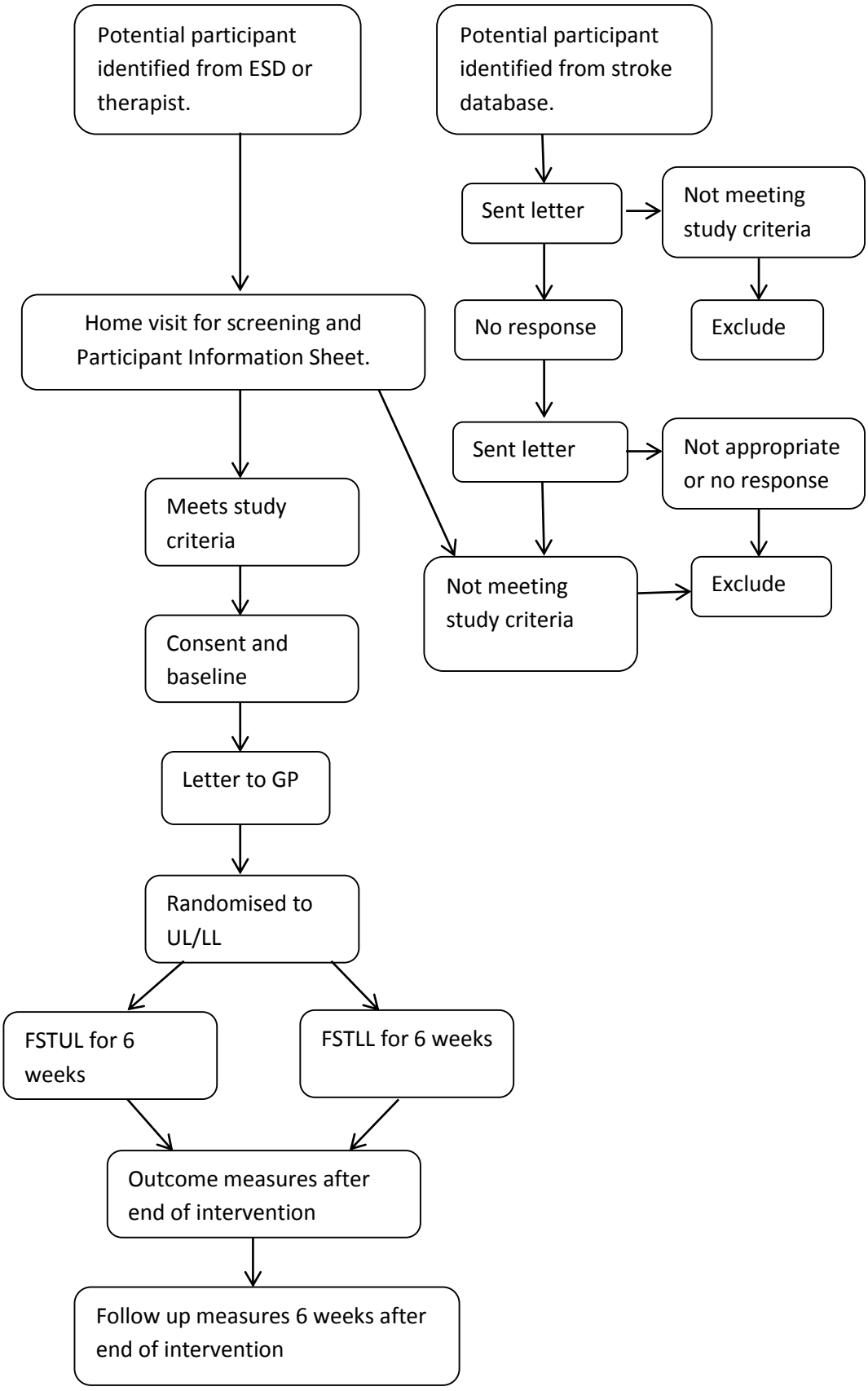


Figure 6: Trial flow chart

## 5.3 Methods

The following section will discuss the process involved in undertaking this study in the following order: participant inclusion/exclusion criteria, sample size, recruitment, randomisation, outcome measures, intervention details, ethics and analysis.

### 5.3.1 Participants

All participants in this trial were:

a) Adults aged 18+ years, six months to five years after a stroke.

This study aimed to evaluate the feasibility of FST in adults within the 'chronic' period of recovery after stroke, thus our inclusion criteria reflected this by including only those people who were between six months and five years after stroke.

b) Diagnosed with either an infarct or haemorrhagic stroke in the territory of the anterior circulation.

People who have been diagnosed with a stroke are a heterogeneous population and present with differing impairments (Bamford and Sandercock, 1991). To reduce the heterogeneity and thus the complexity previous trials have tried to define their population more specifically. One example of this is by using only participants who have been diagnosed with a stroke affecting the middle cerebral artery (Kwakkel et al., 1999). Findings from this study would therefore suggest an effect of the intervention for this group of stroke survivors only. Studies designed in this way have greater specificity but less generalisability. In everyday practice it is unlikely that a therapist will only manage a caseload of stroke survivors with a middle cerebral artery infarct. Thus there is a need to evaluate interventions as they would apply to 'everyday practice' (Haynes, 1999). This study aimed to be as inclusive as possible by including all stroke survivors with movement impairments that would respond to a strengthening programme. The anterior circulation supplies the motor cortex and a blockage or bleed in this area is likely to lead to these impairments. Conversely, the posterior circulation supplies the cerebellum, infarcts affecting this region lead to impairments such as ataxia (Cohen, 1999). There is no clinical evidence to suggest that these patients would respond to a strengthening programme

and therefore it would not be appropriate to include them in this study (Cooke et al., 2010b, Donaldson et al., 2009a). Information pertaining to the site of the stroke was obtained during the recruitment process, when names and addresses of potential participants were obtained via the stroke database. As the study progressed recruitment methods were refined to include referrals from therapists, who were asked to suggest potential participants based on clinical signs and symptoms usually experienced following a stroke affecting the anterior circulation. Recruitment via this method meant that the research team did not have access to the medical records until informed consent was obtained, therefore participants were included if they presented with a hemiplegia but were not included if they had ataxia or other impairments associated with a posterior bleed.

c) able to walk four steps with the continuous support from one person and/or assistive devices, but unable to step on and off a step 7.5cm high greater than fourteen times in fifteen seconds with either their affected or unaffected leg (the step test) (Hill et al., 1996).
d) have sufficient voluntary activity in the paretic upper limb to move the paretic hand from a position on their lap to the table top in front of them, but unable to pick up four £1 coins individually from a table top and stack them evenly in a pile.

Participants were randomised to receive either FST upper limb or FST lower limb. They needed to be able to have sufficient activity in their affected side to enable them to take part in repetitive, progressive functional practice, but not have made so much recovery that they would be unlikely to benefit from the intervention. The initial screening criteria, with respect to lower limb function, had included exclusion from the study on the basis of being able to walk up and down stairs one foot after the other. In practice this was difficult to assess because so few people had stairs, the study by Hill et al. (1996) found that the step test could distinguish between people who were independent walkers and those who could walk independently but still had substantial impairments as a result of stroke.

Precedent for these inclusion criteria were determined by the previous studies of FST (Cooke et al., 2010b, Donaldson et al., 2009a). These studies gave some indication that FST would be feasible for participants

with these clinical presentations. By limiting the inclusion of participants to those with specific clinical features it may be possible to gain some understanding of the effects of FST for the different severities of stroke symptoms as classified by the Action Research Arm Test and Functional Ambulation Categories. The inclusion of participants with a broader spectrum of symptoms in this relatively small study would lead to fewer numbers of participants within each category and therefore less potential for suggesting a causal relationship linked to severity. A finding which may prove useful for the design of future studies.

e) Able to give informed consent and able to follow a 1-stage command with the non-paretic upper limb i.e. sufficient communication/orientation for the interventions in this trial.

In order for participants to be able to fully participate in the exercise programme it is necessary for them to be able to follow commands. This inclusion criteria enables this study to be as inclusive as possible but exclusive of those who may not be able to gain any potential benefit of the intervention. In order to include as many people with stroke who had communication difficulties the design of both Participant Information Sheets and consent forms were informed by the Department of Health (2009), Connect guidelines (Swinburn and Firenza, 2007) and liaison with a Speech and Language Therapist with expertise in working with people with aphasia. Specifically the study used the following strategies (Dalemans et al., 2009):

- Key concepts were written in ‘bold’ text
- Pictures were used to support the text
- One to one information giving was achieved through a home visit
- Carers were involved during the initial information giving event when the potential participant was happy for this to happen.

In addition participants were not:

f) diagnosed with a known pathology which excluded participation in the low intensity exercise training involved in functional strength training.

g) receiving any physical therapy for their upper or lower limb. It was essential that changes that occurred in the outcome measures were

attributable to the intervention and not to any confounding factors such as different therapy that they may be receiving.

### 5.3.2 Sample Size

One purpose of a phase II trial is to determine sample sizes for future studies therefore the calculation of a sample size for the present study seems counter-intuitive. Despite this, it does not seem ethical to direct valuable resources to continue evaluation of an intervention where no effects of such have been detected (Stallard, 2012). Whilst the purpose of a phase II trial is to determine feasibility and it should be possible to obtain funding for a phase III trial based on its findings, funding bodies may be less likely to support the development of an intervention into phase III when there has been no evidence of efficacy at phase II. In order to provide some preliminary data regarding efficacy of the intervention a sample size calculation is required (Altman, 1990). Consensus over the methods for calculating sample sizes for phase II trials have not achieved and in the present study a formal power calculation was not possible because there was insufficient data of the effects of the intervention (Craig et al., 2008). It was estimated though that 26 participants per group would have 90% power at 5% significance (2-tailed) to detect a change of 1 point on the Functional Ambulatory Category (FAC) (Holden et al., 1984) assuming a standard deviation (SD) of 1 and 5.7 points on the Action Research Arm Test (ARAT) (Yozbatiran et al., 2008) (minimal clinically important difference (van der Lee et al., 2001b)) assuming a SD of 5.7. A pragmatic decision was taken in respect of the minimal clinically important difference for the FAC, as this data is not available. The FAC is a 5 point scale which clearly defines advancing levels of functional gain and a change in 1 point on the scale indicates a clinically significant change in functional ability.

To allow for an attrition rate of 10% (estimated from earlier trials) (Cooke et al., 2010b, Donaldson et al., 2009a) the researcher aimed to recruit 58 stroke survivors.

### 5.3.3 Recruitment

Approximately 800 people are discharged from the local acute hospital every year with a diagnosis of stroke. At the planning stage we anticipated recruiting two people per month. This figure was based on recruitment to previous FST trials (Cooke et al., 2010b, Donaldson et al., 2009a).

A record of admissions following stroke, subsequent discharges and clinical information is maintained on a database at the NHS Trust in which the stroke unit is located. Potential participants were initially identified using this database. Anonymised data was sorted by the researcher in an attempt to target discrete geographical areas. The aim was to minimise travel expenses to and from participants' homes. Once sorted the data was sent to the Stroke Research team at the acute hospital. As members of the clinical team they were able to interrogate the Patient Administration System (PAS) and ensure that those patients who had died were excluded from the recruitment strategy. Interpretation of the Data Protection Act (1998) stipulates that only members of the clinical team can access clinical data until the participant gives informed consent for this to be done by the research team. Once identified each potential participant was sent a recruitment letter (appendix VI) with an expression of interest form attached (appendix VII).

If a potential participant was interested in taking part in the study they were asked to send the expression of interest form back, in the supplied stamped addressed envelope or to telephone the researcher directly.

On receipt of an expression of interest from the potential participant the researcher contacted the participant by telephone and determined whether the individual would meet the inclusion criteria for mobility and arm movement. If this was likely then the researcher arranged a home visit.

After four months it became apparent that the study was not meeting the intended recruitment rate. Two people had been recruited whilst the predicted target was eight; consequently, it became necessary to include additional recruitment strategies. Engaging local clinicians had been found to be a key

recruitment factor in the ‘AMBULATE’ trial (Lloyd et al., 2010). This study was based in Australia but had a number of features in common with the current study: the study aimed to evaluate a physical therapy intervention and recruited from the same population of stroke survivors as the current study (stroke survivors between six months and five years after stroke and community-dwelling). The decision was taken therefore to recruit via referrals from both the Stroke Early Supported Discharge team and from therapists employed providing healthcare services for stroke survivors. Other measures to improve the recruitment rate included securing funding from the Comprehensive Local Research Network for increased administration support in order to increase the number of invitation letters that were sent out. In an alternative exercise based trial where letters had also been the source of recruitment, 552 letters had to be sent to recruit 49 participants (Werner and Kessler, 1996) therefore it was anticipated that an increase in the number of letters sent would lead to better recruitment.

Once participants had been identified the Research Therapist (RT) visited them at home to discuss the practicalities of taking part in the study, to ensure that they fulfilled the study inclusion criteria and to go through the Participant Information Sheet (PIS) (see appendix VIII). After a period of seven days, in which the potential participant was asked to reflect on the information provided, the RT telephoned the individual at home and established whether they were still interested in taking part in the study. If they were, then an appointment was made for the ‘blinded’ assessor to visit. At this visit the blinded assessor took informed consent and witnessed the signature of the participant on the consent form (see appendix IX). Once written informed consent had been obtained the participant completed the baseline outcome measures.

As soon as confirmation of informed consent was obtained by the RT, a letter was sent to the participant’s GP to inform them of their patient’s wish to take part in the study. This was necessary to ensure that the participant was medically fit enough to participate in the study.

A summary of the study was attached to the GP letter so that they could make an informed decision about the medical suitability of their patient (see appendices X and XI). No reply within ten working days of the date of sending the letter implied medical suitability for the study. If there was no response from the GP the RT contacted the participant again in order to identify a start date for the study. If there was a response indicating medical unsuitability then the participant was informed and removed from the study at this time.
Following completion of the baseline measures participants were able to be randomised to either FSTUL or FSTLL.

### 5.3.4 Randomisation procedure

As soon as baseline measures had been completed random group allocation to either FSTUL or FSTLL was determined by a telephone call to an independent automated system within the Norwich Clinical Trials Unit. The risk of selection bias could only be minimised if there was a robust method of group allocation (Altman, 1990). The use of an independent computer based system for generating the randomisation sequence ensures very little opportunities for biased allocation to either intervention group and is therefore likely to avoid this risk of bias (Higgins and Green, 2011).

The process of randomisation aims to ensure that the composition of the groups are comparable (Sim and Wright, 2000). In clinical trials with large sample sizes the influence of confounding variables is likely to be avoided by randomisation. Smaller studies, however, may need to use alternative methods in order to ensure that the groups are comparable. One method for ensuring comparability across groups is stratification; however this may not be appropriate where there are a number of factors that need to be taken into consideration (Pocock and Simon, 1975). A previous study has identified severity of stroke to be a potential confounder in future trials of FST and recommended categorising severity of upper limb impairment into three groups according to the score achieved on the Action Research Arm Test (ARAT) (Donaldson et al., 2009a). This current study includes both an intervention for the upper and the lower limb and therefore severity needs to be accounted for

in both the arm and the leg. Modelling a measure of severity on that recommended by Donaldson et al (2009), lower limb severity could be categorised into three groups using the score obtained from the baseline measurement of the Functional Ambulation Categories (FAC). The following table demonstrates the combinations of severity that will therefore have to be taken into account within the randomisation process; UL and LL refer to upper limb and lower limb and mild, moderate and severe refer to the categorisation of severity.

| | | |
|---|---|---|
| UL mild/LL mild | UL moderate/LL mild | UL severe/LL mild |
| UL mild/LL moderate | UL moderate/ LL moderate | UL severe/LL moderate |
| UL mild/LL severe | UL moderate/LL severe | UL severe/LL severe |

Table 24: Combinations of severity that may occur

An alternative method to stratification which is able to manage the allocation of groups according to multiple factors is minimisation (Altman, 1990, Scott et al., 2002). Minimisation has been described as a "largely nonrandom" process (Scott et al., 2002 p. 663) which is based on an allocation sequence which may be predicted. This has the potential to create observer bias (Scott et al., 2002), however the number of variables available suggests that it would be unlikely for group allocation to be 'worked out'.

Minimisation of the baseline imbalance between treatment groups in this study was based on the Pocock and Simon's range method (Pocock and Simon, 1975). Severity of stroke was categorised using each participant's baseline scores for the FAC and the ARAT. The FAC is categorised as: mild, score 4+ (able to walk independently on level ground but needs help on stairs, slopes etc); moderate, score 3 (needs verbal supervision/stand-by help from one person); severe, score 2 of less (needs continuous/intermittent support of one person). The ARAT is categorised as: mild, score 39-57 (57 = able to complete all items normally); moderate, score 20-38 (38 = able to complete all items albeit slowly/abnormally); severe, score 0-19 (19 = able to complete all items partially).

### 5.3.5 Outcome measures

Outcome measures need to be able to evaluate all possible changes that may occur as a result of an intervention (MRC framework, 2008). The choice of outcome measures for this trial was informed by a number of factors. This section will highlight these and then discuss how they have influenced the choice of outcome measures for the present study:

1. Evaluation which will show change relevant to the participant; the Cumberland Consensus Group (2009) identified a need to find therapies that show significant benefit to patients and carers. Without this, it is unlikely that clinical practice will change. The World Health Organisation devised the International Classification of Functioning, Disability and Health (ICF) (World Health Organisation, 2001). The ICF is a framework which enables the researcher to identify outcomes within the context of body functions or structure, activity and participation (see table 24).

| ICF Domain | Definition |
|---|---|
| **Body function/structure** | Physiological functions of body systems and anatomical parts of the body. Impairments are problems in body function or structure. |
| **Activity** | The execution of a task or action by an individual. Activity limitations are difficulties an individual may have in executing activities. |
| **Participation** | Involvement in a life situation. Participation restrictions are problems an individual may experience in life situations. |

Table 25: Table to show definitions of each of the ICF domains

(http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf accessed 3.9.2012)

The aim of the framework is to provide a view of health and disability which is not only from a 'medical' or 'biological' perspective. Using the framework it is possible to 'map' potential outcome measures to each of the domains (Salter et al, 2011 www.ebscr.com accessed 2012). Outcome measures that fall within the activity and participation domains are likely to be those that are most meaningful to a patient or carer.

2. The choice of outcome measures needs to be informed by the intended goal of the study (Craig et al., 2008, Cumberland Consensus Working et al., 2009, Fitzpatrick et al., 1998). A range of measures may be appropriate in order to identify unintended consequences where possible and evaluate the breadth of potential outcomes (Craig, Dieppe et al. 2008). This study aims to determine the feasability of FST on both the affected upper limb and affected lower limb

in people at least six months after stroke. The outcome measures therefore need to measure functional tasks that are likely to be improved by FST in both the upper and lower limb. This can be informed by the previous trials that have been carried out using FST. Consistency of outcome measures across rehabilitation trials is likely to facilitate future meta-analysis and synthesis of findings.

This study aims to include participants who may have made little recovery, for example only able to walk a few steps with one person and a walking aid, to those who have made a relatively good recovery, able to walk outdoors independently with an aid. Attention needs to be paid to the floor and ceiling effects of potential outcome measures to ensure that clinically important functional gains in both these participant groups can be captured.

3. Outcome measures need to be reliable, valid and responsive. Reliability refers to the ability of the measure to produce results that are consistent and that are able to differentiate between participants. This is most frequently measured by determining the internal consistency of the measure, the test-retest reliability and the inter-rater reliability (Finch et al., 2002). An outcome measure that is judged to be valid is one that measures what it is supposed to measure; this has been determined by measuring face validity, content validity, construct validity and criterion validity (Finch et al., 2002). Finally responsiveness refers to the ability of an outcome measure to determine a 'clinically important difference' (Finch et al., 2002).

4. Outcome measures need to be suitable for the environment of the trial. This study was carried out in the community, generally within people's own homes, therefore the outcome measures used need to be valid and able to be applied practically in this setting. Equipment to carry out the measures needs to be portable and simple to set up. Time to complete all the measures also needs to be considered, it would not be appropriate for a participant to become exhausted because of the length of time and effort required to complete the outcome battery.

The following section will discuss each of the outcome measures used in this study in relation to these four factors. Factors one, two and four will be discussed under the heading of ‘suitability and ICF category’ and factor three will be discussed under the heading of ‘psychometric properties’.

#### *5.3.5.2 Primary Outcome Measures*

##### *Action Research Arm test*

- Suitability of measure and ICF category

The Action Research Arm Test (ARAT) is an observer rated scale for assessing both proximal and distal function of the upper limb. Precedent for its use within trials of FST has been set by Donaldson et al. (2009) and it has been found to be responsive to change in people diagnosed with chronic stroke (Van der Lee et al., 2001a). The ARAT was first described by Lyle (1981); it is divided into nineteen items of motor function of the upper limb, these are divided into four subscales evaluating grasp, grip, pinch and gross movement. Each test is given a score of 0 to 3, three being the highest score in each test, the total score for the ARAT is 57.

The ARAT falls within the ‘activity’ domain of the ICF because it measures ability to carry out functional activities or tasks.

The ARAT has been found to have a ‘floor’ effect in people in the acute phase after stroke (Hsueh and Hsieh, 2002a), although this finding was not substantiated by Nijland et al. (2010). Hsueh and Hsieh (2002) found that 51% of participants scored 0 whereas Nijland et al (2010) found that only 12.5% of participants scored below 2.85 (5% of the total score). Both trials were of similar size (n =48 (Hsueh and Hsieh, 2002b) and n = 40 (Nijland et al., 2010)). Nijland et al. (2010) did not report length of time from stroke in their study although participants were taken from rehabilitation centres. This may indicate that participants were in the sub-acute period after stroke suggesting that the floor effects demonstrated by the ARAT are less applicable at this time. This may be due to the fact that people have recovered sufficient movement to obtain a score. Investigation of this effect in people in the chronic phase after stroke has not been carried out.

Pragmatically the ARAT can be used in the community setting and time taken to complete the test will vary depending on how much each participant can do. The test is based on a hierarchy; therefore those participants who are more able may take up to twenty minutes to complete the test (van der Lee et al., 2001b). This would seem to be acceptable as it is those participants who are less able who are more likely to fatigue.

- Psychometric properties

Internal consistency i.e. the measurement of homogeneity of the items was established by Nijland et al. (2010). Measurement was carried out using Cronbach's Coefficient Alpha, this was found to be excellent (α = 0.98). A coefficient this high might however suggest that whilst the measure has strong internal consistency there are some items within the scale that are redundant (Fitzpatrick et al., 1998). Test-retest reliability (Hsueh and Hsieh, 2002b) and inter-rater reliability (Yozbatiran et al., 2008) have been found to be excellent (ICC = 0.99). A standardised approach was established for completion of the ARAT by Yozbatiran et a.l (2008).

Criterion validity of a measure can only be established if there is a 'gold standard' against which to measure it (Finch et al., 2002). To date this is not available for the ARAT, thus the alternative is to determine construct validity. This can be established by comparing the ARAT to alternative measures of upper limb function – convergent validity (Finch et al., 2002). Convergent validity was established in participants within the chronic phase of stroke. Excellent correlation was found between the ARAT and the arm section of the Fugl-Meyer (r = 0.94) (Yozbatiran et al., 2008).

A minimally clinically important difference of 5.7 has been established for the ARAT (van der Lee et al., 2001b). A difference of 5.7 between baseline and outcome scores of the ARAT would therefore indicate a clinically important change in upper limb function for a participant.

### *Functional Ambulation Categories*

- Suitability of measure and ICF category

Regaining the ability to walk is very important to people diagnosed with stroke, and their carers' (Bohannon et al., 1988). Consequently one of the aims for FST for the lower limb is to improve walking ability in people after stroke. Improvements in aspects of walking ability have already been suggested for FST in participants within the acute period after stroke (Bale and Strand, 2008, Cooke et al., 2010b). It follows then that one of the primary outcome measures for this trial needs to be a measure of walking ability. The Functional Ambulation Categories (FAC) (Holden et al., 1984) provide a measure of walking ability relative to the amount of assistance an individual requires. The categories of walking are numbered from zero to five and are hierarchical, with zero being a "non functional ambulator" to five being "a patient who can walk everywhere independently, including stairs" (Holden et al., 1984). The FAC are easy to administer in that they simply require observation of an individual's ability to walk and assessment is consequently not restricted by the environment. The FAC lies within the activity domain of the ICF.

Alternative lower limb outcome measures specific to walking in the previous trials of FST have focussed on walking speed (Bale and Strand, 2008, Cooke et al., 2010b). This is arguably less meaningful to a stroke survivor who is more likely to see the relevance of a scale which gives an indication of the level of assistance that they will require with their walking. Some walking speed measures are also dependent on a relatively large distance over which to complete the measure. The Six Minute Walk Test (6MWT) (Butland, Pang et al. 1982) requires a distance of thirty metres which is unlikely to be achievable in the community setting. The FAC is a common measure within rehabilitation trials for example the LEAPS trial which aims to evaluate so called 'locomotor training' and its effect on mobility post stroke (Duncan et al., 2007). Use of the measure in the current trial will continue to facilitate future synthesis and meta-analyses.

Floor and ceiling effects have not formally been reported for the FAC, although Lord et al (2004) found that the FAC was not able to distinguish between

individuals who were able to walk in their homes to those able to ambulate in the community. There may be a ceiling effect for those individuals who are able walkers.

The FAC is estimated to take between one and five minutes to complete (Marvin, 2011) indicating little burden to the research participant.

- Psychometric properties

No studies have reported on the internal consistency of the FAC. Test retest reliability and inter-rater reliability were tested by Merholz et al. (2007), both were found to be excellent (k = 0.950 and k = 0.905 respectively). No studies have reported on criterion or concurrent validity.

Concurrent validity of the FAC has been established with alternative measures of walking ability. Merholz et al (2007) found that the FAC correlates significantly with walking velocity and the 6MWT ($p=0.953$, $P<0.01$ and $p=0.949$, $P<0.01$ respectively).

Responsiveness to change was moderate to large as measured by the standard response time over a period of six months (Mehrholz et al., 2007). There are no studies to date identifying a minimally clinically important difference, although the hierarchical structure of the FAC suggests that an increase or decrease of one will have an impact on an individual's need for assistance when walking.

#### *5.3.5.3 Secondary Outcome Measures*

##### *Nine Hole Peg Test (NHPT)*

- Suitability and ICF category

The NHPT is a measure of dexterity; the test involves removing nine pegs from a board and placing them in a box and then replacing them on the board as quickly as possible (Kellor et al., 1971). Normative data for adults completing the NHPT were established by Mathiowetz et al. (1985). It is recommended that the NHPT is completed with other measures of upper limb function in order to give a complete overview of upper limb function (Figueiredo, 2011). Whilst

the ARAT does include tasks for measuring dexterity, the addition of the NHPT will ensure that those participants with greater functional recovery are represented explicitly in the measurement battery. The NHPT lies within the 'activity' domain of the ICF.

The NHPT requires little equipment and is easily transported. Time taken to complete the test will vary depending on each participant's functional ability. Normative values for healthy male adults indicate that one test will take approximately nineteen seconds (Mathiowetz et al., 1985) suggesting that the test is not likely to be too onerous for participants in this study.

- Psychometric properties

Intra-rater reliability has been established by Mathiowetz et al. (1985) who found excellent agreement (r = 0.69) for the right hand and adequate agreement for the left hand (r = 0.44) using a Pearson correlation in healthy individuals. Reliability values for this study were based on a wooden board for the holes and a wooden square with wooden pegs. This equipment has been reproduced for the current trial to avoid any confounding data arising from the use of different equipment. The same study established inter-rater reliability which showed excellent agreement for both right and left hand (r=0.97 and r=0.99 respectively) (Mathiowetz et al., 1985).

Test-retest reliability was established in a population of individuals diagnosed with stroke (n = 62) (Chen et al., 2009). Using an Intra-class correlation (ICC), this study found 'good' agreement between the test-retest results. The ICC was similar for both the more affected and less affected arm (0.85 (CI: 0.71-0.92) and 0.89 (CI: 0.82-0.94) respectively).

Criterion validity is not available; however concurrent validity was established for the NHPT correlated to the Box and Block test (BBT) and the ARAT. Using Spearman rank correlation coefficient, concurrent validity of the NHPT correlated with the BBT was good (p = -0.8, P<0.01) and moderate when correlated with the ARAT (p = -0.55, P<0.01).

A minimal clinically important difference has not been established for the NHPT, however Chen et al. (2009) calculated the 'smallest real difference' (SRD) or 'minimal detectable change'. This figure is the smallest change a participant can make that can be attributed to the intervention (Finch et al., 2002). Chen et al. (2009) identified an SRD of 32.8 seconds for the NHPT using the more affected arm; however this was only 6.2 seconds for the less affected arm. This discrepancy may have been caused by the smaller sample size in the more affected group. Only 44 participants were able to carry out the NHPT with their more affected arm compared to 62 using their less affected arm. The presence of spasticity may also have impacted on the high SRD; when the results of the more affected group were classified according to spasticity or no spasticity the SRDs were 67.5 seconds and 24.5 seconds respectively (Chen et al., 2009). Chen et al. (2009) re-emphasised the need to use the NHPT as part of a battery of upper limb measures.

### *Timed Up and Go*

- Suitability and ICF category

The TUG (Podsiadlo and Richardson, 1991) is a timed measure of walking and balance. The participant is seated in a chair and on the 'go' signal is asked to get up, walk three metres, turn around and return to a seated position on the chair. The TUG falls within the activity domain of the ICF. The FAC may have a ceiling effect and therefore may not be sufficiently sensitive to identify those individuals who have made good functional recovery with respect to walking. Conversely the TUG may have a large floor effect; Rockwood et al. (2000) found that 29.3% of participants were unable to complete the TUG. Therefore the use of both the FAC and the TUG should ensure that participants across all spectrums of functional recovery will be reflected in the outcome measures chosen for walking.

The TUG requires little equipment and a distance of three metres over which to walk is feasible within a community setting. The use of the TUG has been established in other strength training trials, most recently Hill et al (2012), therefore seems appropriate as a secondary outcome for the current study.

Time taken to complete the test is approximately one to two minutes and therefore is not expected to be onerous to the participant (Zeltzer and Zaino, 2008).

- Psychometric properties

Test-retest reliability was established by Flansbjer et al. (2005) and Ng and Hui-Chan (2005) in individuals diagnosed with chronic stroke. Both studies found excellent agreement between the two values (ICC: 0.96 and 0.95 respectively). Inter-rater and intra-rater reliability for the TUG has been established as excellent (ICC of 0.99) (Podsiadlo and Richardson, 1991). People included within this study were diagnosed with a variety of impairments including stroke, however this was not found to correlate with the TUG score.

Criterion validity has not been established but concurrent validity of the TUG was established against other gait parameters including the six minute walk test ($p = -0.960$, $P<0.01$) (Ng and Hui-Chan, 2005) and ICC of -0.92 (Flansbjer et al., 2005).

As for the NHPT, a minimally clinically important change has not been suggested for the TUG; however the SRD has been identified as 23% (Flansbjer et al., 2005) indicating that the TUG can detect small changes in participant performance.

### *Modified Rivermead Mobility Index*

- Suitability and ICF category

The two previous outcome measures relate specifically to the activity of walking, it is likely FST will have an effect on other functional activities involving the lower limb. The MRMI is developed from the Rivermead Mobility Index (RMI) (Forlander and Bohannon, 1999) and measures a range of mobility related activities such as rolling over in bed and sitting to standing. The MRMI extends the scoring system of the RMI in order to provide a better description of the difficulties experienced by individuals diagnosed with stroke (Lennon and Johnson, 2000). The MRMI was not found to have either a floor or ceiling effect

when tested on individuals up to 180 days after stroke (Hsueh and Hsieh, 2002a). Coincidentally the original version of the RMI showed significant floor effects (Hsueh and Hsieh, 2002a) indicating that the changes to the scoring system pioneered by Lennon and Johnson (2000) made the test more sensitive for people with significant motor impairment after stroke.

Internal consistency for the MRMI was calculated using Cronbach's alpha, which was found to be high ($\alpha = 0.949$), the reader is referred back to comments made in the ARAT section concerning scores that are found to be this high.

The MRMI requires no special equipment and was reported to take three to five minutes to complete (Figueiraedo, 2008).

- Psychometric Properties

Test-retest reliability of the MRMI was carried out using a paired t-test, Lennon and Johnson (2000) found no significant difference between the two values ($t = 0.732$; $p = 0.47$). Inter-rater reliability was found to be excellent in studies by both Lennon and Johnson (2000), (ICC: 0.98, $P<0.001$) and Hsueh and Hsieh (2003), (ICC 0.95 (95% CI 0.90 – 0.97)). Intra-rater data for this measure does not appear to be available.

Concurrent validity was established for the MRMI against the mobility subscale of the Stroke Rehabilitation Assessment of Movement measure (STREAM) (Daley et al., 1997) and the Motor Assessment Scale (MAS) (Carr et al., 1985). Scoring on items differed by a mean of 7% (SD 4.8%), which equated to a difference of three points on the MRMI; this was felt to be acceptable (Lennon and Johnson, 2000). The MAS is a well-known measure of motor function after stroke, however items on the scale are not restricted to mobility items but include 'upper arm function', 'hand movements' and 'advanced hand activities' (Lennon and Johnson, 2000). The MRMI appears to have been used more frequently in rehabilitation trials than the STREAM, which would suggest that for the purposes of future comparisons between trials, the MRMI remains the better choice for this current study.

A minimally clinically important change has not been established for the MRMI. The standardised response mean was found to be moderate for assessing change before ninety days after stroke, however was low for those participants within the 90-180 day period after stroke (Hsueh and Hsieh, 2002a). To date the responsiveness of the MRMI in participants diagnosed with chronic stroke has not been carried out therefore it would be inappropriate to exclude its use for the current trial on this basis.

### 5.3.6 Adverse Reactions

According to Good Clinical Practice guidelines an adverse reaction is defined as:

> "All untoward and unintended responses to an investigational medicinal product related to any dose administered" (http://www.crncc.nihr.ac.uk/workforce_development/learning_and_development/gcp/gcp_resource/gcp_glossary accessed 8.2.13)

Reporting of adverse reactions is specifically defined for CTIMP (Clinical Trial Involving Medicinal Products) trials. The present study would be classified as a non CTIMP, however Good Clinical Practice guidelines with respect to the reporting of adverse reactions remain the same, because the reporting of adverse reactions is essential for maintaining patient safety (MHRA, 2013). Previous studies of FST revealed no adverse reactions from either the upper or lower limb interventions (Cooke et al., 2010b, Donaldson et al., 2009a). However, it is possible, that as this study is recruiting from people later after stroke, the increased activity that is associated with this intervention may have an impact which did not occur in people early after stroke.

Participants who were within the chronic period of recovery from stroke, by virtue of their physical impairments, may not have engaged in exercise for some time. This study aimed to deliver FST to people four times a week for up to sixty minutes each time, this may be a considerable increase in the amount of exercise that some participants had engaged in. It is possible therefore that some participants may experience joint pain or muscle soreness. Pain or soreness that stops once the exercise stops is unlikely to lead to any

physiological damage, however pain that persists may be an indication that damage has occurred. Adverse reactions for this study were therefore defined as the reporting or exhibiting of pain over four consecutive days. If such pain occurred then the participant was withdrawn from their allocated treatment but included in the measurement battery according to the intention to treat principle, which will be discussed later.

### 5.3.7 Procedure for delivering interventions

The first visit with each of the participants identified the specific activities that they felt were difficult as a result of their stroke. The Research Therapist (RT) identified which muscle groups appeared to be most affected and established therapy goals with the participant. Involving the participant in the goal-setting process aims to ensure that the intervention has relevancy for the participant which may improve motivation (Sugavanam et al., 2012). The intervention was targeted to the specific impairments and level of recovery experienced by each participant.

Participants undertook a six week programme, four days a week for up to sixty minutes a day of either FST for the upper limb (FSTUL) or FST for the lower limb (FSTLL).

In the absence of definitive data from robust rehabilitation trials of people within the chronic phase after stroke, intensity or dose of the intervention in the current study was informed by previous trials of FST (Cooke et al., 2010b, Donaldson et al., 2009a).

It was anticipated that participants could become fatigued during the intervention; this presented itself as an increasing difficulty in performing the activities and reported feelings of tiredness. When this happened the therapist initially offered motivational encouragement and then changed tasks so the focus of the activity was biased toward a different muscle group. Finally the participant was offered a rest period until either one hour of therapy had been completed or it became apparent that the participant was unable to continue

with the rest of the session for that day. Field diaries were completed recording the time spent in either intervention activity or rest within the sixty minute period.

Standardised treatment schedules were used (as developed for and used in the earlier trials of FST) (see appendices XII and XIII) to record the content of the FST intervention (Cooke et al., 2010b, Donaldson et al., 2009b, Donaldson et al., 2009a, Pomeroy et al., 2005).

As this trial intervention was carried out by different therapists over the time that it ran, adherence to the intervention was monitored by the RT. Training for each new therapist who participated in the study took place before they commenced any interventions. During the study, the RT monitored how and what therapy was recorded in both the field notes and the treatment schedules. She also visited all participants at least once during their intervention phase to ensure consistency.

### 5.3.8 Interventions

- **Functional strength training for the lower limb (FSTLL)**

FST for the Lower Limb (FSTLL) focused on functional activities involving the lower limbs, whole or component parts of the movement were practiced.

Activities included:

- Getting on and off the floor
- Sitting to standing
- Stepping on and off a block
- Going up and down stairs
- Dynamic balance exercises such as standing on one leg

Progression was informed by the Oxford programme (Zinovieff, 1951, Trew and Everett, 2005) (see table below). This provided a framework for advancing the strengthening programme. Ten repetition maximum (10RM) refers to the load an individual can lift ten times before the muscle starts to fatigue (this is usually indicated when the muscle starts to 'quiver') (Hollis, 1989). This was ascertained by the therapist who was delivering the intervention. In practice as the objects used to create loading were often functional items such as bottles, or functional tasks such as sit to stand, the therapist judged when the participant was easily able to achieve ten repetitions (10 REPS) and would then increase the load or the difficulty of the task so that the strengthening programme was progressed.

| **Oxford Programme (Trew and Everett, 2005: pp. 119)** | | |
|---|---|---|
| 10 REPS at 10RM<br>10REPS at ¾ 10RM<br>10 REPS at ½ 10RM<br>REPS – Repetition<br>RM – Repetition Maximum | OR | 10 REPS at 10RM<br>Then reduced by<br>5kg for 10sets |

Table 26: The Oxford Programme for muscle strengthening

Increased resistance was given through the use of ankle weights and resistance bands or increasing the task difficulty e.g. increasing the height of the step or lowering the height of the seat when practising sit to stand.

In order to illustrate how one participant would have progressed through a programme of FST, field notes kept over a period of one week for a participant within the lower limb group have been included as appendix XIV

- **Functional strength training for the upper limb (FSTUL)**

FSTUL is based on the key elements of normal upper limb function, i.e. moving the hand into a position and then using it to manipulate objects. The focus is on: improving the power of shoulder/elbow muscles to enable appropriate placing of the hand; improving the production of appropriate force in arm and hand muscles to achieve the specific grasp; and specific interventions for the wrist and finger muscles to maximise ability to manipulate objects. Whole or component parts of the movement were practiced.

Activities included:

- Reaching for a jug and then pouring water from it
- Picking up a jar and unscrewing the lid
- Reaching down to the floor
- Placing pegs on a clothes line

Progression was again informed by the Oxford programme (Zinovieff, 1951, Trew and Everett, 2005) (see table above). Greater resistance was given by increasing the effects of gravity e.g. reaching across a table using a duster was progressed to reaching toward a cup without allowing the arm to rest on the table; auto assisted activities such as reaching to the floor using a stick were progressed to use of the affected arm without assistance; objects to be lifted were made heavier e.g. by increasing the amount of water in the jug.

### 5.3.9 Ethics

In the United Kingdom the Research Governance Framework (DH, 2005) lays out the guidelines which all research within the healthcare environment must comply with and this system is managed by relevant departments within the host NHS site. Ethical approval was granted by the Cambridgeshire 2 Research Ethics Committee (ref: 09 H0308 147). The trial is registered on the Current Controlled Trials database (ISRCTN71632550). For a copy of the ethics form please see appendix XV.

All other aspects of the study conformed to guidelines laid out by Good Clinical Practice (MHRA, 2013) (accessed 29.03.13). Interventions were all conducted

by Physiotherapists or Occupational Therapists registered with the Health Professions Council. Data was anonymised and stored in a lockable cabinet to comply with the Data Protection Act (Government, 1998).

### 5.3.10 Analysis

Analysis of the data obtained from this study was carried out using Stata® version 9. Descriptive data was plotted on a histogram to determine whether it was normally distributed, if this was the case then the results were displayed using mean and standard deviation, if not, then median and interquartile range were used. If the distribution of the data is skewed then it is more appropriate to use median and interquartile range to summarise the distribution of the data (Sim, 2000).

An intention to treat analysis was used to control for the potential for attrition bias, which may occur when participants within a study who drop out or are withdrawn are discounted from the final analysis. Bias may occur if all these participants are from one group or are all those for whom the experimental intervention is not working, this may lead to a Type I error or a false positive. An intention to treat analysis therefore, refers to an analysis where data from each participant is analysed according to the group they were allocated to following the randomisation process, regardless of whether they leave the study or move to a different intervention group (Sim, 2000).

A regression model was used to complete the statistical analysis of the difference between the outcome measures of the two groups. The use of minimisation introduces variables that need to be taken into account within the analysis model used and therefore regression models are deemed to be most appropriate for this (Scott et al., 2002). The process of minimisation reportedly leads to a correlation between the intervention groups because it forces the two groups to be similar for everything (apart from the effect of the experimental intervention). In effect this ‘matches’ the participants in each group preventing the participants from being ‘independent’, this matching needs to be taken into account in the analysis (Kahan and Morris, 2012). In simulated analyses of trial data Kahan and Morris (2012 pp. 335)) found that an analysis that did not

adjust for the stratification or minimisation process led “to biased standard errors, overly wide 95% confidence intervals, type I errors rates that were too low and a reduction in power”. Thus data derived from the ARAT and the RMI were analysed using a rank based analysis of covariance (RANCOVA). Neither of these measures are defined as interval ratio and therefore do not meet the criteria for an analysis based on parametric methods. Parametric methods are deemed to be more sensitive than non-parametric and would therefore be the preferred method of analysis. However in order to undertake parametric analysis the data must meet certain criteria, including being interval ratio and with a normal distribution (Sim, 2000). Data derived from the NHPT and the TUG were plotted on a histogram, as this is interval ratio, if this data is normally distributed then it was analysed using an ANCOVA, if it did meet this criteria then a RANCOVA was used for this data also. The results of the FAC were analysed using a proportional odds ratio; this is recommended as being the most appropriate method for an ordinal scale such as the FAC, where the difference between each of the levels is not equal (Scott et al., 1997).

### 5.3.11 Summary

The previous sections described the justification for the design and methods of a phase II trial intended to answer the following research question:
“Is Functional Strength Training a feasible intervention for improving upper and lower limb recovery later after stroke?”

Following recruitment participants were randomly allocated to one of two treatment groups (FSTUL or FSTLL). Baseline measures were recorded by an assessor blinded to group allocation before the start of the intervention phase. Participants received either FSTUL or FSTLL four times a week, for up to sixty minutes each time, for six weeks. Following completion of the intervention phase (outcome) and six weeks after the end of the intervention phase (follow up) outcome measures were repeated by the blinded assessor. Primary outcome measures for this study were the Action Research Arm Test (ARAT) and the Functional Ambulation Categroies (FAC); secondary outcome measures are the Nine Hole Peg Test (NHPT), the Timed Up and Go (TUG)

and the Modified Rivermead Mobility Index (MRMI). Analysis comparing the outcomes of the two groups at both outcome and follow up was undertaken.

## 5.4. Results

The previous section described the methods used to carry out a phase II trial investigating the feasibility of Functional Strength Training to improve walking and upper limb function later after stroke. This chapter will describe the results for this study, focussing initially on participant characteristics, recruitment and then the results for the primary outcome measures and secondary outcome measures.

### 5.4.1 Participant characteristics

Fifty two people were recruited to this trial from across Norfolk. Table 26 describes the participant characteristics for each group. 27 people were randomised to the upper limb treatment group and 25 were randomised to the lower limb treatment group.

| Characteristics | Upper limb (n = 27) | Lower limb (n = 25) |
|---|---|---|
| **Age/years (median, IQR)** | 70 (60-76) | 74 (61-79) |
| **Right hemiplegia** | 15 | 12 |
| **Time from onset to randomisation / days (median, IQR)** | 520 (337-1306) | 562 (428-1029) |
| **Male** | 18 | 17 |
| **Baseline ARAT score (median, IQR)** | 13 (3-25) | 10(3-23) |
| **Baseline FAC score (median, IQR)** | 2 (1-4) | 2 (1-4) |

Table 27: Baseline characteristics of the participants

Median scores and interquartile ranges (IQR) have been given for age, time from onset to randomisation, baseline ARAT score and baseline FAC score because the range of values for each of these were not normally distributed. When data is skewed a median value gives a better representation of the central score for that range of data (Altman, 1990). Both groups were matched for age and side of hemiplegia. Time from onset to randomisation was also

matched but showed a wide range of values. Within the total sample, time from onset to randomisation had a median of 562 days (approximately 1.5 years) and an IQR of 372 days to 1077 days (approximately one to three years). Participants presented with similar ARAT and FAC scores at baseline between the groups.

Participants were initially screened for diagnosis of a stroke affecting the anterior circulation, however when recruitment strategies moved to include people referred by local therapists it was not always possible to obtain this data. Recruitment was therefore based on a clinical examination of the potential participant, following consent and inclusion in the study it was possible to obtain this information retrospectively. Figure six demonstrates the proportion of people included in the study within each classification according to Bamford and Sandercock (1991). The highest proportion of participants fell within the PACI and LACI classification which corresponds with the original data described by Bamford and Sandercock (1991).

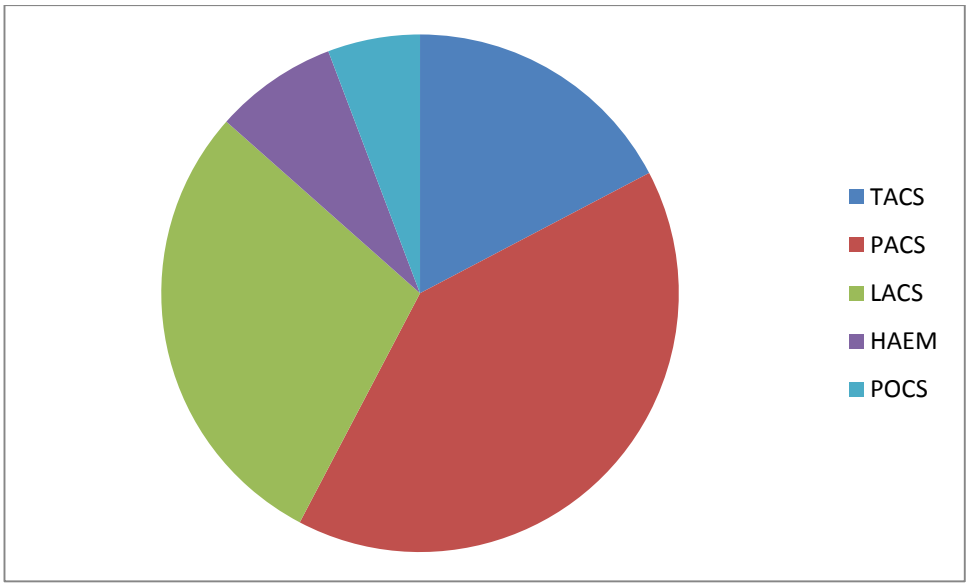


**Figure 7: Proportion of participants diagnosed with each stroke classification according to Bam ford and Sandercock (1991)**

Donaldson et al (2009) suggested that severity of stroke may be a confounding factor and advised that this variable be taken into account in future trials of FST.

Minimisation was therefore used to stratify for this according to the baseline scores for the FAC and ARAT. The following table shows the distribution of severity for the total sample.

| | Action Research Arm Test (ARAT) | | | |
|---|---|---|---|---|
| Functional Ambulation Categories (FAC) | **Mild** | **Moderate** | **Severe** | **Total** |
| **Mild** | **2** | **5** | **13** | **21** |
| **Moderate** | **0** | **2** | **1** | **3** |
| **Severe** | **1** | **9** | **18** | **28** |
| **Total** | **3** | **17** | **32** | **52** |

Table 28: Disutribution of severity across the total sample of participants

Table 27 shows that compared with lower limb impairment there were a high proportion of people included in the study who presented with severe upper limb impairment (61%). Severity for the lower limb was distributed more evenly between the mild and severe groups (25% and 33% respectively). Participant numbers for 'mild' in the ARAT and 'Moderate' for the FAC are small and are unlikely to impact on the analysis, therefore for the purposes of this study the mild and moderate groups for both the FAC and the ARAT were combined. This created a larger number of people which would be more likely to show an effect.

### 5.4.2 Recruitment

Figure seven shows the consort diagram for this study. In total 1127 potentially suitable participants were screened for inclusion in the study. This included those participants who were identified from the stroke database, therapist or were self-referred. 805 people were subsequently excluded because they had died or did not meet the inclusion criteria. This resulted in a total of 52 participants who were randomised to either FSTUL or FSTLL. Following randomisation 27 participants were allocated to the upper limb group and 25 participants were allocated to the lower limb group.

Delays to the start of the recruitment period were incurred because of research governance procedures. Ethical approval for this present study was granted in September but Research and Governance approval was not granted until the following January, this will be discussed later.

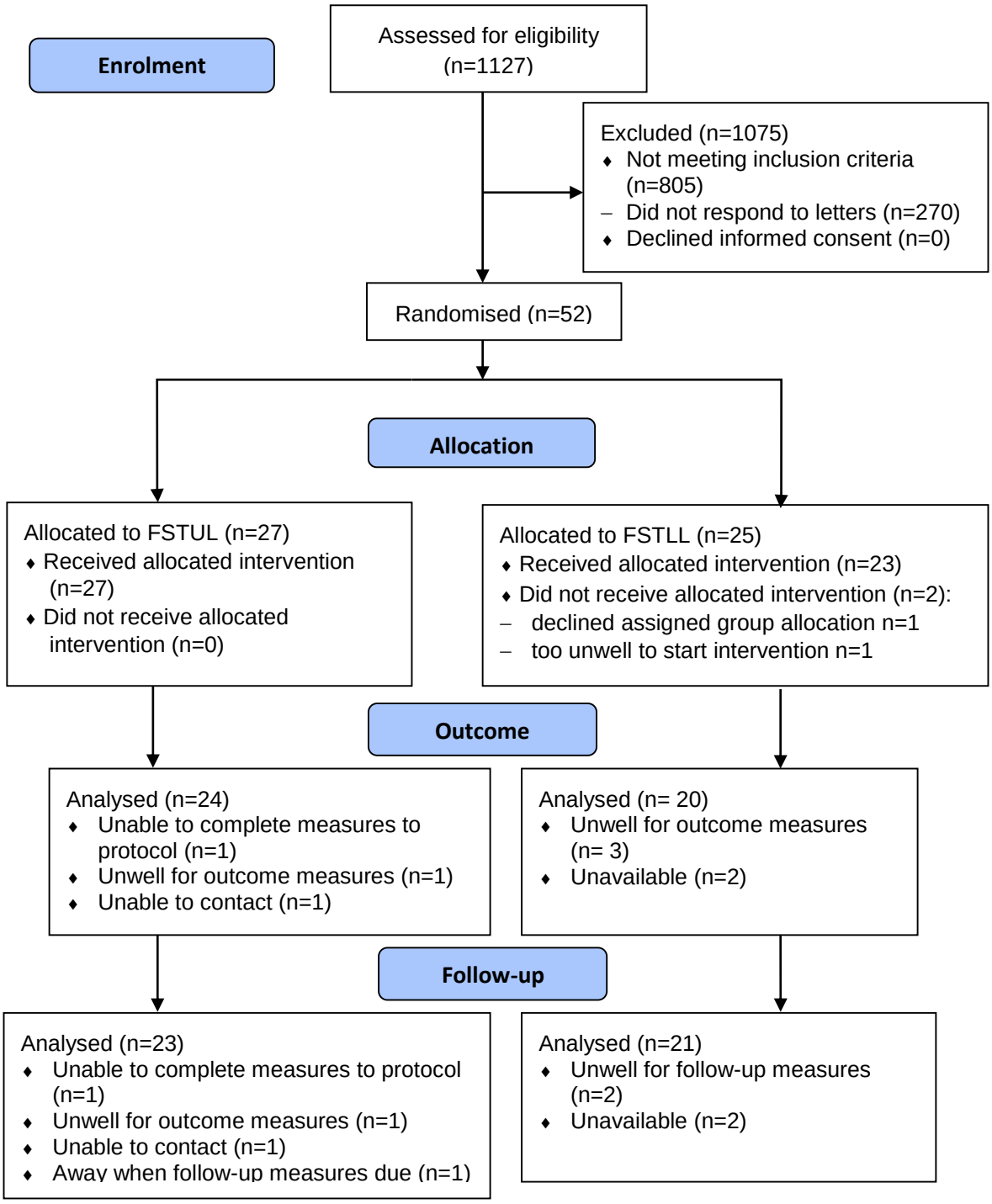


Figure 8: Consort diagram

### 5.4.3 Recruitment strategies

Recruitment was initially predicted to be at the rate of two participants per month, figure eight shows the predicted rate of recruitment against the actual rate of recruitment, which was lower than expected.

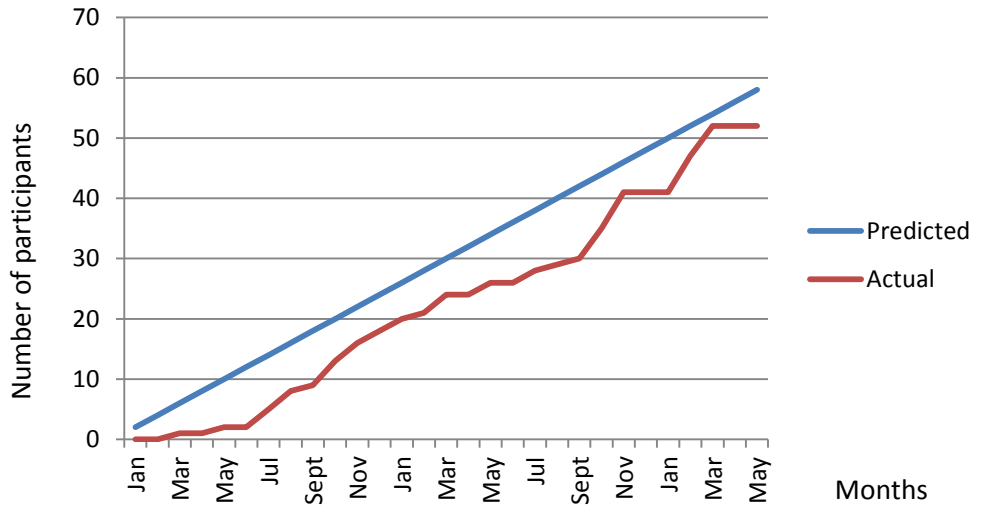


Figure 9: Predicted recruitment against actual recruitment

The initial recruitment strategy was to send letters to people who had been diagnosed with a stroke and who had been admitted to the local acute hospital. 434 first letters were sent, these achieved a 31% response rate, 269 second letters were then sent to non-responders and these achieved an 11% response rate.

Figure eight illustrates the poor rate of recruitment seen at the start of the study when the only recruitment strategy was via letters. Once recruitment strategies opened up to include therapist referral there was a rise in the rate of recruitment. Table 28 shows the proportion of people who were recruited to the study via the different methods used. Referral by therapist was clearly the most successful strategy for recruitment to this trial. The implications for this will be discussed later.

| Recruitment Strategy | Letter | Therapist | Friend | Poster |
|---|---|---|---|---|
| Proportion of total recruited | 27% | 69% | 2% | 2% |

Table 29: Proportion of participants recruited through each strategy

### 5.4.4 Attrition

Following randomisation one participant withdrew because he did not receive the group allocation that he wanted. Two people withdrew from the lower limb group before the intervention was completed; both because of illness not associated with the trial and one person withdrew from the upper limb group because they no longer wished to take part in the study. All participants were entered into the outcome and follow up assessments on an intention to treat basis. One participant allocated to FSTUL was subsequently removed from the analysis because baseline measures had not taken place as per the protocol.

### 5.4.5 Treatment received

The study set out to deliver sixty minutes of FST for either the upper or lower limb for four days a week for six weeks this equates to a target of 24 hours of FST per participant.

The mean time spent on FST per participant in the lower limb group was 14 hours with a standard deviation of 5.7; the mean time spent on FST in the upper limb group was 15.9 hours with a standard deviation of 5.2. Table 29 below shows the total intervention time delivered by group. As this data was not normally distributed a non-parametric analysis using the Mann-Whitney was used to determine whether there was any difference between the groups with respect to time. This revealed no significant difference between the groups ($z = 0.96$, $p = 0.335$).

| | Upper limb group (n = 27) | Lower limb group (n = 25) | Total |
|---|---|---|---|
| **Total intervention time delivered (hours)** | 430.15 | 351.92 | 782.07 |
| **Intervention time as a % of total intended time** | 66.4% | 58.7% | 62.7% |

Table 30: Total amount of FST delivered to each group

One of the aims of this phase II study was to determine whether it would be feasible to deliver FST to people in their homes four days a week for six weeks later after stroke. Figure five demonstrates why sessions were not delivered by group. The highest proportion of cancelled sessions was because of participant illness or in response to a request to cancel from the participant themselves.

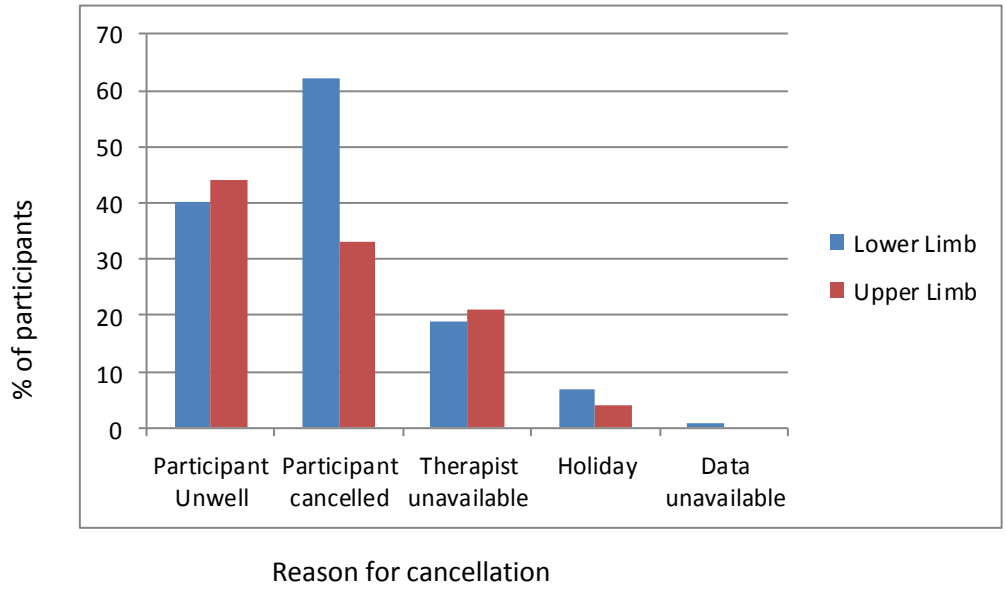


Figure 10: Reasons for cancellation

### 5.4.6 Outcomes

Analysis was carried out as per an intention to treat. Missing data was not imputed for the purposes of analysis except for the Modified Rivermead Mobility Index, this decision was based on the advice of a statistician

#### *5.4.6.1 Primary outcome measures: Action Research Arm Test*

The following table displays the median scores for the Action Research Arm Test (ARAT) for each group at baseline, outcome and follow up.

| Group | | Baseline | Outcome | Follow up |
|---|---|---|---|---|
| **Lower limb** | N | 25 | 20 | 21 |
| | Median (IQR) | 10 (3-23) | 9 (3.5-20.5) | 11 (5-21) |
| **Upper limb** | N | 26 | 24 | 23 |
| | Median (IQR) | 14.5 (5-25) | 21.5 (10.5-29) | 20 (8-26) |

Table 31: Median and IQR of the ARAT for each of the groups at baseline, outcome and follow up

The median score for the ARAT for the lower limb group remains relatively unchanged between baseline, outcome and follow up. The score for the upper limb group however increases between baseline and outcome by 8.5 points and remains at the higher score at follow up. Van der Lee et al (2001) identified a change score of 5.7 on the ARAT to be the minimal clinically important difference (MCID). Clearly the upper limb group have exceeded that MCID.

The ARAT cannot be classified as interval/ratio and therefore a non-parametric ANCOVA was carried out to determine whether there was a statistically significant relationship between the ARAT score at outcome and group allocation. This regression model was used to account for the minimisation procedure which stratified for severity, it found a statistically significant relationship between group allocation and outcome on the ARAT, t=2.06 (p=0.046). There was no statistically significant relationship found for the ARAT score at follow up, t=1.96 (p=0.057).

#### *5.4.6.2 Primary outcome measures: Functional Ambulation Categories*

Table 31 displays the score for each of the groups for the Functional Ambulation Categories (FAC) at baseline, outcome and follow up.

| Group | | Baseline | Outcome | Follow up |
|---|---|---|---|---|
| **Lower limb** | N | 25 | 20 | 21 |
| | Median (IQR) | 2 (1-4) | 2 (1-4) | 2 (1-4) |
| **Upper limb** | N | 26 | 24 | 23 |
| | Median (IQR) | 2 (1-4) | 4 (2-4) | 4 (1-4) |

Table 32: FAC score at baseline, outcome and follow up

Median scores for the FAC remain unchanged between baseline, outcome and follow up for the lower limb group; however there is an improvement in the upper limb group, which shows an increase in the FAC score of 2. The MCID has not been formally identified for the FAC however the broad categorisation of this scale suggests clear differences in walking ability between categories. This suggests therefore that those people who received the upper limb intervention this group also could have improved in walking ability.

Statistical analysis of the FAC scores was to be undertaken using a proportional odds ratio, however the table below indicates that there were insufficient numbers within each group for this to prove useful. Consequently the five groups (-2 to +2) which identify the difference between baseline and outcome score were combined to create two groups (0 and 1), a difference of -2 to 0 was recoded as 0 and a difference of 1 to 2 was recoded as 1. This enabled analysis of results using an ANCOVA model for binary outcomes.

| | | Number of people in Lower limb group with change score | Number of people in Upper limb group with change score | Total |
|---|---|---|---|---|
| Difference between outcome and baseline for FAC | -2 | 0 | 1 | 1 |
| | -1 | 1 | 0 | 1 |
| | 0 | 17 | 18 | 35 |
| | 1 | 1 | 2 | 3 |
| | 2 | 1 | 3 | 4 |

Table 33: Difference between outcome and baseline FAC score for both groups

Logistic regression revealed no statistically significant relationship between group allocation and FAC score at outcome (z=1.19, p=0.235). The same process was carried out for the follow up FAC score which also identified that there was no statistically significant relationship between score at follow up and group allocation (z=0.56, p=0.573).

#### *5.4.6.2 Secondary outcome measures: Nine Hole Peg Test*

According to the protocol for the Nine Hole Peg Test (NHPT) only one participant was actually able to complete this outcome measure. That participant's score at baseline was 44 seconds and at outcome 38 seconds and they had received the upper limb intervention. The use of outcome measures in this study will be discussed later.

#### *5.4.6.3 Secondary outcome measures: Timed Up and Go*

Table 33 shows the median and IQR for the Timed Up and Go (TUG) for baseline, outcome and follow up for both groups.

| Group | | Baseline | Outcome | Follow up |
|---|---|---|---|---|
| **Lower limb** | N | 22 | 19 | 18 |
| | Median (IQR) | 39.0 (19.5-80.5) | 36.67 (18.67-56.33) | 38.0 (17.0-55.67) |
| **Upper limb** | N | 23 | 20 | 19 |
| | Median (IQR) | 30.5 (20.0-49.5) | 19.17(15.83-33.58) | 26.33 (17.67-42.33) |

Table 34: Median TUG time for each group at baseline, outcome and follow up

Rockwood et al (2000) reported a potential floor effect for the TUG with 29.3% of participants being unable to complete this test. This study found that only 11.5% of participants were unable to complete the TUG at baseline.

Median and IQR for the TUG have been used as the data was not normally distributed, table 33 shows that there is little difference between baseline, outcome and follow up for the lower limb group, however the upper limb group showed an improvement of 11 .33 seconds at outcome although this difference decreased at follow up.

Analysis of these data was carried out using the non-parametric version of the ANCOVA, although the TUG is interval ratio data it was not normally distributed, therefore the data does not meet the criteria for carrying out an ANCOVA. Regression analysis found a statistically significant relationship between group allocation and TUG at outcome (t=-2.19, p=0.035), but not at follow up (t=1.01, p=0.319).

#### *5.4.6.4 Secondary outcome measures: Modified Rivermead Mobility Index*

Completion of the Modified Rivermead Mobility Index (MRMI) was in some cases limited by the environmental constraints within people's homes, the final two items were particularly difficult to complete (timed ten metre walk and stairs); only ten people were able to complete the timed ten metre walk at baseline. The MRMI score is a total of all the scores for each of the items, there is a difficulty therefore in comparing total scores for one participant whose environment allowed for the completion of all eight items to another participant whose environment only allowed them to complete six. One option for the purposes of analysis was to calculate a total score based on the first six items only, this however did not allow for missing data when environmental constraints had prevented measurement of other items. Following advice from a statistician the decision was taken therefore to impute data for those items that had missing scores because of environmental constraints; where there was missing data an average of the available scores for each participant was calculated and this value was imputed. Table 34 shows the median scores for MRMI following imputation.

| Group | | Baseline | Outcome | Follow up |
|---|---|---|---|---|
| **Lower limb** | N | 25 | 20 | 21 |
| | Median (IQR) | 35(33-38) | 34(32.5-38) | 37(34-39) |
| **Upper limb** | N | 25 | 23 | 19 |
| | Median (IQR) | 36(32-38) | 37(32-39) | 37(34-39) |

Table 35: Median MRMI scores at baseline, outcome and follow up for each group

A non-parametric RANCOVA was carried out to determine whether there was any statistically significant relationship at both outcome and follow up for the MRMI, neither analysis was statistically significant (t=0.39, P=0.698 and t=0.39, p=0.70).

### 5.4.7 Adverse reactions

There were no adverse reactions reported in the present study.

### 5.4.8 Summary of findings

Fifty two people were recruited to this study, of these 27 were allocated to FSTUL and 25 were allocated to FSTLL, 44 participants were subsequently included in an intention to treat analysis at outcome (n=24 to FSTUL and n=20 to FSTLL) and follow up (n=23 to FSTUL and n=21 to FSTLL). Results from the study found a statistically significant increase in ARAT score in favour of the intervention at outcome (p=0.046), suggesting a positive relationship between FSTUL and clinically significant improvements in upper limb function in participants who were between six months and five years after stroke . The same finding was not observed at follow up (p=0.057). There was no statistically significant effect in favour of FSTLL measured by the FAC at outcome (p=0.235) or follow up (p=0.573) suggesting that FSTLL has no effect on walking function in stroke survivors who were between six months and five years after stroke.

Only one person was able to complete the NHPT and therefore analysis for this measure was not undertaken. Statistically significant results were found for the

TUG at outcome (p=0.035) but not at follow up (p=0.319), although the number of people able to complete this measure was low compared to the number of participants included in the analysis of the primary outcome measures (n=39 compared to n=44). Interestingly the improvement in the TUG was found in the group receiving FSTUL and not FSTLL.

Finally, no statistically significant results were found in favour of either group when measuring change using the MRMI at either outcome (p=0.698) or follow up (p=0.70).

## 5.5. Discussion

The aim of this study was:

- To carry out a phase II randomised controlled trial to determine feasibility of a physical therapy intervention – Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke.

    Objective 2: Establish feasibility of Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke by determining likely rates of recruitment.

    Objective 3: Establish feasibility of Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke by testing procedures for acceptability including the choice of outcome measures and the pragmatics of delivering the interventions.

    Objective 4: Provide information for calculating a sample size for evaluation trials.

In this section the findings from this phase II study will be discussed, including aspects of the methodology that can be usefully taken forward to inform future

trials. is section will go on to discuss the extent to which this present study has or has not achieved these aims.

### 5.5.1 Determining likely rate of recruitment

The present study aimed to recruit two participants a month over an approximate period of 28 months in order to achieve a total sample size of 58 people. This section will discuss the recruitment strategies used throughout the trial in order to make recommendations for future trials of FST. This section will also discuss the implications for future trials in relation to attrition and the impact of the decision to include participants following a clinical assessment to determine site of stroke (as described in section 5.3.3.)

#### *5.5.1.1 Recruitment*

This present study successfully recruited 52 out of a planned 58 participants over a two and a half year period. Recruitment strategies did, however, have to be refined over the period of the study.

Examination of the overall recruitment strategy showed that less than 5% of those participants screened for inclusion were recruited to the study. On further analysis of the relative success of each of the strategies however it seems that the least successful method used in the present study was recruitment via letters. The initial recruitment strategy was to send out letters to stroke survivors listed on a clinical database held at the local hospital. Over one thousand letters were sent out and yet this method yielded only fourteen participants. If all respondents to the letter had been able to be included in the study then this strategy would have yielded 135 participants; The response to the letters suggested that this method of informing people of the study was relatively successful; however there was a problem in converting an expression of interest communicated via the letter into recruitment to the study. The reasons for refusing to participate in the study were not systematically sought during the progress of this study and initiating further contact once individuals had refused to participate was not within the ethical constraints of the study. However some responders had volunteered their reasons for refusal when they returned the expression of interest form. A number of these responses suggested that individuals were unable to take part in the study because they

did not meet the description of the inclusion criteria of “a significant impairment in both the arm and leg following stroke” they met the inclusion criteria for either arm or leg but not both. The impact of this inclusion criteria on this feasibility study will be discussed again later in this section but, in the context of recruitment, if future studies continue to model themselves on the present study then they may have to consider recruiting over longer periods of time or over a greater geographical area in order to achieve the desired sample size. Alternatively it may be useful for future studies to consider broadening the inclusion criteria to reflect individuals with either greater or lesser severity in both the arm and the leg. Although this would impact on the specificity of the findings from any future study it would be more in keeping with the design of a pragmatic trial. Broader inclusion criteria would arguably reflect more ‘everyday practice’ (Haynes, 1999).

As well as potential issues around the inclusion criteria the feasibility study design required a high level of commitment from the participants over the six week period and this may have been off putting for some people, however this ‘worry’ may have been offset by delivering the intervention within people’s own homes. A systematic review of barriers to participation in randomised controlled trials identified that some patients may refuse because of concern over additional procedures and appointments and travel and travel costs (Ross et al., 1999). Data relating to the current study does however need to be sought systematically as at this moment the reasons for refusing to participate can be only speculative. Future trials of FST may benefit from adding something to the ‘expression of interest’ form that would enable them to systematically collect sufficient information on an individual’s reasons for refusing to take part in a study.

Once it became clear that the recruitment strategy initially proposed was unsuccessful an additional strategy was included into the study. This strategy allowed direct referral to the study by therapists involved in the rehabilitation and management of stroke survivors. Following the integration of therapist referrals into the recruitment strategy for the present study, the rate of recruitment was improved, and by the end of the study this strategy had proved

to be the most successful; recruiting 69% of the total number of participants. There appears to be little work evaluating recruitment to rehabilitation trials that are specifically targeted at interventions related to stroke (Lloyd et al., 2010). Therapist referrals were however reported to be a successful recruitment strategy in the 'AMBULATE' trial (Lloyd et al., 2010). This study recruited via advertisements and referral from therapists who were involved in the rehabilitation of stroke survivors. Whilst this method of recruitment was the most successful it may not have produced a study population that is representative of the population of stroke survivors who are within the chronic phase of recovery from stroke. Access to health professionals involved in stroke rehabilitation in the UK is limited in the later stages of recovery (National Audit Office, 2010). A recruitment strategy therefore that only involves therapist referral may not access stroke survivors who no longer receive their input. Conversely an individual, who continues to receive treatment, may feel 'obliged' to participate in a study which is being supported by a therapist to whom they are grateful for any recovery they have achieved following the stroke.

Future trials of FST based in the community should consider including therapist referrals as part of the recruitment strategy, although effort should also be made to identify those stroke survivors who are not accessing those services.

Alternative recruitment strategies that have been shown to increase the rate of recruitment in randomised controlled trials could also be considered. These include monetary incentives, which may or may not be feasible depending on the budget for running the study; and telephone reminders or follow-ups (Mapstone et al., 2007). The use of telephone calls as a follow up to the letters was identified as a recruitment strategy in the original ethics application for the current study. This was however rejected by the ethics committee, who felt that at this point, the researcher should accept the refusal to return either of the two 'expression of interest' forms that had been sent to them, as a clear indication of a wish not to take part in the study.

Findings from the present study suggest that a recruitment rate of 2 participants per month remains a realistic goal; 52 participants were recruited over a period

of 28 months. To allow for the potential for difficulties in recruiting to future studies however, a recruitment rate of 3 participants per 2 months may prove more achievable.

#### *5.5.1.2 Retention and Attrition*

Following the previous studies of FST, sample size calculations for the present study were based on an expected attrition rate of 10% (Cooke et al., 2010b, Donaldson et al., 2009a). Results from this study indicated a similar attrition rate of 12%.

One participant left the study after randomisation but before taking part in the intervention, because he did not receive the group allocation that he wanted. It was the researcher's perception during the design of this study that two intervention groups would prevent attrition based on group allocation, because 'something is better than nothing'. This may not the case however, and therefore future studies of FST do not need to be constrained by this two group design, especially in light of the potential for a cross training effect from the FSTUL group to lower limb function.

A second participant who was allocated to the upper limb group was removed from the analysis as closer examination of the baseline measures revealed that he had been unable to complete the ARAT per protocol. This occurred because of environmental constraints and therefore the decision was taken to remove him from the analysis, this can be avoided in future trials by ensuring that all the equipment needed to carry out the outcome measures is available to the outcome assessor, including a table that can be transported between participants' homes at the beginning of the study.

A further two participants were lost to outcome from the upper limb group and four participants from the lower limb group. One participant was unable to be contacted despite visits to the address where the intervention had taken place, and follow up telephone calls. Contact was discontinued when it was clear that the participant was not going to respond to telephone calls. All other

participants who were lost to outcome and follow up were not available because of ill health unrelated to the trial.

The attrition rate for this present study was estimated at 10% based on the information obtained from previous trials of FST (Donaldson et al, 2009 and Cooke et al, 2010). Forty four out of a potential forty nine participants completed both baseline and outcome measures in the present study indicating the same attrition rate (10%). Comparison of attrition rates between the previous and current trials of FST are limited by the differences in both the time from stroke and the setting in which the trials take place (acute hospital setting versus people's homes). Comparator studies using both the same or similar interventions within the same time frame after stroke and in the same setting are limited; however an attrition rate of 10% for future trials of FST seems to be reasonable based on current findings and published protocols for other trials investigating the effects of exercise based interventions on motor recovery in stroke survivors, even though study populations differ in their time from stroke onset (e.g. Askim et al (2012) estimates an attrition of 15 %, Logan et al (2012), 20% and Pomeroy et al (2012), 10%).

#### *5.5.1.3 Changes to recruitment processes*

Initial inclusion criteria stipulated only those stroke survivors who were diagnosed with a stroke affecting the anterior circulation. Following the amendment to include referrals from therapists it was not possible for the researcher to access the clinical information necessary to determine whether an individual met this inclusion criteria before they had been given and signed the 'Informed consent form'. This would have necessitated the researcher having access to clinical records which was not possible within the context of Good Clinical Practice (MHRA, 2013) and the ethical consent obtained prior to the start of the study. Decisions as to whether or not to include potential participants were therefore based on their clinical presentation. This subsequently resulted in the inclusion of participants who were subsequently identified to have a stroke affecting the posterior circulation (POCI).

The decision to restrict inclusion to those stroke survivors diagnosed with a stroke affecting the anterior circulation was based on the premise that FST was likely to be most effective in this group of individuals. One of the 'movement' consequences of a stroke affecting the anterior circulation is a loss of muscle power to the opposite side of the body affected by the stroke, this results in a so-called hemiplegia (Cohen, 1999). A stroke affecting the posterior circulation can also present with muscle weakness but this may be confounded by the presence of ataxia or problems with coordination of the movement (Cohen, 1999). Evidence has been published in favour of the effects of strength training on muscle weakness after stroke (Ada et al., 2006); however evidence in favour of any specific physical therapy intervention is less well defined in the presence of ataxia (Stoykov et al., 2005).

In order to obtain the information required to determine whether the stroke had affected the anterior circulation, potential participants would have had to have given informed consent to the study before the researcher could have acquired the information. It was deemed inappropriate to ask individuals who were very keen to take part in the study to undergo the visits that were necessary for screening and participant information, and the subsequent wait before informed consent was taken, before they could be told whether they were allowed to take part in the study or not. Logistically, this would also have impacted on the costs of the study as baseline measures were taken just after informed consent was gained. For the participants where inclusion was unclear, a further visit to carry out the baseline measures would have been required following the receipt of informed consent, once it was established that the participant could be included in the study.

Where clinical information relating to the site of the stroke was unavailable at the point of recruitment, individuals referred to the study by therapists were included if their clinical presentation was the same as that usually found in people following a stroke affecting the anterior circulation, i.e. the presence of hemiplegia but with no signs of ataxia. Assessment of treatment suitability based on clinical signs and symptoms may reflect circumstances found in clinical practice, particularly in community based settings where therapists may

not have access to scans and detailed medical notes prior to seeing their patients. In order to ensure generalisability of findings to the clinical setting the design of a trial should take into account 'real clinical practice' (Roland and Torgerson, 1998), therefore inclusion criteria based on clinical presentation may be more appropriate for a study based in this type of setting.

The inclusion of participants with a specific lesion location, even that as general as a stroke affecting the anterior circulation, may inform decisions such as which stroke survivors may respond to which therapy (Kwakkel et al., 1999). A study that includes stroke survivors without specifying aspects of lesion location may therefore be criticised for lacking specificity. There are however, clear examples where well categorised therapy has been associated with clinical presentation rather than diagnostic information such as lesion location. One example of this is Constraint Induced Movement therapy (CIMT), which showed statistically significant improvements in upper limb performance measured by the Wolf Motor Function Test ($P<0.001$) compared to usual care in a group of stroke survivors who had a specific clinical presentation of movement ability (Wolf et al., 2006).

Further work needs to be carried out in order to identify which stroke survivors are likely to respond most effectively to FST, but this work could feasibly focus on aspects of clinical presentation such as range of available movement or the quantification of muscle paresis rather than lesion location. Study designs other than RCT may facilitate the process of identification of individual characteristics. Studies using single case experimental designs for example facilitate more detailed analysis of which patient characteristics may be associated with clinical changes caused by the effect of the intervention, albeit on an individual level (Bowling 2000). Further pilot work investigating who may or may not respond to FST may prove effective before moving on to further evaluative trials aimed at testing efficacy.

### 5.5.2 Testing procedures for acceptability

This section will discuss the findings from this present study in terms of key aspects of the study design including the choice of outcome measures and the pragmatics of delivering the interventions.

#### 5.5.2.1 Study Design

The present study was designed with two intervention groups – FSTUL and FSTLL. This decision was based on the premise that there was not expected to be a cross training effect between the upper and lower limb groups. The findings derived from the TUG, described above, could however suggest that this may not be the case for the upper limb intervention. This interpretation should be made cautiously however as this outcome only reflected a change in the participants who were able to complete the test. Nevertheless it is worth considering this information in light of the need to inform the design of a future trial, especially as this initial decision was based on conflicting findings.

The case for the two group design used in this study was based on findings from a published clinical trial which did not show inter-limb coupling in response to therapy (Kwakkel et al., 2002) and some experimental evidence that did (Dietz, 2002, Zehr et al., 2007). It has been suggested that strengthening the upper limb would have an effect on the lower limb because of the presence of neuronal coupling in tasks such as walking (Zehr et al., 2007) and there is also evidence to suggest that arm training can improve oxygen delivery to the lower limbs which was associated with improved walking speeds (Tew et al., 2009). The TUG is arguably a timed test of aspects of mobility; therefore these mechanisms may explain the statistically significant changes to the TUG in the FSTUL group. Future studies will need to take this finding into account but it is possible that a two group study design where FSTUL acts as the control for FSTLL may not be appropriate.

Forty eight out of a possible fifty one participants who received the intervention fell within the moderate to severe groups for upper limb function categorised by the ARAT. Findings from the present study therefore may not generalise to participants with mild upper limb severity. In a systematic review of factors

affecting upper limb recovery, Coupar et al. (2012) found that less lower limb impairment was moderately associated with better upper limb recovery (odds ratio 11.83, 95% CI 6.53-21.43). It may be that the design of this study i.e. two intervention groups requiring participants to be impaired in both the upper and lower limb has led to the inclusion of a higher proportion of participants who are by default more severely affected than the previous study, where participants could be included with only an upper limb deficit and not both upper and lower limb. In order to ensure that the study population is representative of all categories of upper limb severity a study design which does not necessitate the presence of an impairment in both the upper limb and the lower limb may be more appropriate.

#### *5.5.2.2 Outcome measures*

The outcome measures for this study were chosen because they fulfilled certain requirements; they fell within the activity domain of the ICF, indicating that the findings are likely to be more meaningful to the participant (World Health Organisation, 2002). The outcome measures reflected the functional tasks that were targeted by the intervention, they have been shown to be reliable, valid and responsive but they were not all appropriate for use within the community setting. Findings from the present trial in relation to some of these factors will now be discussed in order to provide information relating to their usefulness within future trials.

##### *Measures of upper limb function*

The Action Research Arm Test (ARAT) (Yozbatiran et al., 2008) appeared to meet all the requirements for the present study and was able to detect change in the movement performance of those participants receiving FSTUL enrolled in the present study. This would suggest that the ARAT has the capacity to evaluate change in motor performance of the upper limb following FST. This measure does fall within the activity domain of the ICF and therefore the assumption is that it should measure functional change that is meaningful to the participant (World Health Organisation, 2002), however future studies may wish to consider a mixed methods approach in order to determine if this is in fact the case.

The only unforeseen circumstance which affected the use of this outcome measure was the lack of a suitable table in participant's homes; this was solved very quickly by the purchase of a suitable, portable table. Future studies using the ARAT in the community setting need to consider purchasing a table prior to its use.

The nine hole peg test (NHPT) (Kellor et al., 1971) proved to be of little use in evaluating change in movement performance within the present study. This measure was chosen because of its perceived ability to be able to distinguish a change in function for those people with less severe paresis in their affected arm, however only one person was able to complete the NHPT as per the protocol. It is possible that the use of this outcome was affected by the severity profile of the participants within this study i.e. there were more participants with moderate to severe impairment than those with mild. Previous studies suggested that the NHPT was a useful outcome for measuring dexterity in future studies (Donaldson et al., 2009a) however if the study population of participants is likely to predominantly include participants with severe upper limb impairments, then global measures of upper limb function that incorporate measures of dexterity such as the ARAT may be sufficient to measure change.

### *Measures of lower limb function*

The Functional Ambulation Categories (FAC) (Holden, 1984) was reported to be easy to administer and seemed to have the capacity to show change in the walking ability of participants within the present study. This outcome measure should therefore be considered for use in future studies.

Findings from the Timed Up and Go (TUG) (Podsiadlo and Richardson, 1991) were inconclusive because the number of people who were able to successfully complete the measure at baseline was too small (n = 39); one participant was unable to complete because of a lack of space and the other five were unable to physically manage the task. Participants in the FSTLL group were classified across all categories of severity therefore an outcome measure that is only measured in 90% of the study population may not be appropriate.

The Modified Rivermead Mobility Index (MRMI) (Forlander and Bohannon, 1999 and Lennon and Johnson, 2000) was chosen to reflect changes in mobility related activities other than walking. This measure proved to be difficult to complete in the community setting because of the environmental constraints incurred using this measure in people's homes. At baseline only eight out of the 52 participants were able to obtain a score for the ten metre walk and only fourteen were able to complete the stairs item. The previous study of FST had completed this measure in a hospital setting and therefore had had sufficient space to lay out a ten metre length over which participants could walk; similarly they also had access to a set of stairs (Cooke et al., 2010b). Findings from the present study indicate that the MRMI is not a useful outcome measure for use within the community setting, where measurement will predominantly be taking place in people's homes. Alternatives to this measure, which were discussed earlier in section 4.3.5, were the Motor Assessment Scale (MAS) (Carr et al., 1985), which also relies on a distance of 10m and a rail to hold on to and the Stroke Rehabilitation Assessment of Movement measure (STREAM) (Daley et al., 1997), which similarly needs at least three steps and a distance of ten metres. Future studies of FST targeted at the lower limb may need to consider whether it would be more appropriate for participants to attend accessible venues, such as a GP surgery, for the measurement sessions so that environment is not a constraint to accurate and complete records of the outcome measures chosen for the study. The cost implications of such a plan would need to be considered, however this would avoid the loss of potentially significant data.

### *Impairment or activity measure?*

The present study opted to evaluate changes in functional activity in both upper limb and lower limb using measures that fell within the activity domain of the ICF. The reasons for this reflected a wish to evaluate a change in movement performance that would be more meaningful to the participant than if the measurement tool fell within the impairment domain. Barak and Duncan (2006) observed however that the link between the impairment experienced as a result of the stroke may not directly correlate with an activity outcome such as the

FAC. This is because functional scales may be influenced by factors other than the one being directly targeted by the intervention. For example, a participant's lower limb muscle strength may be seen to improve throughout the course of an interventional study such as the present trial, but a lack of confidence may mean that this improvement does not enable that individual to walk more independently. Thus by choosing only functional measures that sit within the activity domain of the ICF a study may neglect to show a significant effect of the intervention. Future studies of FST may wish to consider the inclusion of an outcome measure that sits within the impairment domain as well as one that sits within the activity domain of the ICF.

#### *5.5.2.3 Delivering the interventions*

This study was designed to deliver FSTUL and FSTLL to people who were within 6 months to five years after a stroke, in their own homes. The intention was to deliver the interventions for up to sixty minutes at a time over a period of four days a week for six weeks. This section will discuss the pragmatics of delivering FSTUL and FSTLL within the context of this study and the information gained from this experience that can usefully inform future studies.

##### *Geographical location*

The delivery of this intervention to people later after stroke, in their homes, involved considerable travel throughout a widespread geographical area. The original intention for the running of this trial had been to target the intervention at defined geographical areas. Entries to the stroke database were grouped according to postcode so that when responses were received intervention visits could be grouped together in order to minimise the travel distance. As previously discussed the response rate to letters generated so few participants that this strategy was not effective. Subsequently included participants could be based in any part of Norfolk and over the course of the study this resulted in the therapists having to carry out long journeys between individuals. This reduced the number of participants that could be seen in any given day and also carried cost implications in terms of reimbursing travel expenses. When recruitment opened up to include therapist referral geographical spread became less of an issue as therapists are generally situated in one area and

would tend to refer a number of people ‘en bloc’. Future trials of FST delivered in the same way as the present trial may need to consider the time and cost implications of delivering an intervention over a potentially widespread geographical area; alternatively they may need to reflect on a recruitment strategy that could avoid this consequence.

Future research could also be focussed on the feasibility and acceptability of delivering FST by alternative methods than those used in the present trial, this might include for example, delivering FST to a group of people within a local community setting. Group exercise schemes such as circuit classes have been found to be as or more effective than individual therapy sessions when delivering conventional care targeted at improving walking in people who were within the first six months since stroke onset (no statistically significant difference between the two groups in the mobility domain of the stroke impact scale ($p = 0.943$) and statistically significant difference in favour of the intervention group for gait speed ($p < 0.001$), with the conclusion being that circuit classes could effectively replace usual physiotherapy in the outpatient setting (van de Port et al., 2007).

Delivering FST to a group of people might prevent so much travel on behalf of the therapist delivering the intervention, and may prove more cost effective in that one therapist would be able to deliver the intervention to more than one individual at a time. Feasibility of delivering FST in a group setting has not been established and therefore further work evaluating the effects of FST in a group setting is warranted.

### *Intensity of intervention*

This study set out to deliver FST to individuals in their homes for one hour a day over four days per week for six weeks. This equates to an intended delivery time of 24 hours of FST per participant. Analysis of the amount of FST delivered during the study revealed no statistically significant difference between the two groups and participants received on average 15.94 hours of FST over the period of the study. The reasons for being unable to deliver the prescribed intervention time were primarily to do with participant illness or cancellation on

behalf of the participant (see figure nine). Interestingly participant cancellation in the lower limb group was double that of the upper limb group; one can only speculate on the reasons for this but it is possible that participants in the lower limb group found the intervention more physically demanding than participants in the upper limb group. Whilst the lower limb intervention is not intended to increase cardiovascular effort, the nature of some of the strengthening exercises, such as sit to stand, may have proved more tiring for participants within this group compared to those in the FSTUL group. In order to investigate this in more detail future studies of FST could include a qualitative aspect that would generate a better idea of the acceptability of FST particularly for the lower limb in people later after stroke.

Findings from this study in terms of the discrepancy between intended delivery time for an intervention and actual time correlate with other rehabilitation trials such as the EXCITE trial (Wolf et al, 2007). Intervention time was intended to be delivered for up to 84 hours per participant but was actually delivered from between 20.9 hours to 60.5 hours. More recently the study by Cooke et al (2010b), where FST was intended to be delivered for 24 hours but was only delivered for an average of 14.8 (SD 4.3) hours. Evidence in favour of appropriate doses for exercise-based therapies is limited by the lack of dose finding studies (Cooke et al, 2010b); however the results from the present study indicate that it may be possible to see an effect from FST, targeted at the upper limb specifically in less time than that intended for the current study (mean time for FSTUL was on average 17.2 hours per participant compared to the intended 24 hours). A prospective dose finding study would however be necessary to determine the optimal dose for this intervention.

Intervention time was also lost due to therapist sickness and statutory holidays. Over the period of two and a half years, loss of therapy time for these reasons is to be expected, and funded studies need to try and plan for these eventualities if they have to be completed within a discrete time period. One of the strategies highlighted by Bellg et al. (2004) in their position paper on intervention fidelity in health behaviour change studies was planning for implementation setbacks. Hennggler et al. (1997) emphasised that the

increased costs associated with managing these would outweigh the costs of implementing an ineffective treatment because it had not been rigorously tested. Information gained in the course of this study will inform funding applications for future trials of FST

### *Governance procedures*

This section will discuss the impact that the delays associated with governance procedures for research trials had on this present study. Ethical approval was granted in September but subsequent Research and Governance approval was delayed by a further three months. Delays incurred as a result of the administration of these guidelines is not unique to this study; Elwyn et al (2005) reported a median delay of 61 days (95% CI 51-81 days) in gaining research governance approval over twenty sites, the total delay for gaining approval for all the sites was 150 days (103 days for research governance approval and 47 days for ethics). Further correspondence by Galbraith et al (2006 p.238) has stated that researchers are becoming put off by the "idiosyncratic R&D departments". Delays incurred as a result of Research and Development approval also has cost implications. Al Sahi Salman and colleagues (2007) created a measure called the 'number not treated' (NNT). This was the number of participants that could have been randomised to each of the studies included in their review over the period of time that the study coordinators were waiting for Research and Development approval. By multiplying the NNT by an approximate per capita cost the total cost that could be attributed to the delays found in their study was £53,743. They compared this to the cost that would be incurred if Research and Development processes could be reduced to a delay of four weeks, which they felt could be perceived to be acceptable. Costs incurred over this shorter period of time equalled £37,700 for the same studies, a saving of £16,000 to the funders. Since these studies were carried out the Department of Health (2006) has published a document called "Best Research for Best Health", one of the goals for this strategy is to "strengthen and streamline systems for research management and governance". Despite this, the delays incurred by the present study (conducted from 2009) still suggest that work needs to be completed in order to reduce delays to the possibly more reasonable time period of four weeks. This is reinforced by the case study

presented by Thompson and France (2010) whose trial was conducted at a similar time, where Trust approval took 97 days. They have concluded that this and other delays incurred as a result of delayed governance procedures across the multiple sites have led to recruitment problems and believe that the scientific integrity of their study has been compromised as a result. Interestingly their trial required working with the governance procedures in Scotland, which they reported to be easier (approval was granted in 44 days within the appropriate department), which seems to indicate that it is possible for the process in England to be more efficient.

### 5.5.4 Sample Size

Finally, phase II trials are designed to provide information that will allow the calculation of a sample size for future evaluative trials (Craig et al., 2008). In light of the potential for a cross training effect from FSTUL to lower limb function, sample size calculations for individual trials evaluating FSTUL and FSTLL separately have been calculated.

Based on the findings from the present trial a two group evaluative study of FSTUL versus a placebo in people within six months and five years after stroke would require 208 participants (104 per group). This sample size would have 80% power at 5% significance (2-tailed) to show a 5.7 point change on the ARAT (minimal clinically important difference (MCID) (van der Lee et al., 2001b)) assuming the standard deviation of 14.66 found in this study. In order to account for an attrition rate of 10%, also determined from the present trial, this study would need to recruit 228 participants.

Again, based on the findings from the present study a two group evaluative study of FSTLL versus a placebo in people within six months and five years after stroke would require 68 participants (34 per group). This sample size would have 80% power at 5% significance (2-tailed) to show a 1 point change on the FAC assuming the standard deviation of 1.47 found in this study. An MCID of a change in the FAC of 1 point remains a pragmatic decision.

### 5.5.5 Clinical Findings

As previously highlighted in section 5.3.2 phase II trials are not designed to determine efficacy of an intervention, however future evaluations of interventions that have shown no effect are unlikely to result in being taken forward into phase III trials (Stallard, 2012). Consequently whilst a formal power calculation was not possible a sample size for the present study was carried out. It was estimated that a sample size of 52 would have 90% power at 5% significance to detect a change in 1 point on the FAC and 5.7 points on the ARAT. As the present study met this sample size it is possible to gain some estimate of the clinical effect of the interventions in this study. The finding of a statistically significant increase in ARAT score in favour of FST for the upper limb group at outcome (21.5 (10.5-29.0); p=0.046), and the absence of a statistically significant change of the FAC for the FST lower limb group (2 (1-4); p=0.235) suggests therefore that there may be some evidence for the efficacy for FSTUL on motor function recovery of the upper limb late after stroke. It is important to note however that these results were not maintained at follow up and thus the intervention was seemingly only effective in the short term. This will be discussed in more detail later in this section.

The findings from the present study correspond with the results from the earlier study of FSTUL in people early after stroke, where clinically significant changes were also found in favour of the upper limb intervention (Donaldson et al., 2009a). One may cautiously suggest therefore, that there is some preliminary evidence that FST is effective as an intervention for improving motor function recovery in the upper limb both early and later after stroke. This hypothesis would however need to be tested further in a subsequent adequately powered definitive trial.

The earlier studies of FSTLL showed conflicting results; Bale and Strand (2008) found in favour of FSTLL for both habitual walking speed ($p<0.05$) and maximum gait speed ($p<0.05$). Comparison between this and the present study is however limited because of a difference in the choice of outcome measures. Findings from the previous lower limb study by Cooke et al (2010b) however, do correspond with the present trial. Interpretation of the findings from both the

present study and that of Cooke et al (2010b) could lead to the hypothesis that FSTLL has little or no effect on motor function recovery either early or late after stroke. This interpretation should be made cautiously however, as neither study was based on a formal power calculation from previous data, and therefore may not have been sufficiently powered to detect a change in the FAC which could either refute or support the efficacy of FSTLL. Similarities between the findings in the present study and that of Cooke et al., (2010b) may also be reflective of the fact that aspects of this study design were informed predominantly by the earlier work. Inclusion criteria for both were similar but the other study investigating the effects of FST on lower limb recovery by Bale and Strand (2008) seemingly included a much broader population of stroke survivors. Inclusion criteria for the study by Bale and Strand (2008) included all participants who were assessed to have reduced muscle strength in their affected leg. This present study applied more rigorous criteria and excluded those who were able to step on and off a block greater than fourteen times in fifteen seconds. The aim for this selectivity was to ensure that participants would be sufficiently able to take part in a strength training programme but not be so able that they would gain little benefit from the intervention. This premise may however have been incorrect as the study by Bale and Strand (2008) showed the capacity for further recovery despite the fact that they presumably included participants who were less severely affected. Arguably this capacity for further recovery may have been greater as the participants were earlier after stroke. Although in an earlier described case study a participant who received strength training and task specific practice and had already made a good recovery was still able to show further improvement despite being fifteen months post stroke (Sullivan et al., 2006). Baseline characteristics of the severity of participants in the Bale and Strand (2008) study were not provided so it is not possible to determine whether they did indeed include participants that were functionally better than those included in the present study. As discussed previously further work needs to be done to identify individual characteristics for those participants who either do or don’t respond to FST and future studies may need to be designed with broader inclusion criteria.

Lack of a statistically significant finding in favour of FSTLL could also be attributed to other factors, for example Cooke et al (2010b) identified that the dose for FSTLL may not have been sufficient within their study to effect a change in lower limb function. Only approximately 60% of the intended dose for FSTLL was delivered in both that and the present study (table 29) which equated to a mean of 14.8 hours per participant in the study by Cooke et al (2010b) and 14.5 hours in the present study. It is possible therefore that FSTLL was not delivered in sufficient dose to effect a change in lower limb function. The pragmatics of attempting to deliver the intended dose of FST will be discussed later.

A further reason for the findings in favour of FSTUL but not FSTLL could also be attributed to the current clinical context in which rehabilitation is taking place. It is possible that current clinical practice offers little therapy to improve upper limb function. Donaldson et al (2009a) recorded an average of 2.81 hours of upper limb therapy over a period of six weeks for those participants receiving only conventional physiotherapy. This contrasts with Cooke et al. (2010b) who recorded an average of 9.2 hours over the same period of time for those participants also receiving conventional physiotherapy but this time targeted at the lower limb. It may be therefore, that as rehabilitation interventions seem to be targeted predominantly at the lower limb early after stroke, there is more capacity for clinically significant changes in upper limb function, when additional experimental therapy for the upper and lower limb are delivered in the same intensity over the same period of time. Further research comparing FSTUL to an upper limb placebo in a matched group of participants later after stroke would be necessary to determine whether this was in fact the case.

An alternative hypothesis which would account for the findings from the present study would be to suggest that the upper limb recovers more slowly than the lower limb and that the results of the present trial were simply the product of late stage spontaneous recovery. Findings from this study would not support this as the ARAT score for the FSTLL group did not increase which would be the expected scenario if late stage spontaneous recovery were occurring. This hypothesis is also unlikely as the rate of recovery of both the upper limb and

lower limb have been shown to occur over similar time scales (Duncan et al., 1994). In addition a recent systematic review has highlighted the capacity for lower limb recovery late after stroke following physiotherapy interventions (Ferrarello et al., 2011).

Interpretation of the findings from the secondary outcome measures was equivocal except for the findings from the Timed Up and Go (TUG). Measurement using the TUG found a statistically significant effect in favour of the upper limb intervention at outcome (19.17 (15.83-33.58); p=0.035), although this calculation was based on a relatively small number of participants (n=39 of 52). One should be cautious therefore about assigning importance to this finding because an inappropriately small sample size may lead to the risk of a Type I error; a Type I error being a false positive (Altman, 1999). Despite this, this result was unexpected as the TUG is a measure of mobility and therefore any changes in this outcome measure were expected within the FSTLL group, as they were receiving an intervention that would have been expected to improve mobility measures. This finding was discussed earlier as it pertains to the testing of procedures.

Finally, this study found no statistically significant effect of either intervention at follow up for any of the outcome measures. This suggests that any effects that were observed in the outcome measures were not maintained once the intervention phase had ended; ideally this would not have been the case as one of the aims of movement rehabilitation after stroke would be to promote motor learning and therefore effect a longer term change in functional activity. There are a number of things that could be explored in future studies that might help to enhance the uptake of the activities that were learnt during the intervention phase.

One of the factors highlighted in the earlier discussion of intervention fidelity was ‘enactment’. This referred to the incorporation of components that tested whether or not the participant was incorporating the techniques learnt as part

of the trial into everyday life (Bellg et al., 2004). Strategies for doing this included assessment with a questionnaire and self-monitoring using practice logs (Bellg et al., 2004 and Carpenter et al., 2013). Self-monitoring of practice through a diary could have been incorporated into the present study and checked each time the therapist visited. The concept of practice however would need to be explicitly stated as one expectation of participation in the study. By ensuring enactment it is possible that the participant will be more able to maintain and use the skills taught as part of the intervention study.

In a study measuring adherence to a home-based exercise programme in people later after stroke Jurkiewicz et al. (2011) found that individuals were more likely to carry out exercises at home if they were also taking part in a structured exercise programme requiring attendance at another venue. Graduation from the exercise group resulted in less adherence with the home-based programme. It is possible that FST could be delivered over a longer period of time with greater intensity at the beginning of the programme which is then gradually decreased. This might place greater responsibility on the participant to carry out their own exercises, whilst ensuring that the therapist is able to monitor the self-practice, possibly leading to better self-efficacy and empowerment. Interestingly in a RCT which compared two intervention groups – one receiving supervised exercises and the other unsupervised with written and verbal instructions, both groups made gains in the clinical outcomes but there was no difference between the groups at either six months or one year after the end of the intervention ($p>0.05$), suggesting that self-directed practice can be effective. The authors speculated however that as participants were aware of the follow up time points that this degree of 'long arm' supervision may have maintained their motivation to continue with the exercises (Olney et al., 2006).

One of the main issues identified within the literature is in relation to non-adherence with home exercises in a group of elderly participants six months post stroke was the lack of understanding on behalf of the participant regarding their responsibility in the rehabilitation process (Karingen et al., 2011). Goal setting was a key aspect of engaging and motivating the participant and is

recommended in relevant guidelines (e.g. RCP and NICE). Although initial goal setting was carried out with participants in this present study, the discussion centred on what they hoped to achieve following receipt of the intervention, and long term aims were not explicitly discussed. Future studies could reflect on this and facilitate discussion around longer term goals.

The incorporation of explicit behavioural techniques that might enhance motivation and ongoing adherence could also be considered. The role of the therapist in motivating the participant is likely to have been an important aspect of the present study. Once this was withdrawn then the participants' ability to remain motivated in carrying out the exercises could have lessened. Current research has explored the use of technology as an adjunct to home based therapy in order to promote motivation and facilitate monitoring of practice. Early phase clinical trials have proved feasible but have yet to be tested in a definitive study (Pang et al. 2006).

A recent systematic review revealed that group exercise classes were also reported to be motivating, although as access, transport and cost were identified as environmental barriers and embarrassment as a personal barrier then this type of intervention would need to be carefully investigated first (Nicholson et al., 2013).

Finally it is possible that the dose or intensity of FST delivered in this study was insufficient to effect long term change. Dose finding studies need to be carried out with a particular emphasis on long term follow up. The aim of this study was to consider the feasibility of a study design investigating a well-defined physical therapy intervention – FST. Effects of the intervention that carry over into the long term are clearly desirable but were not evidenced within the present study design. The previous paragraphs have offered some reflection for this lack of effect at follow up and some suggestions for the future development of FST.

## 5.5 Summary

The present study aimed to assess the feasibility of delivering FST to people in the chronic stage of recovery from stroke. Delivering a trial of both FSTUL and FSTLL in people's homes was feasible. The amount of travel impacted on the cost of the study and the number of people who could receive an intervention in any one day. Future studies based in community settings will need to consider the impact of travel on both the time taken to complete the study and the costs involved. Alternatively other methods for delivering the intervention, such as via groups, could also be explored

The initial recruitment strategy via letters of invitation proved to be unsuccessful at meeting the target recruitment rate of two participants per month, therefore the study's strategy widened to include direct referral from therapists working within stroke services. This proved to be the most successful means of recruiting participants to this present study, with 69% of participants being recruited via this route. Future studies within the community setting should consider including therapist referrals as part of their recruitment strategy and whilst the present study found the recruitment rate of two participants a month may be achievable three participants per two months may be more realistic.

The present study included two intervention groups (FSTUL and FSTLL), where each group was intended to act as control for the other. A statistically significant finding for the TUG in the FSTUL group suggests the potential for a cross training effect of FSTUL on lower limb function made possible by the presence of neuronal coupling. In order to evaluate the effects of FSTLL on lower limb function, future trials should include a comparator that targets the lower limb, so that confounding results induced by the effects of neuronal coupling will not affect the outcome of the study.

The effects of FSTUL were determined using the ARAT and the NHPT, whilst the ARAT appears to be a suitable measure for future trials; future use of the NHPT should be made judiciously. Findings from the present study suggest

that the NHPT may not be useful in detecting change in a population of stroke survivors who present with a severe impairment of their upper limb.

The effects of FSTLL were determined using the FAC, the TUG and the MRMI. It appears that the TUG may have been more sensitive than the FAC although there were a number of people that were unable to complete this measure at baseline. Future trials of FSTLL where lower limb impairment ranges from mild to severe will need to consider a choice of outcome measures that are capable of showing change in both these groups of participants. The MRMI was found to be an ineffective outcome measure for use within the community setting because of the environmental constraints that limited measurement of the final two items on this scale. A more acceptable alternative for measuring lower limb function other than walking will need to be used in future trials conducted in the same setting.

The intervention seemed to be acceptable to the participants in the present study however this would need to be investigated in future studies; a qualitative component would have facilitated discussion of this aspect of the study.

Based on findings from the present trial future studies evaluating FSTUL versus a placebo should aim to recruit 228 participants and studies evaluating FSTLL versus a placebo should aim to recruit 74 participants. These calculations are based on measuring change in upper limb function using the ARAT and lower limb function using the FAC.

The purpose of this phase II trial was not to investigate clinical efficacy, however results from this and previous studies suggest that FSTUL might be an efficacious intervention for improving upper limb function both early and late after stroke. This hypothesis requires testing in a subsequent trial. In this study findings in response to FSTLL were equivocal; however this may have been because of inadequate power to detect a change in lower limb function measured using the FAC. It is also possible that FSTLL was delivered in too small a dose for it to have been effective. Future studies could include dose finding trials for both the upper and the lower limb intervention. It would also be

useful to consider the specific clinical characteristics that would respond to these interventions, so that FST can be targeted at those who are most likely to gain the greatest functional improvement.

# 6.0 Secondary analysis

This chapter describes the secondary analysis of the results from the phase II study of functional strength training in the upper limb and the lower limb. The intention for this chapter was to determine whether there was any information that could be derived from the study that might contribute to the discussion around it's feasibility. The implications of any findings will be discussed in the following chapter (seven). Secondary analysis of the upper limb group will first be presented followed by the analysis of the lower limb group. In both cases analysis will focus on the primary outcome measures, further analysis of the secondary outcome measures is limited because of the quantity of missing data for all of these.

## 6.1 Secondary analysis of upper limb group

The following box plot shows the Action Research Arm Test (ARAT) scores for each group at baseline, outcome and follow up. As expected from the main analysis discussed in chapter five, participants who received the upper limb intervention have shown a positive change in the ARAT score indicating some effect of FST-UL, although this effect was reduced by the follow up measurement time point.

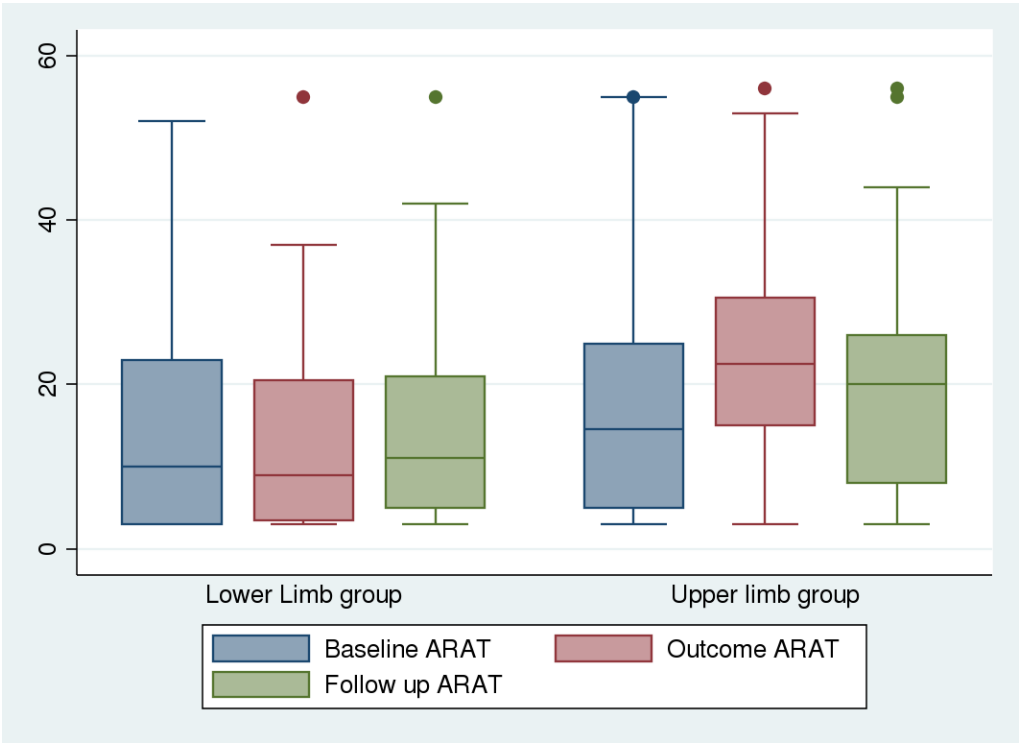


Figure 11: Boxplot showing ARAT score at baseline, outcome and follow up for both groups

The following analysis will investigate the individual participant responses to FST-UL by examining their respective scores at each of the time points above. For the purposes of this plot only, where data was missing the last value was carried forward.

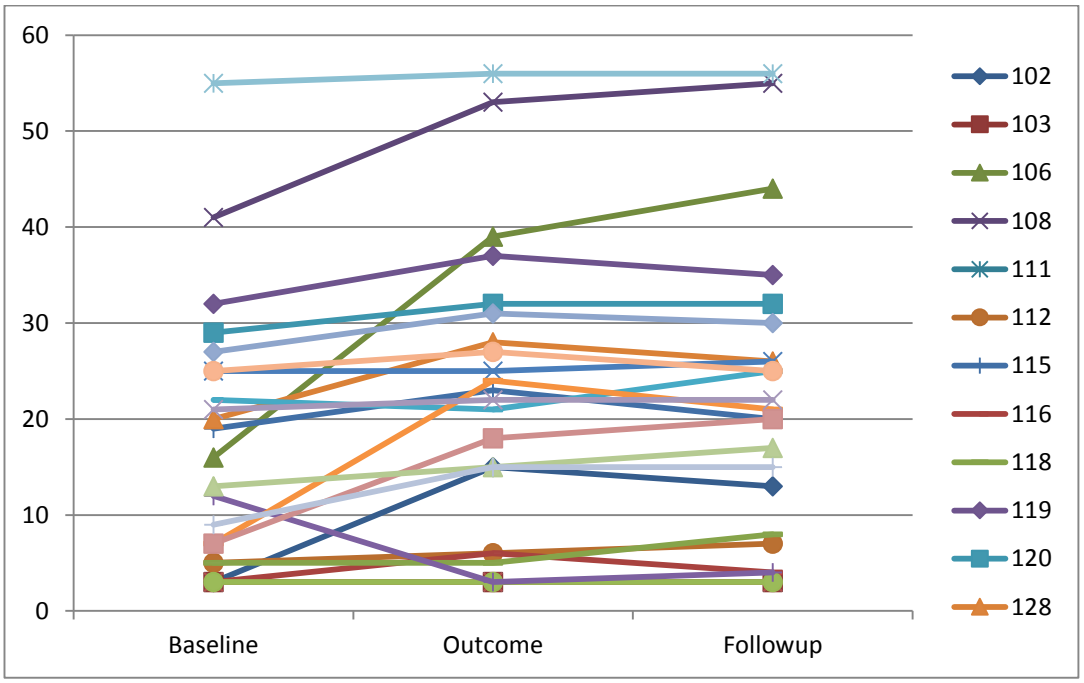


Figure 12: Line graph showing individual scores for each participant at three time points

Figure eleven shows the individual responses to FST-UL, participants who were found to have a change score on the ARAT between outcome and baseline or follow up and outcome of greater or less than 5.7 were then extracted and a second chart was created. A change score of 5.7 was deemed to be clinically significant (van der Lee et al., 2001b) thus the individual characteristics of participants showing a change score of greater or less than this were examined.

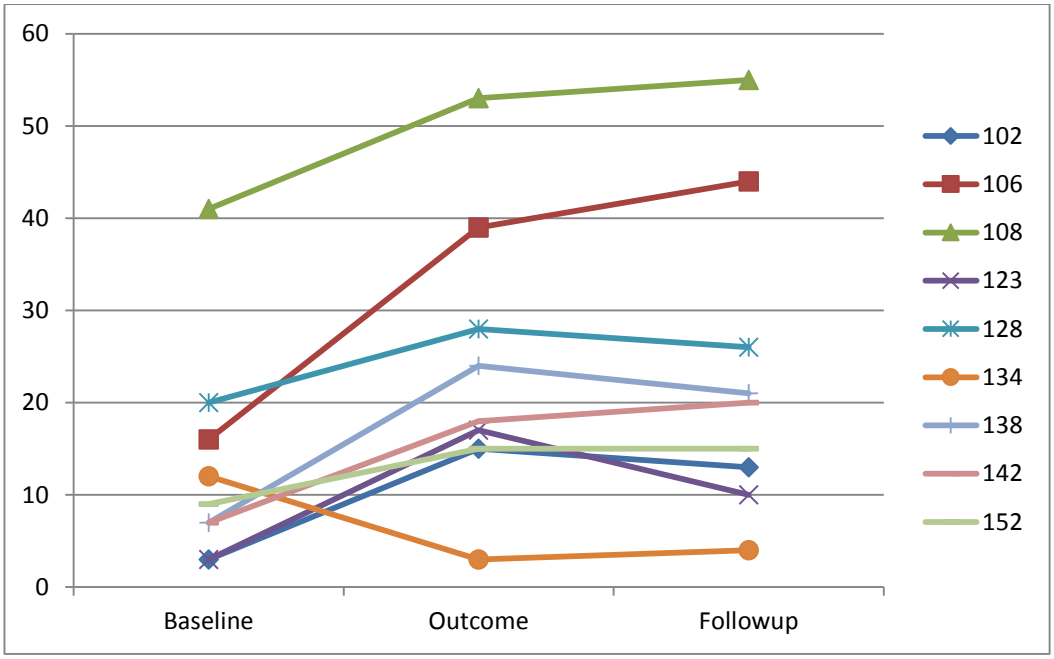


**Figure 13: Line graph showing baseline, outcome and follow up scores for participants with a change score greater than or equal to 5.7**

In order to determine whether there were any particular characteristics that might be associated with either a positive or negative change on the ARAT score at outcome the following table lists each of these participants and the individual variables that were collected as part of the main study. The first participant listed was the only individual with an ARAT score which decreased by greater than or equal to 5.7 points. All other individuals in this sample showed a clinically significant improvement and have been displayed in ascending order of change score on the ARAT.

Participant FEST134 became ill during the study and therefore was not able to fully take part (he received only 26% of the intended dose of the intervention), this may have accounted for his deterioration in the ARAT score at outcome. FEST106 made the most improvement in the ARAT score at outcome and went on to improve at follow up and yet it appears that he received the least amount of FST-UL of those participants displayed in the table below (excluding FEST134). 50% of the participants who showed a clinically significant change at outcome deteriorated at follow up, although only one participant decreased by greater than 5.7. This participant was the only participant to receive the intervention at the day centre she attended three times a week; she lived alone and received daily care for all activities of daily living.

It appears from this table that there this little to guide future studies in terms of individual participant characteristics collected as part of this study for those who did or did not respond to FST-UL.

The following analyses will go on to investigate whether there is any correlation between the change scores on the ARAT at outcome and follow up and the total sample of participants who received the upper limb intervention and the variables that were collected as part of the main trial. As shown in the table above these variables are: therapy time, age, side of stroke, male/female, time since stroke and severity of stroke. The relatively small number of participants in this study is likely to prevent any definite conclusions being made about the presence of a relationship or not between the variables. But they may be able to suggest avenues for future investigations.

| Participant | Change score Outcome | Change Score Follow up | Age (years) | Time since stroke onset (months) | Type of stroke | Left/right hemiplegia | Intervention time (mins) | Severity | Male/female |
|---|---|---|---|---|---|---|---|---|---|
| FEST134 | -9 | 1 | 80 | 6.4 | PACS | Right | 371 | Severe | Male |
| FEST152 | 6 | 0 | 87 | 10.9 | PACS | Left | 1125 | Severe | Male |
| FEST128 | 8 | -2 | 76 | 17.1 | POCS | Left | 1220 | Moderate | Female |
| FEST142 | 11 | 2 | 71 | 14.0 | TACS | Right | 987 | Severe | Male |
| FEST102 | 12 | -2 | 67 | 43.5 | PACS | Right | 1170 | Severe | Female |
| FEST108 | 12 | 2 | 70 | 45.9 | LACS | Right | 1350 | Mild | Male |
| FEST123 | 14 | -7 | 78 | 12.0 | LACS | Left | 1040 | Severe | Female |
| FEST138 | 17 | -3 | 36 | 6.7 | POCS | Left | 1020 | Severe | Male |
| FEST106 | 23 | 5 | 60 | 48.3 | LACS | Right | 970 | Severe | Male |

**Table 36: Individual characteristics of participants with a change score at outcome of greater than or equal to 5.7**

### 6.1.1 Analysis of correlation between baseline and outcome difference for the ARAT and therapy time.

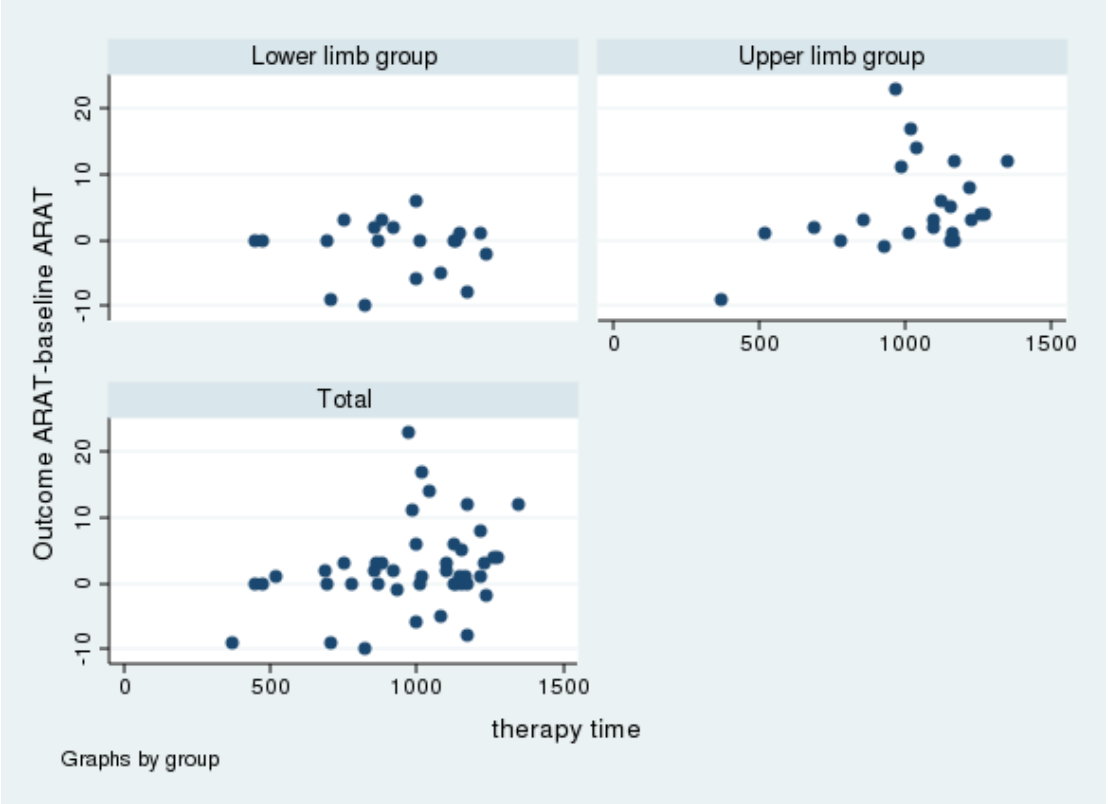


Figure 14: Scatter plot to show correlation between therapy time and change score of the ARAT at outcome

This scatterplot shows the relationship between the change score at outcome for the ARAT and the amount of therapy time that each participant received for each of the intervention groups and also for the total sample. The graphs show the possibility of some correlation between the amount of therapy received and greater change scores for the ARAT in the upper limb group, however this relationship is not statistically significant (p=0.11). As previously mentioned the lack of a statistically significant relationship is not unexpected given the small sample size, future studies may however wish to consider the potential for a dose response relationship between FST-UL and the amount of therapy received.

### 6.1.2 Analysis of changes occurring between baseline and outcome for the ARAT and age of the participant.

The scatterplots below show no relationship between age and the change in ARAT score at outcome for either group. Participants spanned a wide age range with arguably some clusters of participants around 50-60 years and 70-80 years.

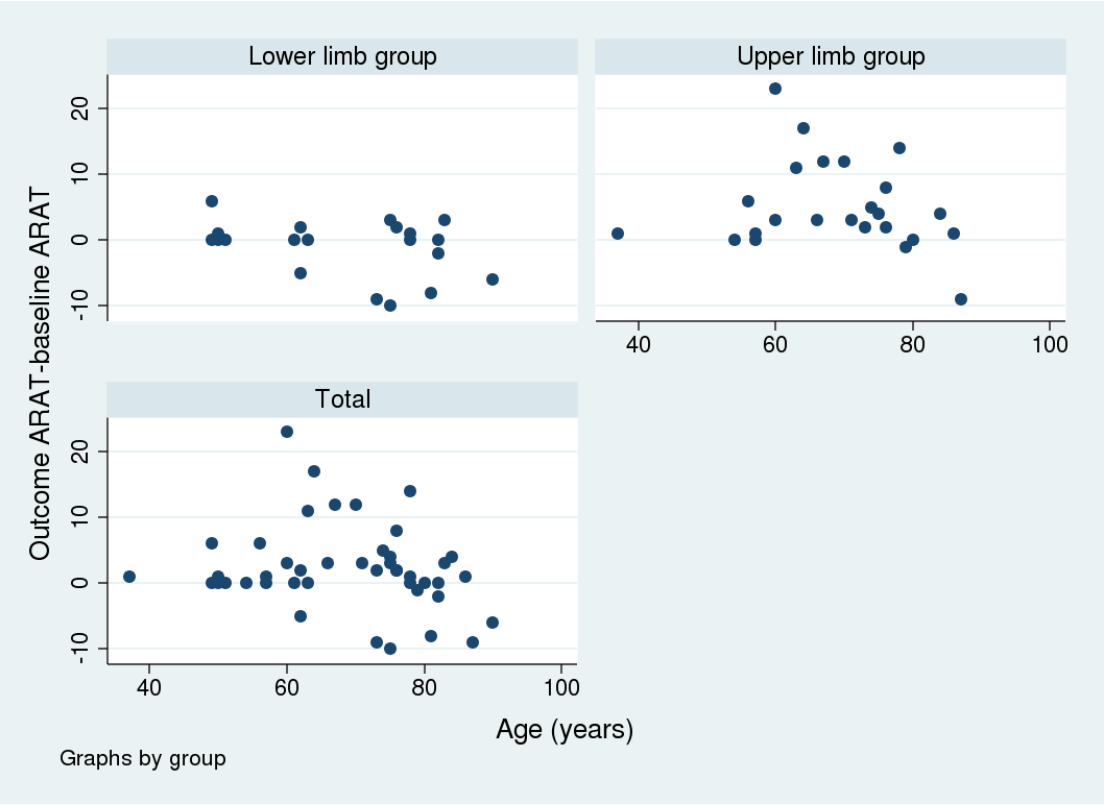


Figure 15: Scatter plot to show correlation between age in years and change score of the ARAT at outcome.

In this study, age was found to correlate significantly with the baseline ARAT score (p=0.01). Figure 13 shows this relationship which indicates that as age increased so did the baseline ARAT score, suggesting that older participants were more severely affected by the stroke with respect to upper limb activity at the point of admission to the study.

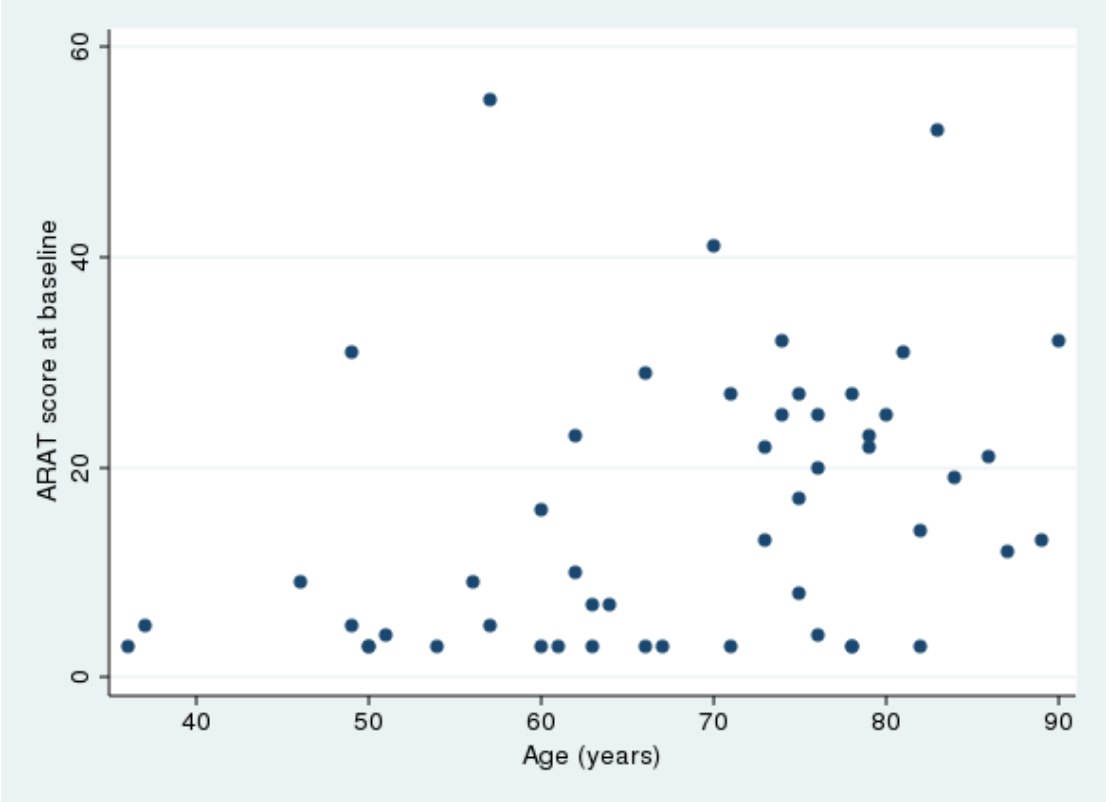


Figure 16: Scatterplot to show the correlation between age and the baseline ARAT score

### 6.1.3 Analysis of changes occurring between baseline and outcome for the ARAT and the side of the hemiplegia for each participant.

The histogram below shows the relationship between the change in ARAT score at outcome and the side of hemiplegia in the upper limb group. and then the lower limb group. There doesn't appear to be a relationship between these two variables, there appears to be similar proportions of participants with both right and left sided hemiplegia who have achieved similar outcomes measured by the ARAT.

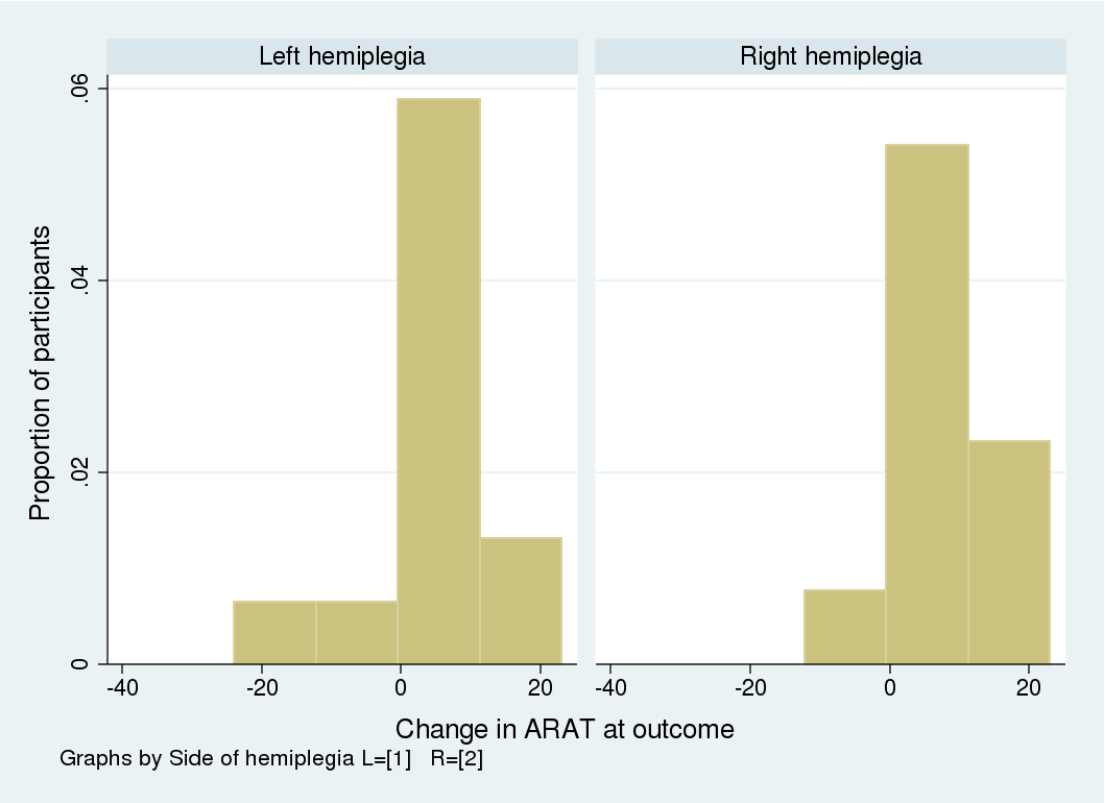


Figure 17: Histogram showing relationship between side of hemiplegia and change in the ARAT score at outcome for the upper limb group

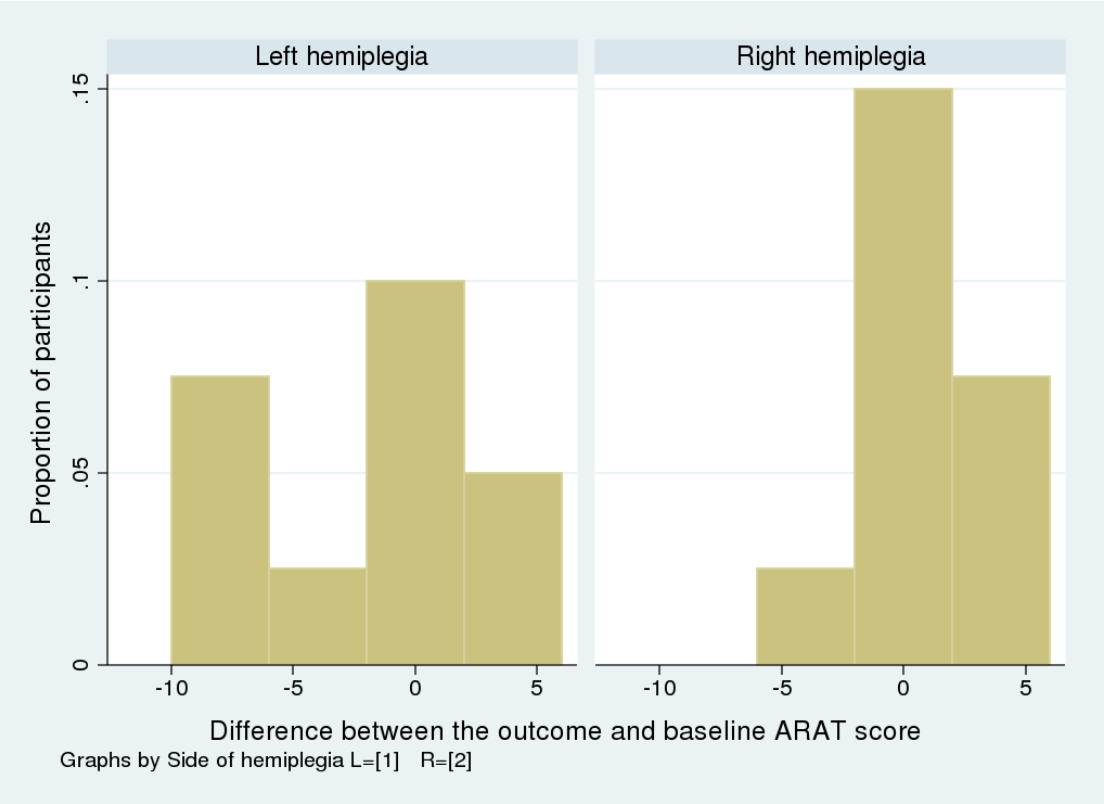


**Figure 18: Histogram showing the relationship between the side of hemiplegia and change in the ARAT score at outcome for the lower limb group**

### 6.1.4 Analysis of changes occurring between baseline and outcome for the ARAT and gender of each participant.

The following histogram shows the relationship between the gender of the participant and the change in ARAT score at outcome. As for the previous charts these seem to show little correlation between these two variables.

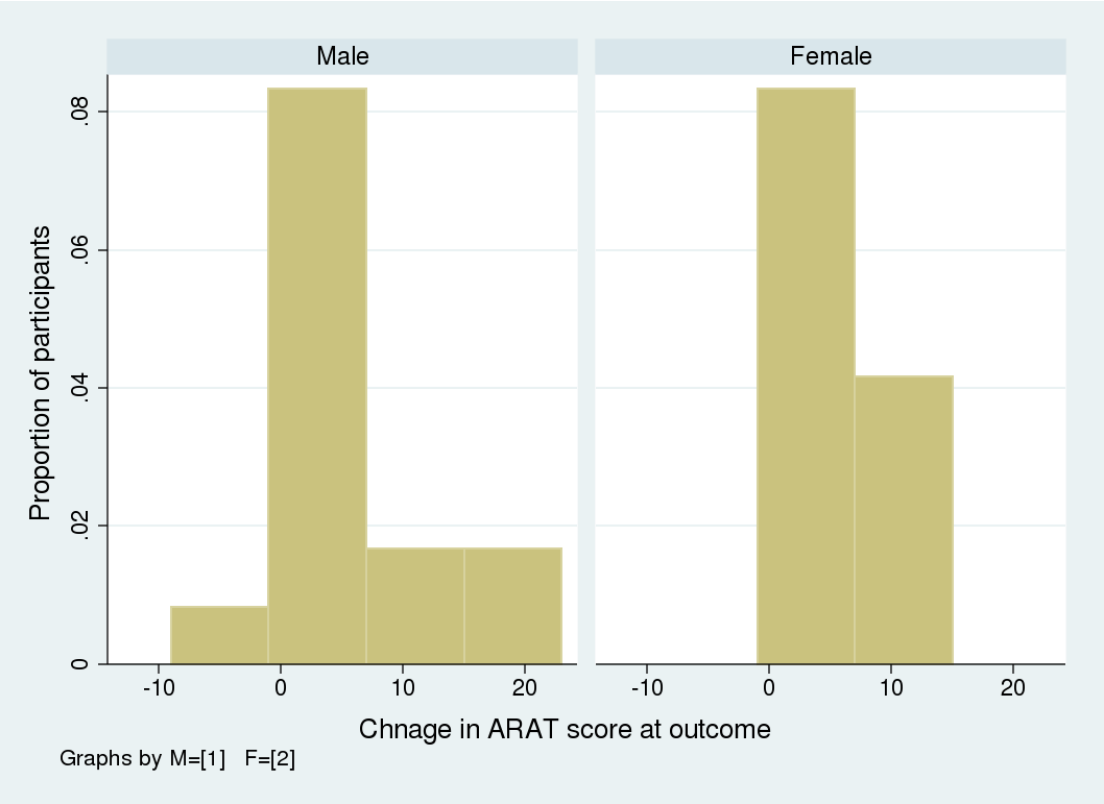


Figure 19: Histogram to show relationship between the gender of the participant and the change in ARAT score at outcome for the upper limb group

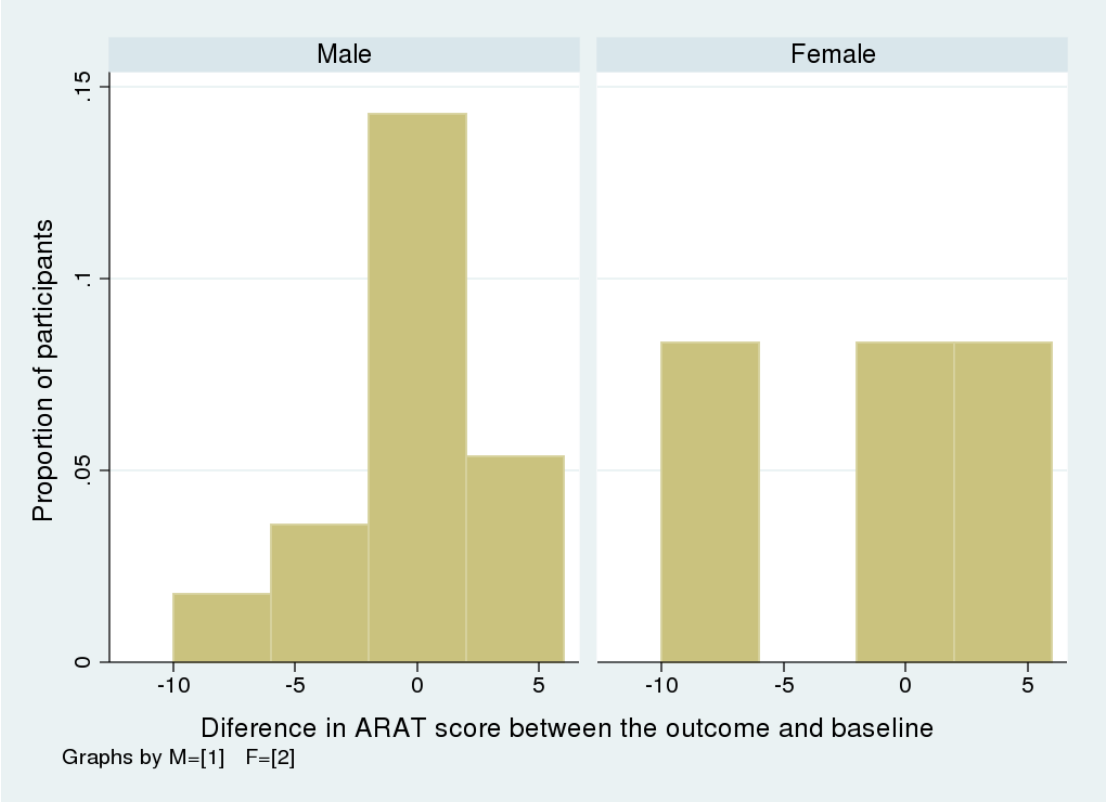


**Figure 20: Histogram to show relationship between the gender of the participant and the change in ARAT at outcome for the lower limb group**

### 6.1.5 Analysis of changes occurring between the baseline and outcome for the ARAT and time since stroke onset.


Figure 21: Scatterplot of change in ARAT score at outcome and time between stroke onset and recruitment to the study

This scatter plot shows the time between stroke onset and recruitment to the study plotted against the change score in the ARAT at outcome. None of the plots show a relationship between these two variables.

### 6.1.6 Analysis of changes occurring between the baseline and outcome for the ARAT and severity.

In order to determine whether there is any relationship between the severity of the stroke and the change in ARAT score at outcome, the change score has been plotted against the baseline ARAT score. Higher scores on the ARAT indicate the participant has been mildly affected by the stroke in terms of upper limb recovery and lower scores indicate increased severity.

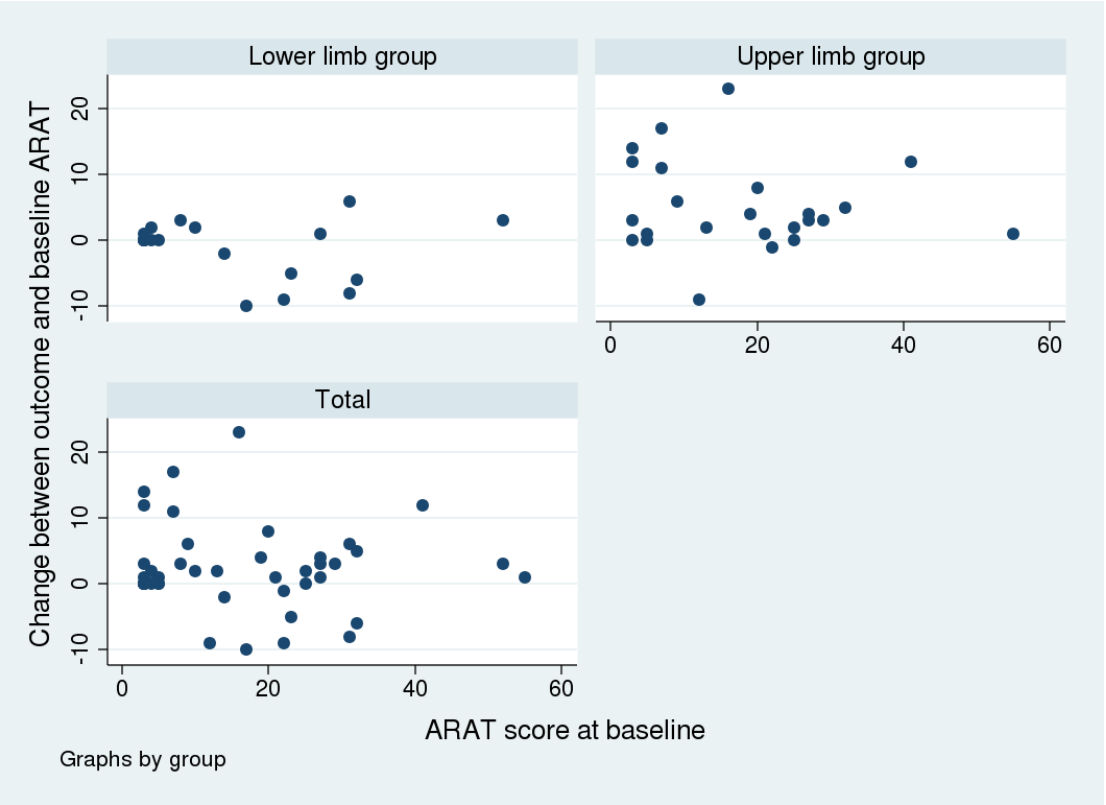


Figure 22: Scatterplot to show relationship between change in ARAT at outcome and ARAT score at baseline

These plots appear to show no relationship between the change in ARAT at outcome and the baseline ARAT score as an indicator of severity. For the purposes of the study the ARAT was classified as mild (39-57), moderate (20-38) and severe (0-19). The following plot shows the change in ARAT score at outcome plotted against these three categories.

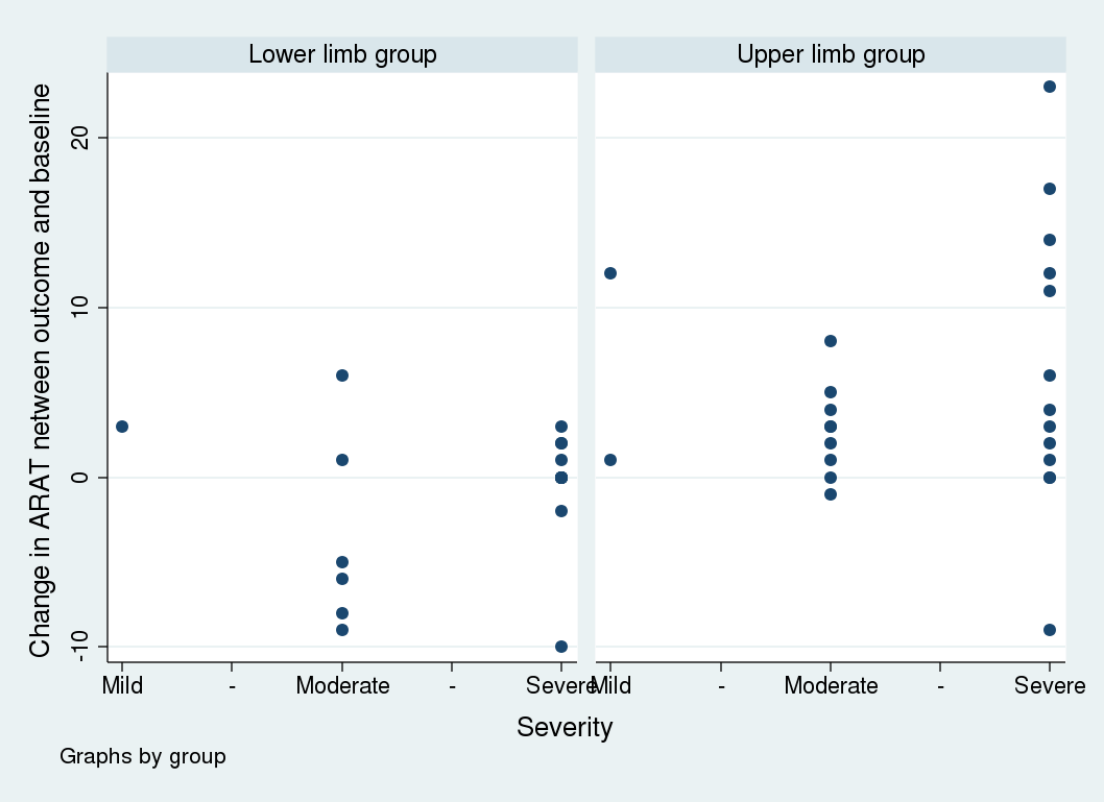


Figure 23: Scatterplot to show relationship between Change in ARAT at outcome and severity as categorised by the baseline ARAT score

This plot seems to suggest that those participants who have been more severely affected by the stroke in terms of upper limb function have shown greater changes on the ARAT at outcome. Six out of the eight participants with a clinically significant change on the ARAT at outcome were also categorised as severe, suggesting that there may be some correlation between these categories and changes on the ARAT. This will be discussed in the following chapter.

## 6.2 Follow up

Figure 11 indicates no change at follow up, secondary analysis was carried out for each of the variables as for the results at outcome. There was nothing to note from these analyses. Subsequent plots and graphs have been included in the appendix (appendix XVII)

## 6.3 Secondary analysis of lower limb group

The following analysis will consider the relationships between the changes incurred by the lower limb group following FST-LL. The box plot below shows the range of scores obtained by each group at baseline, outcome and follow up for the Functional Ambulation Categories (FAC). This plot shows no change in the FAC for the group receiving the lower limb intervention at either outcome or follow up. The change in lower limb function measured by the FAC seen in the upper limb group has been discussed in chapter five.

Once again further analysis of the potential for a relationship between the variables and any change in outcome in the lower limb group will focus on the primary outcome measure as there was insufficient data from the secondary outcome measures.

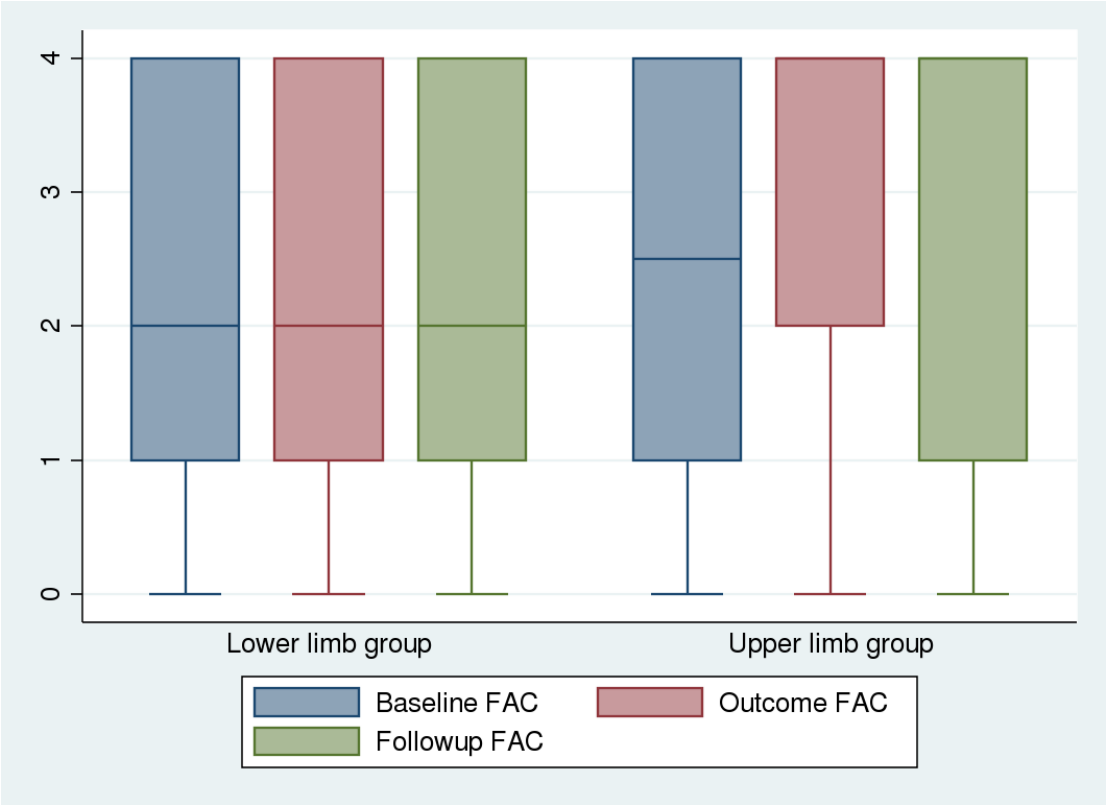


Figure 24: Box plot of FAC scores at baseline, outcome and follow up

The following plots show the individual responses to FST-LL. Any participant who increased or decreased their score by 1 (clinically significant difference) at either outcome or follow up was then extracted in order to better identify

individual characteristics for those who responded well or badly to the intervention. These plots are shown below.

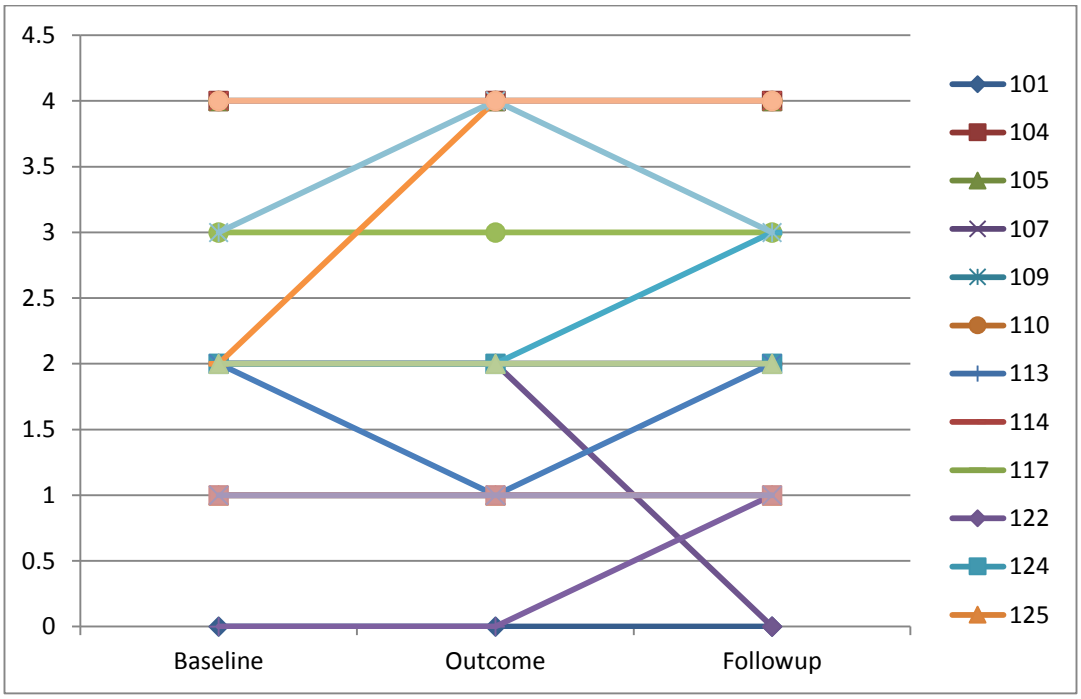


**Figure 25: Line graph showing baseline, outcome and follow up FAC score for all participants in the lower limb group**

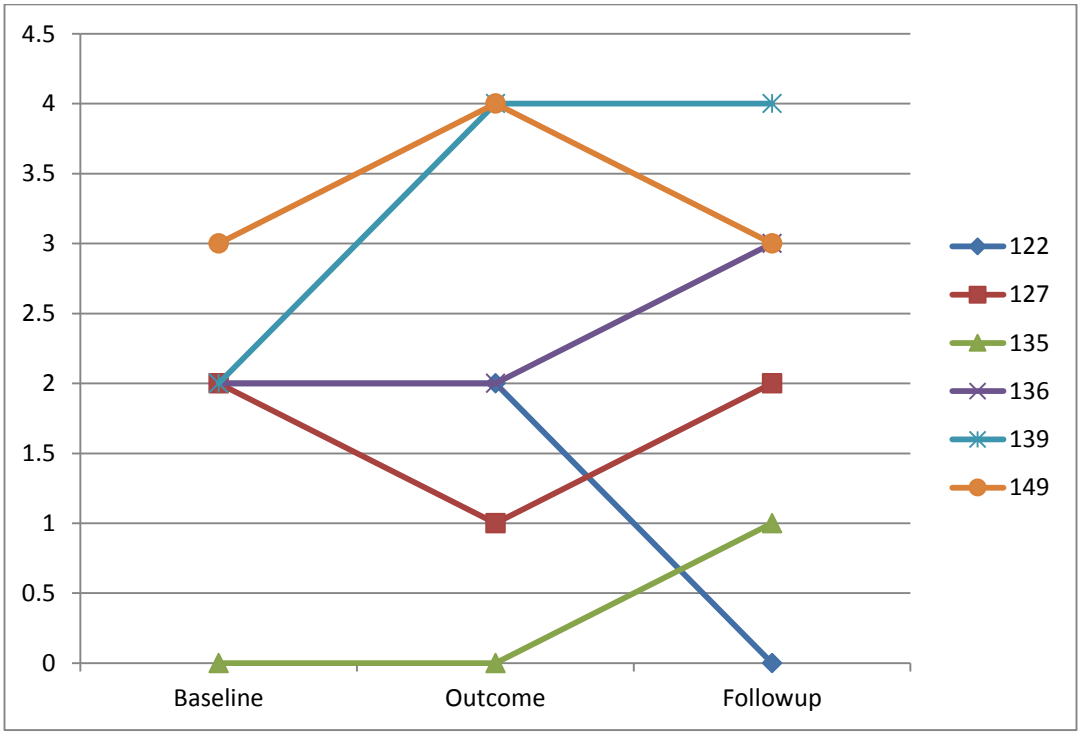


**Figure 26: Scatterplot showing participants who showed a clinically significant increase or decrease in the FAC at outcome or follow up**

The following table shows the characteristics collected as part of the main study for each of the participants in the plot shown above. FEST127 was the only participant to show a drop in the FAC score at the outcome measurement time point although this was reversed at follow up. There appears to be nothing of noteto suggest why this participant responded in this way. He was a relatively young gentleman who lived with his partner and who received 75% of the intervention. FEST139 made the most improvement in the lower limb group at outcome (2 points on the FAC). Again there appears to be little of note in the characteristics that were collected as part of this study that would suggest any reason for this. This lady lived alone in a bungalow but received only 52% of the intervention. She missed two of the appointment dates because of ill health but was only able to tolerate a mean of 32 minutes of FST-LL per session although this increased incrementally as the study progressed.

FEST122 showed the greatest drop in FAC score at follow up, however this was likely to be due to factors unrelated to the study. Following the study the gentleman was diagnosed with an infected hip replacement which would have had a huge impact on his mobility and thus his score on the FAC.

| Participant | Change score Outcome | Change Score Follow up | Age (years) | Time since stroke onset (months) | Type of stroke | Left/right hemiplegia | Intervention time (mins) | Severity | Male/female |
|---|---|---|---|---|---|---|---|---|---|
| FEST127 | -1 | 1 | 50 | 10.7 | TACS | Right | 1080 | Severe | Male |
| FEST135 | 0 | 1 | 63 | 21.7 | POCS | Left | 856 | Severe | Male |
| FEST122 | 0 | -2 | 51 | 14.9 | PACS | Right | 445 | Severe | Male |
| FEST136 | 0 | 1 | 49 | 18.7 | PACS | Right | 917 | Severe | Male |
| FEST149 | 1 | -1 | 79 | 6.2 | PACS | Right | 752 | Moderate | Male |
| FEST139 | 2 | 0 | 62 | 14.3 | TACS | Left | 704 | Severe | Female |

**Table 37: Individual characteristics of participants who showed clinically significant changes in outcome or follow up for the FAC**

The following analyses will go on to investigate whether there is any correlation between the change scores on the FAC at outcome and the total sample of participants who received the lower limb intervention and the variables that were collected as part of the main trial. Once again these variables are: therapy time, age, side of stroke, male/female, time since stroke and severity of stroke. The analysis will not be repeated for the follow up scores as there was no change for the total sample between outcome and follow up (see figure 21). This analysis is likely to be limited by the finding that the majority of participants within the lower limb group experienced no effect of FST-LL. Therefore it is unlikely to provide any further information than that that's has been determined from the individual participant descriptions above.

### 6.3.1 Analysis of correlation between baseline and outcome difference for the FAC and therapy time.

The following scatterplot plots the difference between the outcome and baseline FAC score against the intervention time. The plot shows no correlation but the outliers and analysis of individual participants described above show a negative relationship between therapy time and improvement in the FAC score after FST-LL.

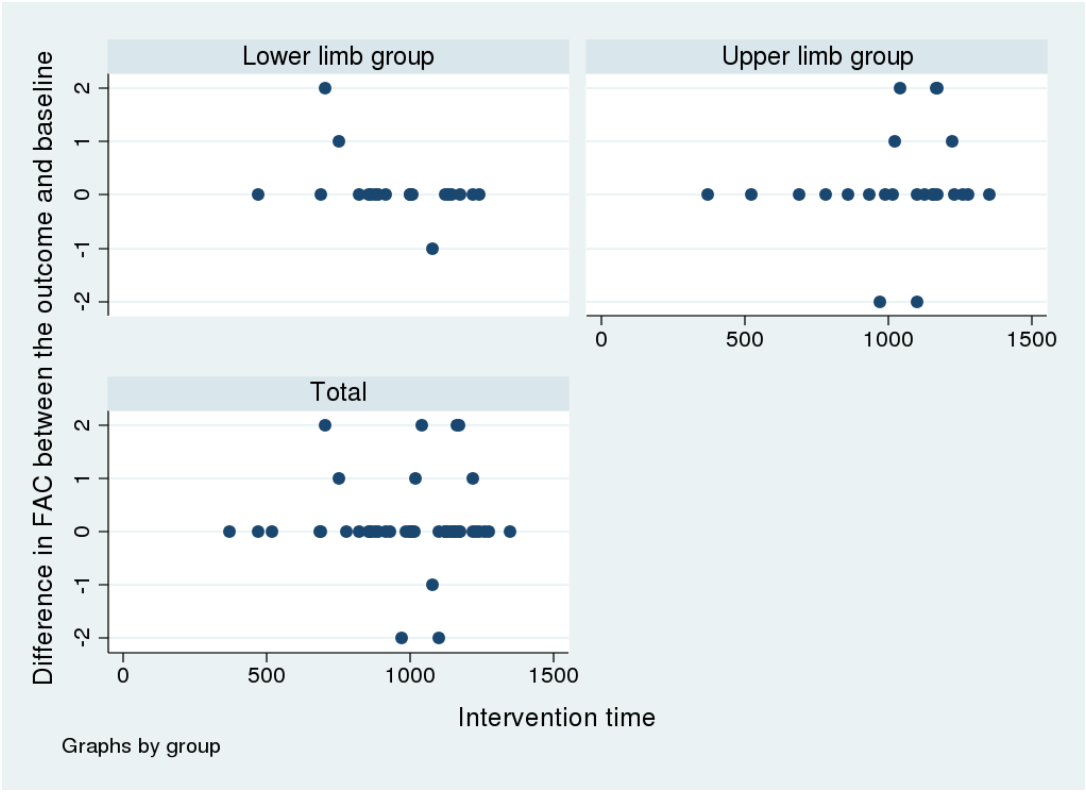


Figure 27: Scatterplot to show correlation between therapy time and change score on the FAC at outcome

### 6.3.2 Analysis of correlation between baseline and outcome difference for the FAC and age.

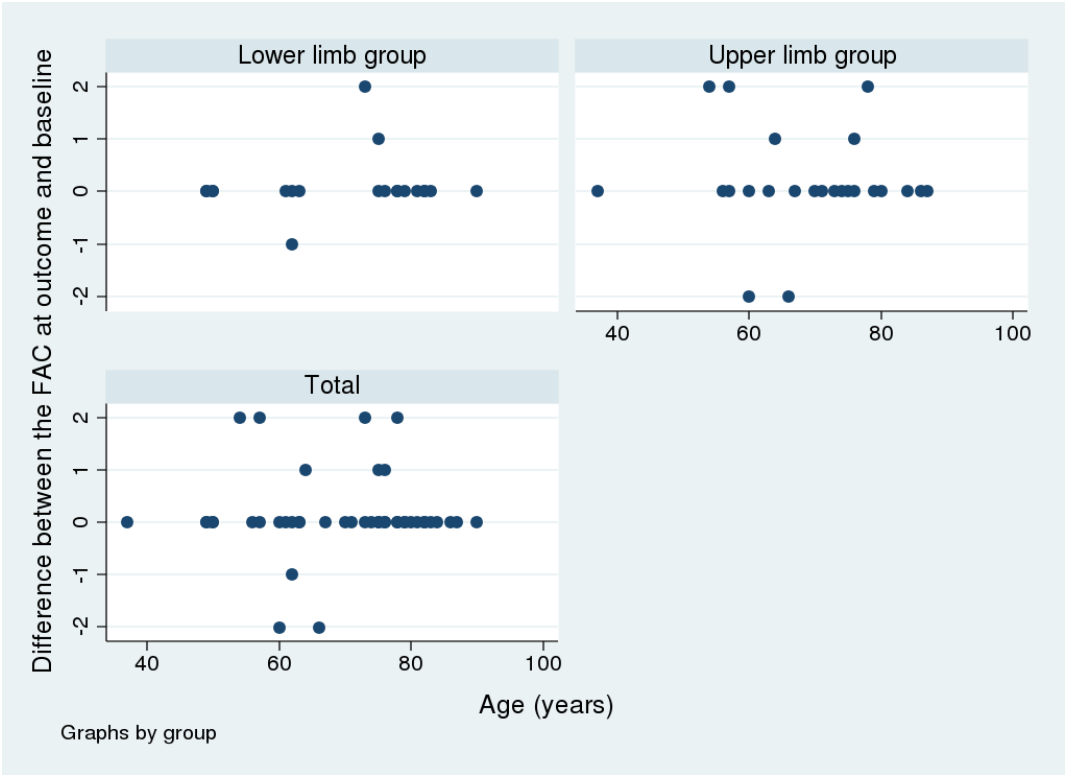


Figure 28: Scatterplot to show the correlation between age and change score on the FAC at outcome

These graphs suggest no correlation between age and change score at outcome for the FAC.

Age was subsequently plotted against the baseline FAC score to see if there was any relationship between age and severity of stroke as measured by the FAC.

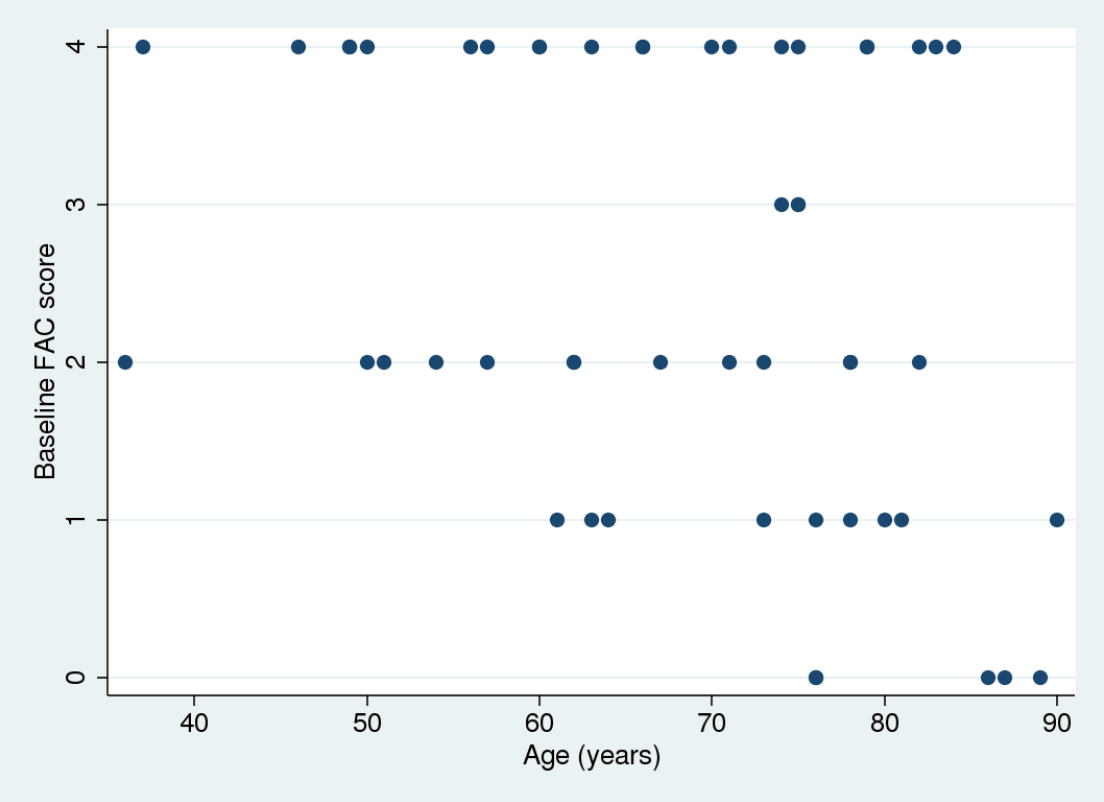


Figure 29: Scatterplot to show relationship between age and the baseline FAC score

This plot suggests that age was negatively correlated with the baseline FAC score suggesting that older participants were more likely to present with a severe lower limb impairment compared to younger participants. This relationship was statistically significant (p=0.01).

### 6.3.3 Analysis of correlation between baseline and outcome difference for the FAC and the side of the hemiplegia.

The following histogram shows more variance in the change scores at outcome for the FAC in those participants with a left sided hemiplegia in the lower limb group but in light of the low numbers of participants this is unlikely to be indicative of any relationship between these two variables.

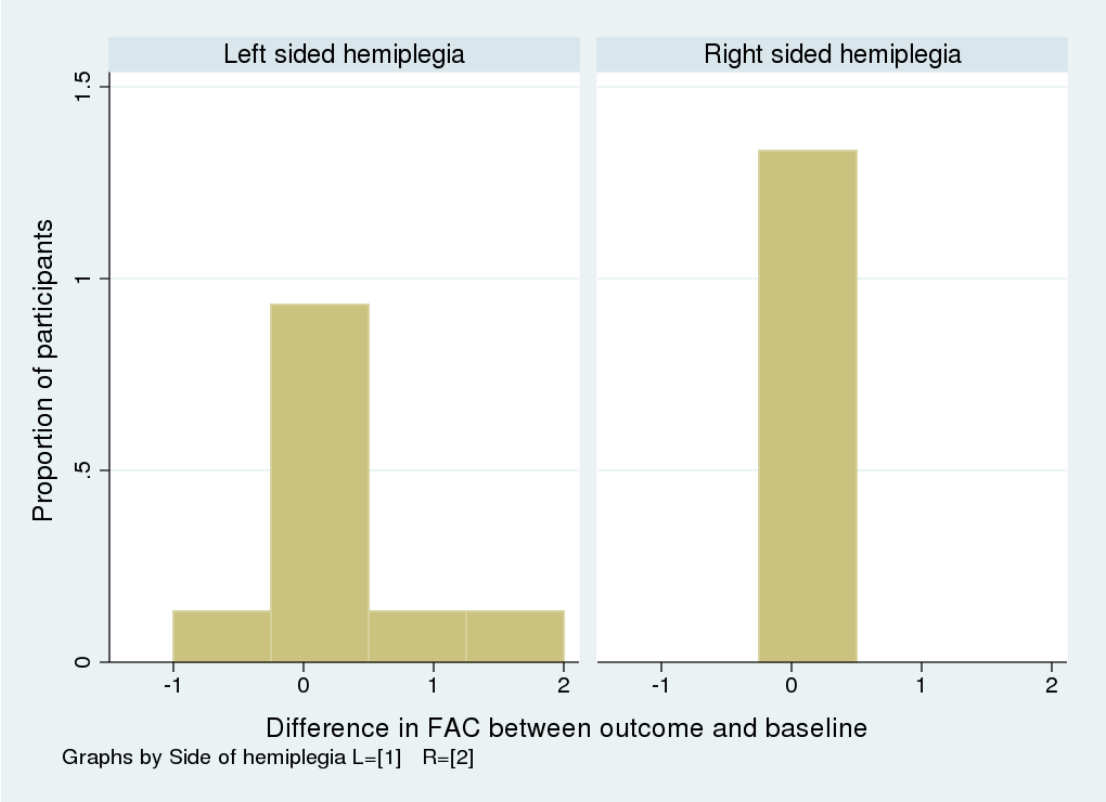


**Figure 30: Histogram showing the relationship between the side of hemiplegia and change in the FAC score at outcome for the lower limb group**

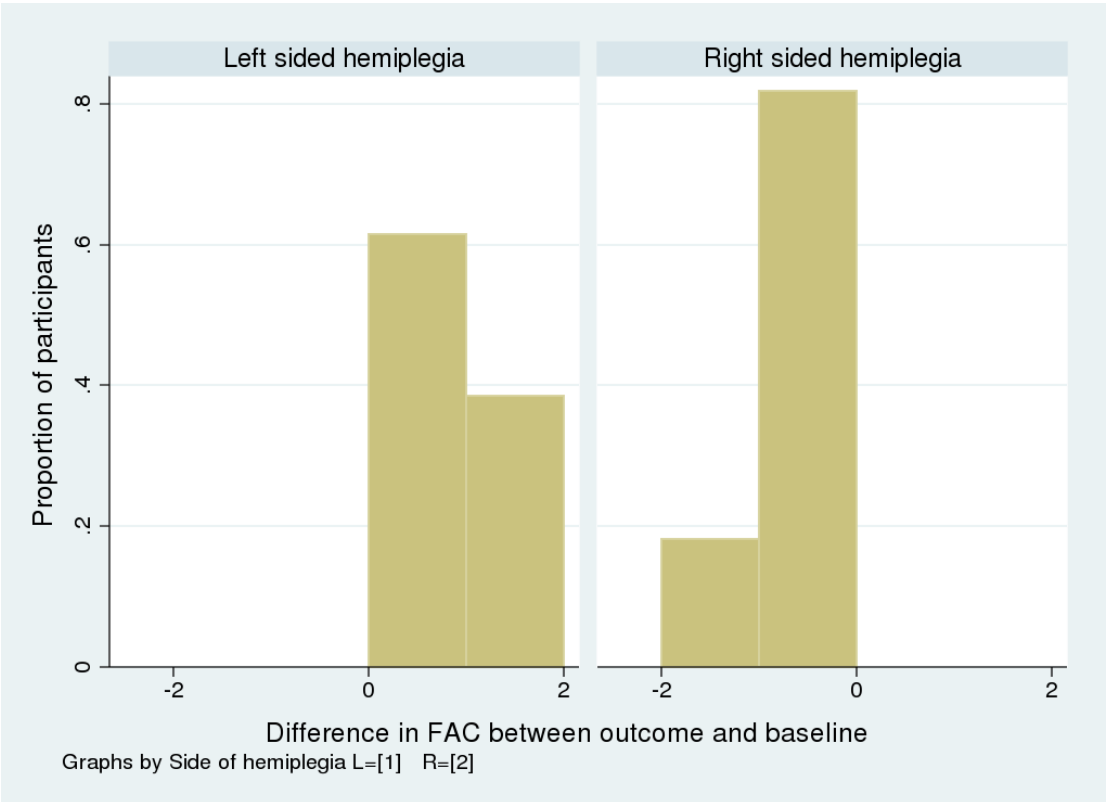


**Figure 31: Histogram showing the relationship between the side of hemiplegia and change in the FAC score for the upper limb group**

### 6.3.4 Analysis of the correlation between the baseline and outcome difference for the FAC and gender difference

The following histograms show the relationship between the gender of the participant and the change score in the FAC at outcome. As for the graphs displayed above there appears little of note for future studies.

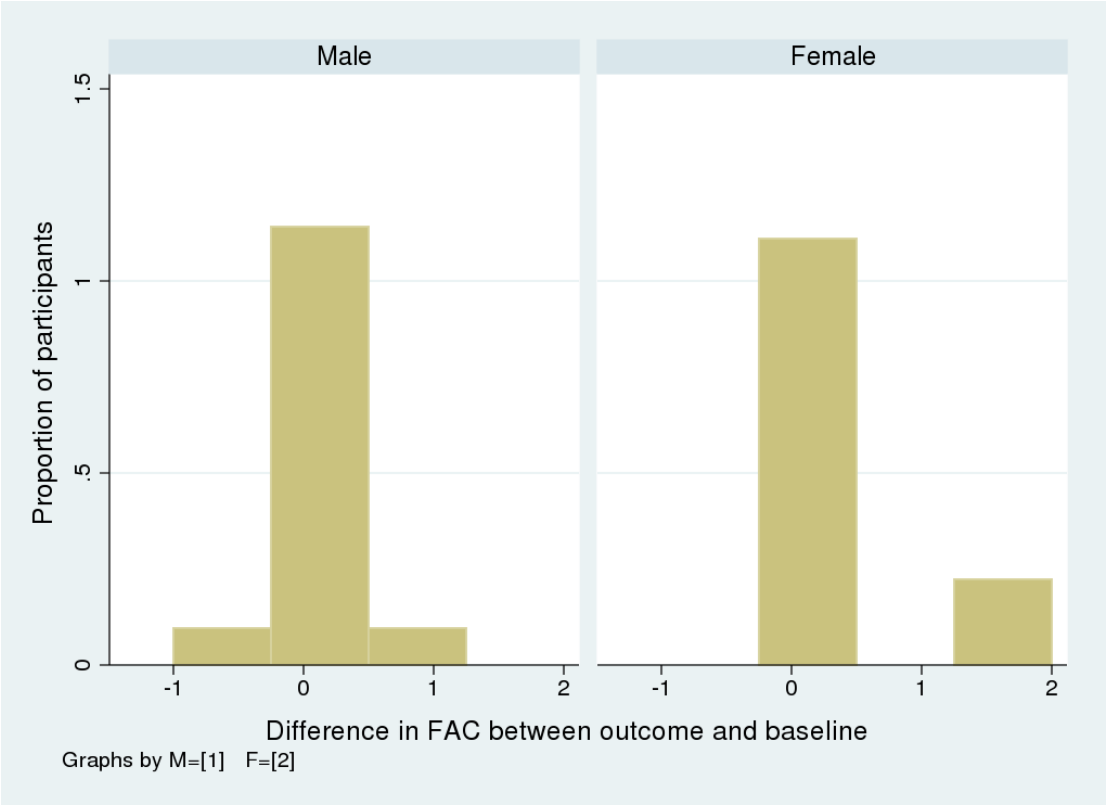


Figure 32: Histogram to show the relationship between the gender of the participant and the change in the FAC at outcome for the lower limb group

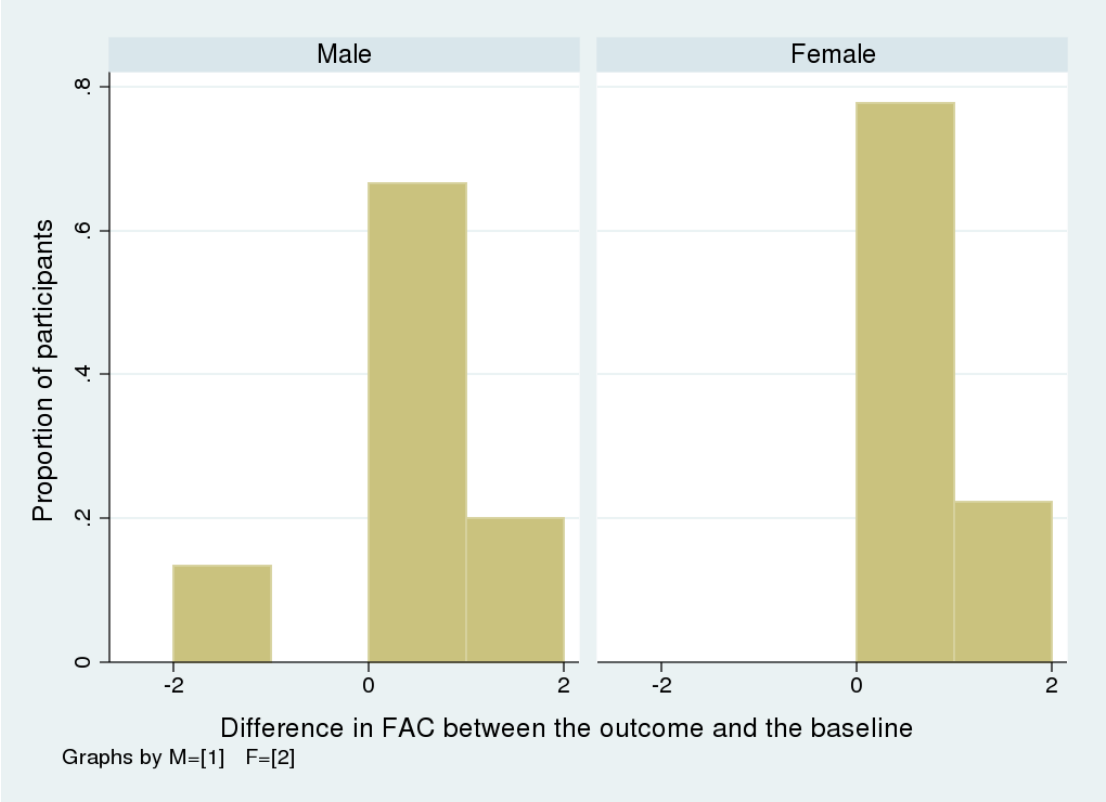


Figure 33: Histogram to show the relationship between the gender of the participant and change in the FAC at outcome for the upper limb group

### 6.3.5 Analysis of the changes occurring between the baseline and outcome score of the FAC and time since stroke onset

The scatterplot below shows no relationship between the change scores in the FAC at outcome and the time since stroke onset.


Figure 34: Scatterplot of change in FAC score at outcome and time between stroke onset and recruitment

### 6.3.6 Analysis of the changes occurring between the baseline and outcome score of the FAC and severity

The change score in the FAC between baseline and outcome has been plotted against the baseline score of the FAC to see if there is any correlation between the two. The plots show no relationship.

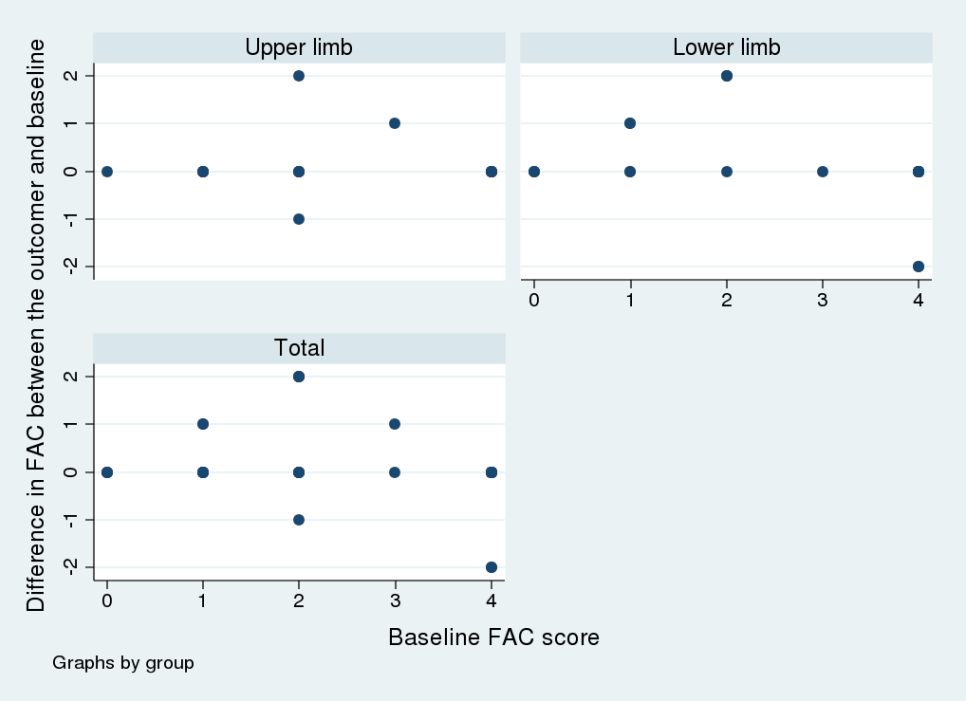


Figure 35: Scatterplot to show relationship between change in FAC at outcome and FAC score at baseline

Severity according to the FAC was categorised in the following way: a score of 4+ indicates mild, 3 indicates moderate and less than or equal to 2 indicates severe. The following plot shows the change score of the FAC at outcome plotted against these categories. The plot does not show a relationship between the two variables.

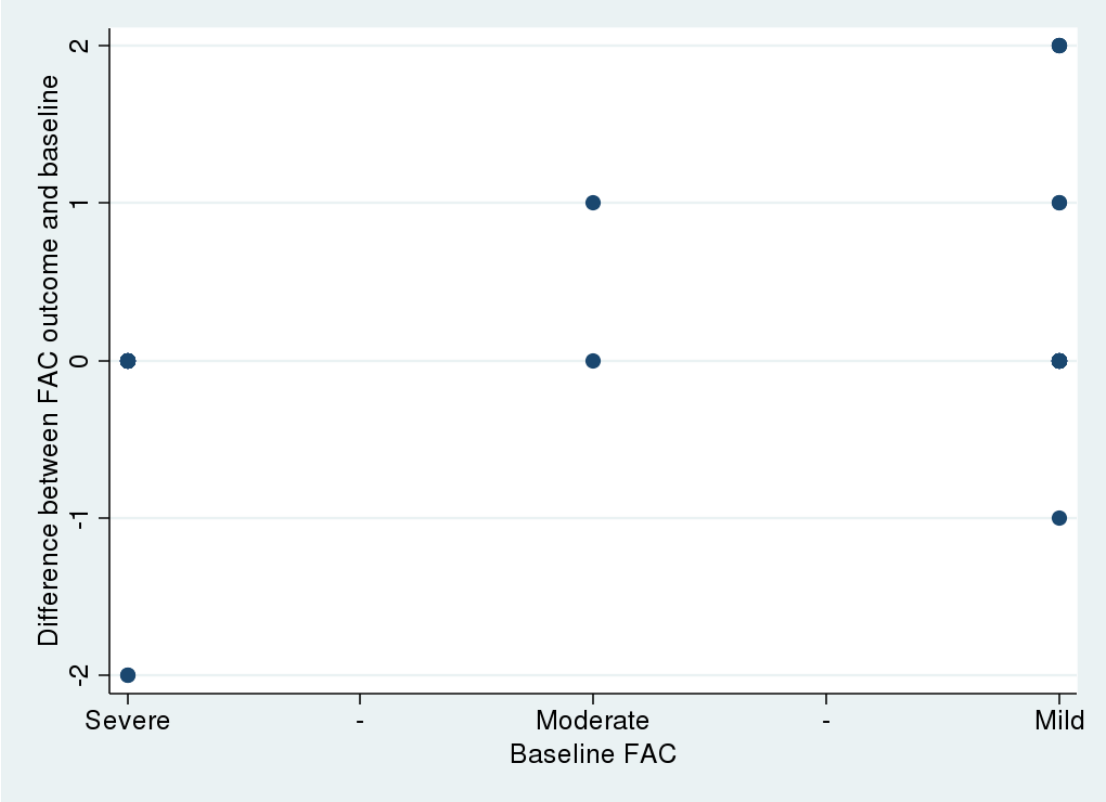


Figure 36: Scatterplot to show relationship between the change in FAC at outcome and severity as categorised by the baseline FAC score

## 6.4 Follow up

Figure 21 indicates no change at follow up, secondary analysis was carried out for each of the variables as for the results at outcome. There was nothing to note from these analyses. Subsequent plots and graphs have been included in the appendix (appendix XVIII)

# 7.0 Development of FST within a motor learning framework (Aim 4)

## 7.1 Introduction

The aim for this chapter is to reflect on the findings from both the systematic review and the feasibility study presented earlier in order to consider the final aim stated in chapter three.

> Aim 4: To present a novel intervention combining the results of the studies conducted fulfilling aims one, two and three in order to suggest how a motor learning framework could inform the delivery of physical therapy interventions as part of movement rehabilitation after stroke.

The MRC Framework for developing and evaluating complex interventions described in chapter two has been used throughout the thesis to underpin the conceptual development of both the systematic review and the phase II study. This current chapter goes on to present a novel intervention which has evolved from the findings of the two previously described studies. Reflection on these studies and the secondary analysis presented in chapter six as well as the other literature that has been incorporated within this thesis suggests several ways in which this novel intervention could be designed and developed. The MRC Framework illustrated by the diagram presented in section 2.1 shows a cyclical process with arrows indicating a two way relationship between 'feasibility and piloting' and 'development' (Craig et al., 2008). Thus within the context of the framework it would be desirable to return to the 'development' stage in order to refine both design and delivery of the novel intervention.

Discussion of the findings from both the systematic review and the phase II study have identified further consideration could be given to developing broader aspects of the novel intervention in terms of motor learning principles, the identification of characteristics for people who respond most to the intervention and dose of the intervention. Aspects of study design that could be further refined include the incorporation of different methods of delivery such as tele-rehabilitation and groups, as well as the inclusion of more explicit goal

setting and follow up strategies after the end of the intervention phase to improve adherence.

This chapter will present a summary and key findings from both studies as discussed in chapters four and five and embed these findings into the presentation of the novel intervention. Further potential steps to develop both the intervention and future study designs will then be discussed.

## 7.2 Summary from Systematic Review

A review of the background literature supporting the development of motor learning principles identified principles of mental practice, instructions, feedback, practice intensity, variability of physical practice and practice specificity. Mental practice of an action is believed to increase excitation within the movement execution system of the brain, in a manner that is similar to the action being performed. This increase in CNS activity has been referred to as priming (Stinear et al., 2008). The motor learning principle 'mental practice', was therefore renamed 'priming'. Thus the following definitions for each of the motor learning principles were established:

Priming - Interventions that are reported to have a motor learning effect because they increase neural excitability in the movement execution system.

Instructions – given to the participant directing their attention to either an external or internal focus.

Feedback - refers to information given to an individual about their performance, and which can be used as a basis for improvement.

Practice Intensity – refers to the amount of practice required to achieve learning.

Variability of practice – refers to the scheduling of practice, which can be blocked or random.

Practice specificity – refers to the similarity between the task practice conditions and the final task that needs to be learnt.

Stroke survivors may not recover sufficient movement to take part in physical practice, therefore the motor learning principles were subsequently grouped into two categories which reflected whether they could be applied where there

was ‘little/no movement’ recovery or whether they would be used to ‘augment’ the physical practice.

Evidence suggesting that stroke survivors may not be able to engage in implicit learning in the same way as individuals without a CNS lesion was discussed. This established a need to identify the effectiveness of the application of motor learning principles with stroke survivors. The narrative review of the published literature in this field revealed that robust systematic reviews existed for the application of intensity of practice and aspects of practice specificity i.e. task specific practice. These were therefore not included within the subsequent systematic review for this thesis. The application of feedback had also been investigated, however, there were limitations in this body of work, therefore this was included within the present review.

Twenty five studies were subsequently included. Closer examination of these studies revealed considerable heterogeneity of outcome measures within the impairment domain of the ICF. In order to provide summary findings from this review therefore, the decision was taken to exclude studies that had not evaluated outcome using a measure within the activity domain. Sixteen studies were subsequently taken forward into the summary analysis and where more than one study had used an outcome measure meta-analysis was carried out.

Table 23 in chapter four provides a summary of the findings from the systematic review. Individual studies showed statistically significant results in favour of the experimental intervention for the application of motor learning principles within the no/little movement/lower limb category for the Timed Up and Go ($p>0.01$ Ng and Hui-Chan, 2009) and in the no/little movement/upper limb category for the Frenchay Arm Test ($p=0.0005$ Ertelt et al., 2007). Where more than one study used the same outcome measure meta-analysis was carried out. The meta-analysis results for both these categories for timed walking speed and the Action Research Arm Test were not statistically significant (Timed walking speed, $p=0.57$ and Action Research Arm Test, $p=0.11$). The only motor learning principle included within the no/little movement category was ‘priming’,

therefore these results represent the effects of the application of this motor learning principle only.

Meta-analysis of three outcomes in the augmenting/lower limb category found no effect of the motor learning principles included in this category (Berg Balance Scale, p=0.77; Timed Up and Go, p=0.84 and timed walking speed, p=0.73). Results of the augmenting/upper limb category were derived from three individual study findings as meta-analysis was not possible, these studies all showed a statistically significant result in favour of the experimental intervention. (Box and Block Test, p=0.015 (Carmeli et al., 2011); Action Research Arm Test, p=0.05 (Crow et al., 1989) and Chedoke Arm and hand Inventory, p=0.025 (da Silva et al., 2011). Interpretation of findings from the augmenting/lower limb category reflected the effects of different motor learning principles (practice specificity and feedback). The inclusion of more than one motor learning principle within a category for the purposes of meta-analysis was criticised in chapter four as it prevented any ability to discern an effect of either motor learning principle. A recommendation for reviews in the future to avoid such categorisations was therefore made.

The systematic review limited the inclusion of studies to only those which were designed as RCTs. It was intended that this inclusion criteria would increase the validity and reliability of any subsequent findings of the review. In light of the lack of RCTs within this field of rehabilitation however further reflection was given to this decision. Alternative study designs may offer different insights into understanding alternative aspects of the application of motor learning principles (Black, 1996). Thus their inclusion within the formal review may have proven useful. It is worth noting though that the extensive literature search that was undertaken as part of the systematic review identified a number of studies which did not meet the inclusion criteria but were reviewed as part of the background chapter for this thesis. This body of work has also been used to inform the development of the novel intervention discussed later on in this chapter.

The paucity of empirical evidence surrounding the application of motor learning principles in physical rehabilitation of movement impairments following stroke would suggest that further work needs to be carried out before moving forward. However their application to clinical practice is already established through the work of pioneers such as Carr and Shepherd (2003). Further pilot/evaluative work does need to be continued into the application of each of the motor learning principles, but as was proposed in chapter two of this thesis, the use of a framework could help to reduce the heterogeneity currently observed within both research and clinical practices and provide a common method of communication. The framework presented below (see figure 37) has been modified from that used in the systematic review because that framework included the categorisation of the motor learning principles into the two categories of 'no/little movement' and 'augmenting'. During the discussion of the findings of the systematic review this categorisation was deemed inappropriate because motor learning principles related to instructions, practice specificity and practice intensity could be applied to a physical therapy intervention even when there is no movement recovery.

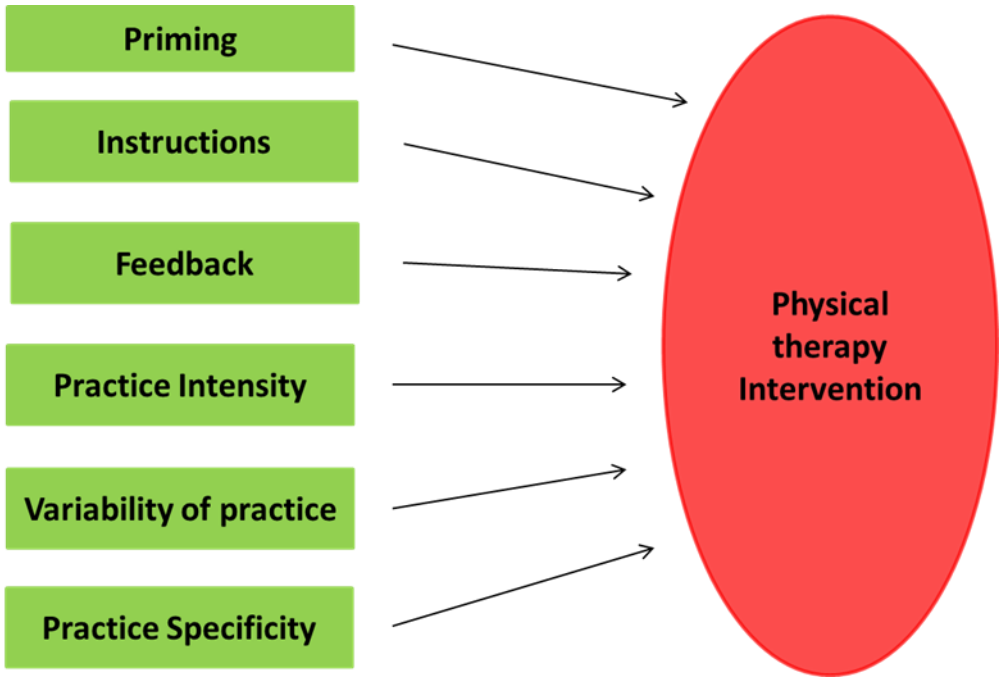


Figure 37: Revised motor learning framework

The following section summarises the findings from the feasibility study of FST in people later after stroke.

## 7.3 Summary from Functional Strength Training Trial

Muscle weakness is a common symptom of stroke, therefore strength training interventions are recommended as part of therapies targeting movement recovery following stroke (NICE guidelines, 2013). Functional Strength Training is designed to increase muscle strength and subsequently increase an individual's ability to participate in activities of daily living. Previous work designed to investigate the feasibility of delivering FST was limited to stroke survivors who were within the first three months after stroke. Physiological differences underpinning the recovery processes in the early and chronic phase of recovery may mean that the impact of FST is different in people within these different time phases of recovery. Delivery of FST to people in their own homes as opposed to a hospital setting may also affect the feasibility of studying this intervention in this group of stroke survivors. A phase II trial was therefore carried out to investigate the feasibility of conducting a study which delivers FST to improve upper limb and lower limb activity in people who were between six months and five years after stroke. The following provides a brief summary of the findings, the implications and further discussion of these has been given in section 5.4.

Delivering the intervention to people in their own homes had resource implications in terms of both time and cost. The initial recruitment strategy had to be expanded to include therapist referral as well as via the original plan for invitation by letter. By expanding the recruitment strategy the study was however able to achieve its' target of two participants per month. Inclusion criteria were altered to include those individuals who presented with the clinical features of an anterior circulation stroke rather than relying on imaging information only. This change reflected the need to assess participants for inclusion when neither the research team nor the clinical team were able to

access imaging information at the time of screening. This resulted in the inclusion of some individuals with a posterior circulation stroke.

Findings from the study suggested that two intervention groups (FSTUL and FSTLL) each acting as the comparator for the other may not be suitable for future studies because of the potential for a cross training effect. This was noted because participants receiving the upper limb intervention made improvements in the lower limb measures. These findings should be interpreted cautiously as the number of participants able to complete the outcome measure were small and therefore may not be generalisable. Despite this a more appropriate comparator for FST to the lower limb would be desirable as the control group intervention in future investigative studies.

The intention had been to deliver the intervention for up to 24 hours per participant however this did not prove possible because of cancellations by both the research team and the participants. On average each participant received 15.94 hours of the intervention. Arguably speaking some cancellation is to be expected when attempting to deliver such an intense intervention however methods for managing sickness or leave on behalf of the research team could be planned for prior to study start up. Future studies may also benefit from systematically investigating reasons for participant cancellation so that where possible these could also be addressed.

The clinical findings from the study suggested an effect for FSTUL for the ARAT ($p=0.046$) but not FSTLL for the FAC ($P=0.573$) and there was no effect from either intervention at follow up. Reasons for this have been explored in more detail in chapter five however it is possible that neither intervention was delivered at a dose sufficient to achieve any long term effects. It is also possible that the participants were not able to transfer the functional activities that they were practising within the intervention phase into ‘real-life’.

The following section will go on to discuss the development of the ‘novel’ intervention by incorporating findings from the formal studies presented in this thesis and evidence from the literature presented earlier in this thesis.

## 7.4 Developing FST within a motor learning framework

It was the intention of this chapter to present a novel intervention which had been developed from the findings of both the systematic review and the phase II study in order to fulfil the final aim of this thesis. However in light of the reflections made following both studies it is likely that further development work is required before proceeding to the identification of a definitive intervention and subsequent evaluation. The following sections reflect on the findings from the systematic review and phase II study in order to suggest future developmental steps that relate firstly to a novel intervention and secondly to future study designs.

### 7.4.1 Development of novel/refined intervention

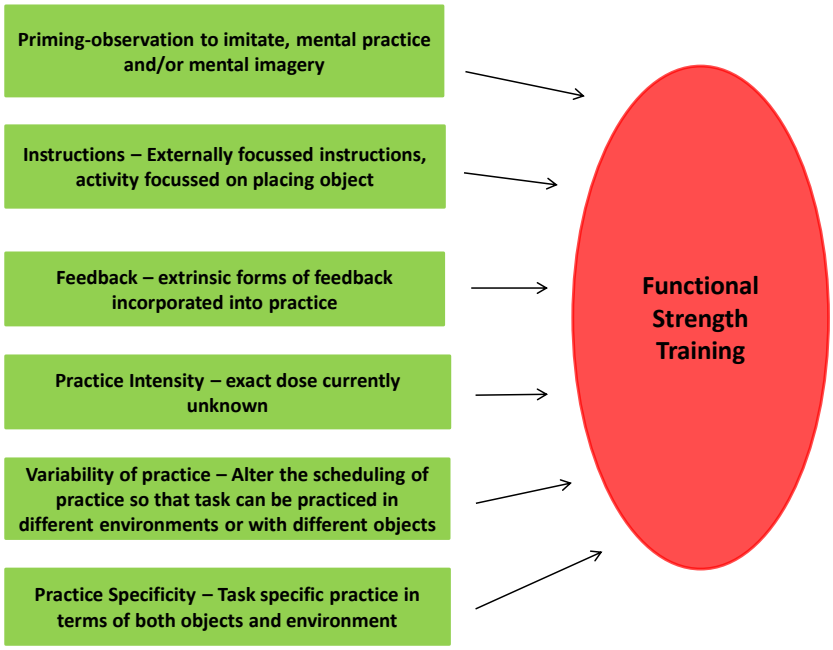


Figure 28: Diagram to show how Functional Strength Training could be placed in motor learning framework

The diagram above illustrates how Functional Strength Training could be refined to incorporate motor learning principles. The description for each of these is given below.

- Priming (evidence from present systematic review)
  The participant will be asked to engage in interventions that apply the priming motor learning principle, this could include observation to imitate, mental practice and mental imagery as some examples.
- Instructions (Fasoli et al., 2002b)
  The instructions for the physical practice of the task will incorporate an external focus. In the drinking scenario the participant will be asked to take the cup to their mouth and not to focus on the position of the arm.
- Feedback (evidence from this systematic review)
  Extrinsic forms of feedback incorporated within the physical practice.
- Practice intensity (Cooke et al., 2010a, Veerbeek et al., 2011)
  Exact dose is currently unknown.
- Practice variability (Cauraugh et al., 2007, Deprey, 1999)
  In the drinking scenario this could be applied by changing the type of cup that the participant drinks with or changing the environment where the activity is practiced. Random scheduling of the practice would be applied.
- Practice specificity
  This refers to the similarity between the task practice conditions and the final task that needs to be learnt. Task specificity as one application of this principle is an integral part of functional strength training and is strongly advocated in movement rehabilitation therapies after stroke (Langhorne et al., 2010). The functional activity that will be focussed on will therefore be identified before commencing any of the experimental intervention (goal setting). The environment can also form another aspect of practice specificity with practice taking place in context specific environments (evidence from present systematic review).

As identified in chapter four synthesis of the findings from the systematic review was limited because of a lack of robust clinical trials investigating the application of motor learning principles promoting movement recovery after

stroke. Development of this new/refined intervention was therefore made using evidence gained from the literature included in both the systematic review and the narrative review of literature described in section 2.1.3. A critique to this approach is given in chapter 8, in the following sections developmental work relating to the intervention will be described.

#### *7.4.1.1 Proposals for future developmental work of the novel/refined intervention*

- Participant characteristics

Reflection on the inclusion criteria for the phase II study investigating FST in section 5.5 led to the suggestion that further work needs to be carried out in order to investigate which participants would respond most effectively to FST. Secondary analysis of the findings from the study revealed no relationship between any of the participant characteristics that were collected and change in the outcome measures for either the FST upper limb or lower limb intervention, although this outcome was to be expected in light of the relatively small numbers of participants within this study. A review of the individual studies included as part of the systematic review similarly revealed no apparent relationship between data collected on participant characteristics and response or not to the application of the motor learning principles.

Future development of FSTML therefore could include investigations to determine whether any participant characteristic (either aspects of behavioural clinical presentation or clinical presentation based on lesion location) could indicate relative responsiveness to FSTML. Studies using single case methodology may be a good way of identifying the characteristics that could be entered into an algorithm as a means of predicting response to the intervention, as this particular methodology lends itself to detailed analysis based on a sample of n=1 (Bowling 2000). An algorithm using a profile with both clinical and imaging features has already been proposed by Stinear (2010) for predicting the recovery of motor function after stroke; therefore this approach seems feasible.

Other characteristics that could be explored may be best determined through qualitative methodology. Previous qualitative studies looking at the use of exercise in people after stroke identified that personal aspects such as lack of motivation and lack of energy inhibited uptake of exercise (Rimmer at al., 2008) but that a desire to improve functional abilities and reduce musculoskeletal problems could motivate people to take part (Jurkiewicz et al., 2011). The inclusion of a qualitative component into any future study of FSTML may help to provide key personal characteristics that would suggest participants were more likely to respond to the intervention or identify characteristics that the future development of the intervention would need to overcome in order to gain participation. The interpretation of these findings would however have to be made cautiously as presumably the participants' willingness to take part in the study in the first place indicates some personal motivation toward exercise. It would also be useful to explore reasons for non-participation in any study of FSTML.

- Dose of FSTML

The phase II study of FSTUL and FSTLL aimed to deliver the interventions for sixty minutes a day over four days a week for six weeks. In the absence of robust data from studies with people in the chronic phase of recovery this dose of FST was informed by the previous trials of FST (Cooke et al., 2010b, Donaldson et al., 2009a). This has been discussed in greater detail in section 5.5. with the conclusion being that a prospective dose finding trial would be desirable. Subsequent secondary analysis of the study findings did suggest the possibility of a dose response relationship for the FSTUL group which supports the premise that further investigation of this aspect of FSTML is warranted.

Confounders within previous studies that have tried to determine dose have tested the study intervention against a placebo or another intervention and therefore have not compared different doses of the same experimental intervention (Cooke et al., 2010a, Veerbeek et al., 2011). Designs which may be more suitable could test FSTML in different doses and measure the point at which an effect plateaus, one example of this is seen in the dose finding trial for mobilisation and tactile stimulation (MTS) which compared doses of MTS of

30 minutes, 60 minutes and 120 minutes (Hunter at al. 2011). This model has been repeated in a more recent study by Han et al. (2013) who investigated the relative effects of either 1 hour, 2 hours or 3 hours of an upper limb rehabilitation programme. Despite an attempt to control for dose, interpretation of the findings from these studies may still be confounded by differing views on what factors constitute dose. For example, it is unclear whether one hour of practice refers to an hour of repetitions of the same movement which, from a pragmatic point of view would seem difficult to sustain from both the point of view of muscle fatigue and/or participant motivation, or whether this refers to an intervention which incorporates all upper limb movement regardless of repletion or body region. The convention applied in the phase II study of FST presented in this thesis was to record time spent carrying out the intervention irrespective of whether this time was spent focussing on wrist and hand movements, shoulder movements or both. Until consensus can be reached the interpretation of the results from dose findings trials need to be supported by the publication of clear protocols identifying how dose has been applied within each study.

Findings from the feasibility study of FST presented in this thesis found no evidence of continuing effect of the intervention at follow up and changes that occurred at outcome following FSTUL were not sustained. Early phase studies of strengthening interventions suggested that there is the potential for a ‘carry-over’ effect of the intervention at least six months after the end of the intervention phase (Patten et al. 2006 and Sullivan et al. 2006). Both Patten et al. (2006) and Sullivan et al. (2006) suggested that the longer term effects of the intervention were the result of the intensive training programmes.

Prospective dose findings studies of FSTML also need to include an investigation into the relative effects of the varying doses of the intervention at time points following the end of the intervention phase. This will determine whether dose could influence the possibility of sustained effects for FSTML.

The previous sections have described how the novel/refined intervention FSTML could be developed, reflection on the findings of both the systematic

review and the phase II study of FST suggest further work needs to be carried out to understand who might or might not respond to FSTML and the need for prospective dose finding trials. The following sections will consider how future studies could be designed.

#### *7.4.1.2 Proposals for future development of the study design*

As discussed earlier one of the findings from the phase II study of FST was the absence of data suggesting that the participants had any lasting effects of the intervention six weeks after delivery of the intervention had ceased. Further investigation into the effects of different doses of FSTML was suggested as one means of determining whether effects could be sustained in the longer term. However if the increased dose of FSTML was delivered as per the phase II study of FST there would be continued reliance on the presence of a therapist to deliver the intervention. Domain two of the NHS outcomes framework emphasises the need to help people with long term conditions such as stroke to live as independently as possible. (NHS England, 2014). The continued development of an intervention that leads to dependency on a healthcare practitioner therefore seems counterintuitive. Thus the design of a future study delivering FSTML could include methods for reducing the reliance on a therapist.

Strategies suggested in section 5.5.5 that have emerged from the literature around the application of motor learning principles, and that might enable participants to engage with FSTML without the presence of a therapist, were through the use of adjuncts such as virtual reality (VR). Virtual reality has the potential to offer a learning environment which is more enjoyable, task and environment specific and is able to provide feedback on performance characteristics (Laver et al. 2011). The systematic review presented in this thesis identified three studies that had used VR as a method for applying motor learning principles (Yang et al., 2008, Mirelman, 2010 and Da Silva Cameirao et al., 2011). The studies by Yang et al. (2008) and Da Silva Cameirao et al. (2011) used VR to facilitate practice specificity and the study conducted by Mirelman (2010) used it to apply feedback. Each of these studies described the presence of research personnel during the delivery of the intervention via VR so it is unclear whether the intervention would be appropriate as a means of

enabling independent practice. The interventions were however successfully delivered by a VR system and resulted in little attrition suggesting that the participants were engaged with the activities and motivated to take part. One method for facilitating independent practice and a reduced reliance on the presence of a therapist which has emerged alongside the use of VR is the concept of tele-rehabilitation. Tele-rehabilitation involves the use of remote conferencing facilities with virtual reality systems to provide training to people in their home without the presence of a therapist or healthcare professional on site (Holden et al., 2007). Tele-rehabilitation can be used to deliver many aspects of stroke care such as nursing interventions as well as exercise programmes and a systematic review of these has reported high levels of satisfaction with interventions delivered in this way (Johansson and Wild, 2011).

Piron et al. (2009) investigated the effects of a tele-rehabilitation programme for delivering an upper limb rehabilitation programme at home compared to traditional physical therapy in a small group of stroke survivors (n=36). The experimental intervention was delivered via a VR system which could be monitored by the therapist through a videoconferencing tool. The VR system was able to provide application of the motor learning principles ‘feedback’ and ‘instructions’ and enabled the participant to practice five virtual tasks. There was no difference between the descriptive characteristics of the groups at the beginning of the study and both groups received equal amounts of the intervention. At the end of the intervention phase both groups had made improvements in the Fugl-Meyer upper extremity test ($p<0.05$) although these improvements were greater in the experimental intervention group (mean change of 5.1 compared to 2.2). Follow up measurements were taken one month after the end of the intervention, results were not statistically significant and graphic representation of the findings did suggest a downward trajectory although this was inconclusive as no further follow up measures were taken. The Fugl-Meyer used in the study by Prion et al. (2009) is a measure of impairment and therefore does not indicate transfer to function (Van der Lee et al., 2001a). This study was also relatively small and there was no evidence of a power calculation therefore findings may not be robust or generalisable (Altman, 1990). Despite this the study does suggest that tele-rehabilitation may

be as effective at delivering exercises to people after stroke as traditional therapy. Future development needs to investigate how best to use this method of rehabilitation for facilitating sustained recovery and also transfer to functional activities.

FSTML delivered via tele-rehabilitation may be able to provide methods for 'long arm supervision', enhanced motivation and remote contact with therapy staff which could prevent the need for intense face to face delivery and possibly facilitate adherence to the exercise regime. Thus the development of FSTML within this model of delivery may be a useful developmental step as part of future study designs.

Another method for delivery of FSTML that could be explored would be via groups. Group exercises have been shown to be as effective in delivering exercises to people after stroke as one to one physical therapy (van de Port et al., 2007) and participants have reported that exercises in a group setting were enjoyable because of the social interaction (Pang et al., 2006). Olney et al. (2006) investigated the relative effects of either supervised exercises in a group setting or unsupervised exercises, participants in both groups showed statistically significant improvements in some outcome measures one year after the completion of the supervised intervention (e.g. six minute walking test: supervised group (0.09+/-0.02 $p<0.001$), unsupervised group (0.05+/-0.02 $P<0.05$)), suggesting some clinical benefit of either intervention however the results were better for the supervised group (Olney et al., 2006). Therefore it may be useful to consider whether FSTML could feasibly be delivered in a group setting and then investigating how this form of delivery would compare to 'one-to-one'. It is possible that the costs of delivering FSTML in a group format may be less than one-to-one however as some stroke survivors have indicated that travel may be a barrier to participation in exercise programmes (Rimmer et al., 2008) the venue for this research study would need to be carefully considered.

Assuming FSTML has the potential to be an effective intervention then one could assume that continued engagement with the exercise programme after

the end of the intervention phase would lead to improved results at follow up. Chapter two discussed some of the barriers to this in people who are within the chronic phase of recovery from stroke. Overcoming some of these barriers such as reduced levels of activity is likely to require a change in behaviour. A review of the literature surrounding intervention fidelity in chapter two identified how certain strategies could be incorporated into a study design to promote behaviour change. Strategies aimed at 'enactment of the treatment skills' relate to the transference of the skills learnt within the research study to 'real-life' settings (Bellg et al., 2004). Presumably if this can be achieved then it is possible that the participants will be able to perceive the 'real-life' effect of the intervention and therefore be motivated to continue with the exercise programme.

One way of achieving this could be through the process of goal-setting. The active engagement of stroke survivors in the rehabilitation process through goal-setting is identified as key within recent guideline and standards documents (RCP, 2012; NICE, 2013). In this case goal setting would facilitate the identification of relevant task specific exercises which could subsequently be incorporated into the FSTML programme. As well as helping to identify contextually relevant activities the process of goal setting is believed to empower the individual, something which has been identified as a factor in increasing adherence to physiotherapy home exercises (Karingen et al., 2011).

Empowerment per se was believed to be the most important factor affecting adherence to exercise programmes (Karingen et al., 2011). As well as goal-setting another factor that was identified as influencing empowerment was the awareness that the individual would be followed-up (Karingen et al., 2011). A strategy which Olney et al. (2006) also identified as a reason for continued engagement in an exercise programme. A feature such as telephone contact for 'long-arm follow up' could be incorporated into future studies investigating FSTML, alternatively the use of 'homework diaries' or log books which are regularly reviewed by the research team may also improve the uptake of the exercise programme. Log books recording engagement with the intervention were used in two studies included in the systematic review however the

reliability of the information obtained from them was not reported (Ng and Hui-Chan 2007; 2009). It is difficult to determine from these studies therefore whether these would be effective in ensuring continued engagement as part of future studies of FSTML.

## 7.5 Summary

The intention for this chapter was to demonstrate how both studies within this thesis, could lead to the development of a physiotherapy intervention that would aim to improve functional activity after stroke. This intervention incorporated the findings from both studies to produce a potential design for a future study evaluating FST with applied motor learning principles (FSTML). Findings from both studies in this thesis indicated further developmental work was required . Therefore suggestions have been made for studies that would investigate who would respond most effectively to FSTML, how much FSTML should be delivered to effect a change in functional performance and methods for altering the delivery of FSTML so that functional changes are sustained in the longer term.

The following chapter will discuss and critique the approach to the development of a physical therapy intervention targeting movement rehabilitation after stroke.

# 8.0 Discussion

Seventy six per cent of stroke survivors are left with movement impairments following stroke (Intercollegiate Stroke Working Party, 2011). Physical therapy interventions after stroke aim to eliminate or minimise the effects of these impairments so that people can return to activities of daily living. This thesis has presented a novel approach to the development of a physical therapy intervention by combining the findings from a feasibility study of Functional Strength Training with that of a systematic review evaluating the effectiveness of motor learning principles used as part of movement rehabilitation after stroke. Physical therapy interventions created within this context may enhance motor learning and facilitate a better return to movement and activities of daily living. Interpretation and discussion of the individual study findings have been reported separately within the context of the studies themselves. This chapter will discuss and critique development of this novel intervention.

Support for the concept of developing a physical therapy intervention within a motor learning context lies within the theoretical stance that recovery of movement following stroke is a form of motor learning (Carr and Shepherd, 2003). This interpretation has been supported by neuroscientists who have used experimental findings to conclude that current physical therapy interventions are founded within a motor learning construct (Krakauer, 2006). It has also been supported by findings from imaging studies that have shown that the physiological changes that underpin both motor learning and movement recovery from stroke are the same (Kleim and Jones, 2008, Nudo and Milliken, 1996, Taub et al., 2002).

The concept of aligning motor learning with movement recovery after stroke is not new as evidenced within the Motor Relearning Programme (subsequently renamed a Movement Science Approach) (Carr and Shepherd, 2003). Despite this the uptake of motor learning principles in movement rehabilitation after stroke has been fragmented (DePaul, 2013). There is evidence of the application of aspects of practice specificity i.e. task specific practice which is widely advocated for use in movement rehabilitation after stroke (Langhorne et

al., 2011), and the application of both feedback and practice intensity have been the subject of systematic reviews (Molier et al., 2010, Subramanian et al., 2010, Veerbeek et al., 2011). There is limited evidence however of the application of the other motor learning principles identified in this thesis as priming, instructions and environmental aspects of practice specificity.

Kleynen and colleagues (2013) have suggested that one reason for the limited uptake of motor learning principles in movement rehabilitation after stroke, observed by DePaul et al. (2011) may be because of a lack of consensus around terminology. The intervention developed in chapter seven of this thesis (FSTML) has embedded a physical therapy intervention within a motor learning framework. The motor learning principles described in this present framework were identified within the context of their theoretical development. This work has led to clear definitions for each of these although it is important to note that these were the result of the author's interpretation of this body of work only, so would still not represent a consensus of opinion.

The greatest potential for failing to achieve consensus arguably lies in the decision to rename the motor learning principle 'mental practice' to 'priming'. The action underpinning the effectiveness of mental practice as a motor learning principle was an increase in excitation within the movement execution system on the CNS. Precedent for the use of the word 'priming' to describe this type of activity had already been established in the literature. This term was not used however within the context of motor learning, but rather to describe a state in which the brain may be more responsive to rehabilitation therapies (Stinear et al., 2008). Continued use of this term within either context may not necessarily be exclusive, but as previously discussed a lack of consensus around terminology has been cited as one reason for the poor uptake of motor learning principles, therefore an agreed 'term' and definition of this motor learning principle would be advantageous for the future development of physical therapies within this framework (Kleynen et al., 2013). Work related to this is currently being undertaken by Kleynen and colleagues through a Delphi study (Kleynen et al., 2013), but the theoretical foundation that underpins the definition of these within the present thesis could contribute to this.

Subsequent application of the motor learning principles in this framework was informed by evidence from studies which evaluated their effectiveness in movement recovery following stroke. In light of the potential differences that stroke survivors may have in engaging in motor learning compared to that of healthy individuals, this is advantageous as the framework can arguably be more effectively generalised to physical therapies designed to improve movement recovery after stroke. This is in contrast to the framework designed by DePaul et al (2011), which has used evidence from studies with healthy volunteers to direct the application of some of the motor learning principles in their framework.

Application of the framework presented in chapter six may be limited by both the changes that were made to the existing framework and inadequacies that are inherent within the studies that have been used to support the motor learning principles.

Chapter seven presented a revised framework of motor learning principles, which had been developed through a critique of the framework used to underpin the systematic review. The existing framework had synthesised the evidence relating to ‘practice specificity’ and ‘feedback’ within one category. For the purposes of the intervention presented in chapter six, meta-analysis was not viable because of the heterogeneity present within the outcome measures, so it was possible to extrapolate findings from the individual studies to inform the delivery of the motor learning principles. If the intervention had been targeted at lower limb movement recovery however this could not have been achieved as meta-analysis had combined the findings from studies evaluating both interventions. Until synthesis of the evidence supporting the application of the individual motor learning principles has been achieved transferability of the revised framework in chapter seven may be more appropriately limited to integration with physical therapies targeting upper limb movement recovery,

The evidence that has been used to guide the application of the motor learning principle to FST&ML have been critiqued within sections of this thesis, whether this is evidence that has been derived from the present systematic review (chapter four) or discussed in the background chapter (chapter two). The weaknesses that have been identified within each of these studies therefore compromise the integrity of the present framework. However, until new evidence emerges in support of the application of the motor learning principles, the design of this framework reflects the available knowledge to date. It is likely that as more robust evidence is published this framework will evolve.

## 8.1 Summary

If motor learning and motor recovery from stroke are effectively the same then it seems appropriate that physical therapy interventions targeting movement recovery after stroke should be informed by motor learning principles. This thesis has sought to present a novel approach to developing physical therapy interventions by establishing feasibility of one such intervention and then embedding it within a motor learning framework.

## 9.0 Conclusion

This thesis set out to address the following aims:

The aims of this thesis are to:

- Aim 1: To systematically identify the relevant literature for inclusion in a literature review according to a motor learning framework.
- Aim 2: To seek to quantify the findings from the review through meta-analysis where appropriate.

    Objective 1: Establish the evidence for the effectiveness of the application of motor learning principles to promote motor learning after stroke.

- Aim 3: To carry out a phase II randomised controlled trial to determine feasibility of a physical therapy intervention – Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke.

    Objective 2: Establish feasibility of Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke by determining likely rates of recruitment.

    Objective 3: Establish feasibility of Functional Strength Training for improving upper limb function and walking in people between six months and five years after stroke by testing procedures for acceptability including the choice of outcome measures and the pragmatics of delivering the interventions.

    Objective 4: Provide information for calculating a sample size for evaluation trials.

- Aim 4: To present a novel intervention combining the results of the studies conducted fulfilling aims one and two in order to suggest how a motor learning framework could inform the delivery of physical therapy interventions as part of movement rehabilitation after stroke.

Aim 1 and 2:

A systematic review of the effectiveness of the application of motor learning principles applied to people after stroke to promote motor learning was conducted within the context of a motor learning framework that had been developed through a review of the theoretical literature. Interpretation of the findings from the review offered some support for the effects of the application of motor learning principles as part of movement rehabilitation after stroke. Although summary analysis was limited by heterogeneity of the outcome measures used in the individual studies. Findings about the effects of 'practice specificity' and 'feedback' were difficult to extrapolate because of the categorisation used within the design of the motor learning framework. Future reviews of the motor learning principles should avoid any categorisation and evaluate the evidence for each of the motor learning principles separately.

Aim 3:

A phase II randomised controlled trial of Functional Strength Training in people between six months and five years after stroke proved that both Functional Strength Training for the upper limb and Functional Strength Training for the lower limb were feasible. Although not inherent within the aims of a phase II study, the results suggested some initial evidence of efficacy for the upper limb intervention but not the lower limb. However this interpretation needs to be tested in an appropriately powered definitive trial. The findings from the present study suggested the possibility of a cross training effect between the two intervention groups therefore future trials should avoid this design and include a control group for both the upper limb intervention and the lower limb intervention.

Aim 4:

The findings from both the systematic review and the phase II trial were combined to suggest a future intervention that might enhance movement recovery of stroke survivors within the chronic phase of recovery from stroke. Proof of concept and feasibility of this intervention (Functional Strength Training with Motor Learning) needs to be tested.

The underlying goal behind both motor learning and physical therapy interventions targeting movement recovery after stroke is inherently the same. Thus, by embedding physical therapies within a motor learning context it may be possible to enhance their effects. This thesis has aimed to present a novel intervention developed within this approach; this work was supported by a robust investigation of the relevant literature evaluating the application of motor learning principles as part of movement rehabilitation after stroke. The findings from this work were then added to the findings from a study of a physical therapy intervention. Thus feasibility of this intervention was established before developing it within the motor learning context, future work is now required to achieve consensus for this approach.

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## Abbreviations

| | |
|---|---|
| 6MWT | Six Minute Walk Test |
| AMED | Allied and Alternative Medicine |
| ARAT | Action Research Arm Test |
| BBS | Berg Balance Scale |
| BBT | Box and Block Test |
| CI | Confidence interval |
| CINAHL | Cumulative Index to Nursing and Allied Health Literature |
| CNS | Central nervous system |
| CPT | Conventional physiotherapy |
| CTIMP | Clinical Trial Involving Medicinal Products |
| DLPFC | Dorsolateral prefrontal cortex |
| EMBASE | Excerpta Medica Database |
| EMG | Electro Myographic |
| FAC | Functional Ambulation categories |
| FAT | Frenchay Arm Test |
| fMRI | Functional magnetic resonance imaging |
| FST | Functional Strength Training |
| FSTLL | Functional Strength Training lower limb |
| FSTUL | Functional Strength Training upper limb |
| GP | General Practitioner |
| ICC | Intraclass correlation |
| ICF | International Classification of Functioning, Disability and Health |
| IQR | Interquartile range |
| LACI | Lacunar infarct |
| LL | Lower limb |
| MAS | Motor Assessment Scale |
| MCID | Minimal clinically important difference |
| MEDLINE | Medical Literature Analysis and Retrieval System Online |
| ML | Motor learning |
| MRC | Medical Research Council |
| MRMI | Modified Rivermead Mobility Index |
| N | Number of participants |
| NHPT | Nine Hole Peg Test |
| NNT | Number not treated |
| OTI | Observation to imitate |
| PACI | Partial anterior circulation infarct |
| PAS | Patient Administration System |
| PEDro | Physiotherapy Evidence Database |
| PET | Positron emission tomography |
| PIS | Participant Information Sheet |
| POCI | Posterior circulation infarct |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RA | Research Associate |
| RANCOVA | Rank based analysis of covariance |
| RCTS | Randomised control trial |
| REPS | Repetition |
| REVMAN | Review Manager |

| | |
|---|---|
| RM | Repetition maximum |
| RT | Research Therapist |
| SD | Standard deviation |
| SMD | Standardised mean difference |
| SRD | Smallest real difference |
| STREAM | Stroke Rehabilitation Assessment of Movement |
| TACI | Total anterior circulation infarct |
| TENS | Transcutaneous Electrical Nerve Stimulation |
| TMS | Transcranial magnetic stimulation |
| TUG | Timed Up and GO |
| UL | Upper limb |
| VR | Virtual reality |
| WHO | World Health Organisation |
| WMFT | Wolf Motor Function Test |

# Appendices

## Appendix 1

Mares K, Cross J, Clark A, Barton G, Poland F, Watson W, McGlashan K, Myint PK and Pomeroy VM. Functional Strength Training could enhance upper limb function but not walking 6+ months after stroke: FeSTivaLS Trial. Archives of Physical Medicine and Rehabilitation, in review.

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Abstract: Abstract
Objective: Functional Strength Training (FST) might enhance recovery after stroke. The aim was to evaluate the efficacy of FST for enhancing upper and lower limb motor function at least six months after stroke.
Design: Randomised, observer-blind trial. Measures were undertaken before randomisation (baseline), after six weeks intervention (outcome) and six weeks thereafter (follow-up).
Setting: Participants' own homes.
Participants: Participants (n = 52) were six months to five years post-stroke with difficulty using their paretic upper (UL) and lower limbs (LL)
Interventions: Participants were randomised to FST-UL or FST-LL by an independent randomisation service with allocation concealed from the research team until after baseline. Interventions were delivered for up to four days each week for six weeks.
Main outcome measures: Primary outcomes were Action Research Arm Test (ARAT) and Functional Ambulation Categories (FAC). ARAT analysis ranked individuals and compared mean rank, based on a regression model, between the two groups using the non-parametric bootstrap. Analysis of FAC used the proportional odds model.
Results: ARAT scores were significantly lower in the FST-LL group at outcome (14.2, 22.9, p=0.042) and follow-up (15.6, 20.3, p=0.019). There was no difference in FAC scores between groups at outcome (p=0.654) or follow-up (p=0.925). The proportional odds assumption for FAC was tested and no reason was found to reject the fit of the model (outcome: p=0.964); follow-up: p=0.821).
Conclusion: This early-phase trial found that FST could improve motor function of the upper but not lower limb between 6 months and 5 years after stroke.

**Cover Letter**

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16 September 2013

Professor A W Heinemann
Co-Editor-in-Chief
Archives of Physical Medicine and Rehabilitation

Dear Professor Heinemann,

**Re: Functional Strength Training could enhance upper limb function but not walking 6+ months after stroke: FeSTivaLS Trial**

As requested in your e-mail of 4th September the above manuscript reporting the FeSTivaLS Trial has been edited to reduce the duplicative content with the publication of the protocol (Mares et al Int J Stroke 2012;7:86-93). If this present version of the paper still evokes copyright problems then please let me know and I will edit some more.

On behalf of my co-authors I would be grateful for your consideration of the above revised paper for publication in Archives of Physical Medicine and Rehabilitation. I confirm that this paper has not been published elsewhere and is not submitted to another journal.

This paper has ten authors. Each person qualifies for authorship because (a) they made a substantial contribution to conception and design or acquisition of data, or analysis and interpretation of data; (b) drafted the article or revised it critically for important intellectual content; and (c) provided final approval of the version to be published. This was a randomised controlled trial of a complex intervention requiring the intellectual and hands-on research expertise of the authors of this present paper.

I confirm that people named in the acknowledgements section have provided permission.

Any comments that you and reviewers may have on this paper we will be pleased to consider.

Yours sincerely,

VM Pomeroy

Professor Valerie M Pomeroy
Professor of Neurorehabilitation
Director Acquired Brain Injury Rehabilitation Alliance (UEA)

*Title page with author details

**Running head**: Functional Strength Training after stroke

**Title: Functional Strength Training could enhance upper limb function but not walking 6+ months after stroke: FeSTivaLS Trial**

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Conflicts of interest: None declared

Clinical trial registration number: ISCTN71632550

## Abstract

Objective: Functional Strength Training (FST) might enhance recovery after stroke. The aim was to evaluate the efficacy of FST for enhancing upper and lower limb motor function at least six months after stroke.

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Interventions: Participants were randomised to FST-UL or FST-LL by an independent randomisation service with allocation concealed from the research team until after baseline. Interventions were delivered for up to four days each week for six weeks.

Main outcome measures: Primary outcomes were Action Research Arm Test (ARAT) and Functional Ambulation Categories (FAC). ARAT analysis ranked individuals and compared mean rank, based on a regression model, between the two groups using the non-parametric bootstrap. Analysis of FAC used the proportional odds model.

Results: ARAT scores were significantly lower in the FST-LL group at outcome (14.2, 22.9, p=0.042) and follow-up (15.6, 20.3, p=0.019). There was no difference in FAC scores between groups at outcome (p=0.654) or follow-up (p=0.925). The proportional odds assumption for FAC was tested and no reason was found to reject the fit of the model (outcome: p=0.964); follow-up: p=0.821).

Conclusion: This early-phase trial found that FST could improve motor function of the upper but not lower limb between 6 months and 5 years after stroke.

**Keywords**: Stroke; rehabilitation; walking; upper extremity; physical therapy; exercise; functional strength training

**Abbreviations:** FST: Functional Strength Training; UL: upper limb; LL: lower limb; ARAT: Action Research Arm Test; FAC: Functional Ambulation Categories.

## List of abbreviations:

FST: Functional Strength Training

UL: upper limb

LL: lower limb

ARAT: Action Research Arm Test

FAC: Functional Ambulation Categories

MRMI: Modified Rivermead Mobility Index

TUG: Timed Up and Go Test

9HPT: Nine Hole Peg Test

IQR: interquartile range

LACS: lacunar anterior circulation stroke

PACS: partial anterior circulation stroke

TACS: total anterior circulation stroke

POCS: posterior circulation stroke

## Introduction

People often experience permanent disability after stroke which impacts adversely on everyday life. This is an unsatisfactory outcome which could be ameliorated by the provision of task-specific re-training of everyday function[1]. Participation in functional re-training, however, requires the production of sufficient voluntary activation of paretic muscle to attain the muscle strength thresholds required for everyday activity[2]. Potential way forward is suggested by early phase evidence that Functional Strength Training (FST), for people up to three months after stroke, could enhance upper limb (UL) recovery although it might provide little advantage for the lower limb (LL)[4], except for habitual gait speed [5]. It is not known if these findings are applicable to people who are six months or more after stroke.

Most spontaneous recovery occurs during the first three months after stroke[6]. People who are six months or more post-ictus are often considered have "plateaued". However, further motor recovery in the chronic phase after stroke does occur[7]. Consequently, people who are at least six months after stroke could gain further motor recovery in response to FST. Benefit might not be restricted to people in the sub-acute phase after stroke.

The emergent ***hypothesis*** is that people who are six months or more after stroke gain better motor function in response to FST. The first step in testing this hypothesis is presented in this article which reports a single-centre pragmatic randomised controlled trial. This early-phase trial is congruent with (a) the UK Medical Research Council framework for trials of complex interventions[8] and (b) recognition that advances in stroke rehabilitation will emerge from progressive staging of trials[9]. The aims of the early phase trial reported here were:

- To determine whether FST for upper and lower limb can enhance motor function in people who are 6 months to 5 years after stroke and therefore should be evaluated in a subsequent definitive trial:
- To estimate the sample size and recruitment rate for a subsequent definitive clinical trial.

## Methods

A summary of the methods is given here. A full description is given in the published protocol [10].

### Design, setting, randomization and ethics

A two-group, randomised, observer-blind, early phase trial based in participants' own homes. The assessor who conducted the measurement battery at baseline, outcome and follow-up time-points remained blinded to participants' group allocation throughout the trial. Participants were recruited from: (a) the discharge database of one acute stroke service; (b) the 6-month post-stroke clinic of the same stroke service; and (c) therapist referral. After providing informed consent participants undertook the measurement battery (baseline). An independent randomisation service, who concealed group allocation until contacted by a researcher, then used the baseline Functional Ambulation Category (FAC)[11] and Action Research Arm Test (ARAT)[12] scores to minimise any imbalance in allocation of participants to either FST-UL or FST-LL. In this trial the FAC was categorised as: mild, score 4+ (walk independently on level ground but requires assistance with stairs, slopes etc); moderate, score 3 (requires the verbal supervision and/or stand-by help of one person); severe, score 2 or less (the continuous or intermittent assistance of one person is needed). The ARAT was split into categories of: mild, score 39-57 (when 57 indicates normal completion of all items); moderate, score 20-38 (38 = able to complete all items but either slowly or abnormally); severe, score 0-19 (when 19 indicates the ability to complete all items in part). The design of allocation of participants to either to FST-UL or FST-LL was used to minimise the potential confounder of one group receiving(a) less therapy than the other and (b) an inactive therapy[10]. Although there could be a clinical expectation of a cross-training effect between the upper and lower limbs this is not supported by clinical research evidence[10].

A research therapist provided participants with their allocated intervention for up to one hour a day, four days a week for six weeks. On completion of the intervention phase participants undertook the measures (outcome) and 6 weeks thereafter (follow-up) (Fig 1).

Ethical approval was granted by a local Research Ethics Committee (ref: 09 H0308 147). The Current Controlled Trials registration ID was ISRCTN71632550.

## Study Population and sample size

Study criteria were similar to those in our earlier studies[3,4]:

- aged 18+ years between 6 months to 5 years after a stroke (infarct or haemorrhage) in the anterior circulation (anterior or middle cerebral artery);
- able to walk four steps with support from one person and/or an assistive device, but in 15 seconds unable to step on and off a 7.5cm high block, with either leg, more than 14 times (Step test[13]);
- able to move the paretic hand from lap to table surface, but unable to pick up £1 coins individually and stack four in an even pile;
- able to follow a 1-stage command with the non-paretic upper limb;
- no known pathology contraindicating participation in FST;
- not participating in formal upper or lower limb physical therapy.

A power calculation estimated that 26 participants per group would have 90% power at 5% significance (2-tailed) to detect a change of: (a) 1 point on the FAC[11] with the assumption that the standard deviation (SD) would be 1; and (b) 5.7 points on the ARAT[12,] with the assumption that the SD would be 5.7 [14]. The authors were unable to find published data to inform the choice of the clinical important difference for the FAC. Choice of 1 FAC point was therefore based on the clinical experience that the broad categories reflect walking recovery milestones for stroke survivors.

## Functional Strength Training

FST provided in the present study has been previously described therapist[3,4,10]. In essence FST involves repetitive progressive resistive exercise during goal-directed functional activity[3,4,10]. Examples of exercises used in this trial include variations of:

- reaching, picking up a jug containing water and pouring contents into a container;
- picking up a container and removing the screw lid;
- reaching down to a foot and then using both hands to lace up a shoe;
- picking up and then moving everyday objects of various weights and size to position them in a different locations of diverse heights.

FST-LL exercises included:

- Standing up and sitting down;
- Ascending and descending stairs and/or using a block for step up/step down exercise;
- Practice of balance activity including one-leg standing;
- Walking whilst avoiding and/or stepping over obstacles.

Activities were progressed systematically, increasing the amount of resistance and number of repetitions. Resistance was varied using external resistance bands/weights and also increasing task difficulty through strategies such as decreasing seat height for sit/stand activities and increasing/decreasing the requirement for hand grip span. If participants became fatigued, presenting as increasing difficulty in performing the activities, the therapist initially changed activities or offered a rest period until either one-hour of therapy was completed or it became apparent that the participant was unable to continue with the intervention that day.

## Outcomes

At six months or more after stroke the changes of interest are largely those that make a difference to how people are able to use their more affected limbs for functional activity. Primary outcomes were therefore the FAC[11] for lower limb function, and the ARAT[12] for upper limb function. Secondary outcomes were the Modified Rivermead Mobility Index (MRMI)[15] and the Timed Up and Go Test

(TUG)[16] to assess mobility (lower limb function) and Nine Hole Peg Test (9HPT)[17] to assess hand dexterity (upper limb function).

## Statistical analysis

First, a full-case analysis was performed in which all individuals with outcome data were included according to the assigned treatment group. Second, an intention-to-treat analysis with all individuals included was conducted by imputing the values for those missing. The method for imputing the missing data was iteratively chained equations with all outcome measures included, prognostic baseline factors and treatment group.

ARAT was analysed by ranking each individual and comparing the mean rank, based on a regression model with the minimisation variables included, between the two groups using the non-parametric bootstrap. FAC categories were compared using the proportional odds model with group and minimisation variables included. The proportional odds model assumption was tested. FAC categories were further categorised to ensure that sufficient numbers were included in each category; the classification was 0-1, 2-3 and 4-5. The MRMI was compared between groups by bootstrapping the difference in the mean rank based on a regression model with the minimisation variables included. The TUG was analysed by firstly comparing those individuals who could complete the task and then by comparing the time using a log-transformed linear regression model including group and the minimisation variables. Data for the 9HPT was analysed by comparing the number of people in each group who could complete all 9 pegs in 50 seconds on at least one of three attempts.

To estimate the parameters needed for a formal sample size calculation for a subsequent pragmatic trial the variation in outcome measure was estimated from the primary analysis and the recruitment and attrition rates predicted from those in this trial.

The analysis was undertaken according to the predefined statistical analysis plan, agreed with the Trial Steering Committee prior to the un-blinding of the data. This led to using different specific statistical tests as were specified in the protocol

## Results

### Recruitment, attrition and characteristics of participants

The CONSORT flowchart gives details of screening, recruitment and attrition during this early phase trial (Fig 1). In brief, 1,127 stroke surviors were assessed for eligibility and 1,075 were excluded. The remaining 52 provided informed consent. Twenty-seven participants were allocated to FST-UL with all receiving their allocated intervention and 25 to FST-LL with 23 receiving their allocated intervention. Attrition rates were 11% and 15% for FST-UL and 20% and 16% FST-LL at outcome and follow-up respectively.

Table 1 provides participants' characteristics. In summary, participatns were a mean of 24.4 months after stroke with a mean age of 68.3 years. The median scores for ARAT and FAC were 15.7 (total possible is 57) and 2.5 (total possible is 5) respectively. All characteristics were balanced across the two groups except for stroke classification. The FST-UL group had a higher percentage of people with a partial anterior circulation stroke and the FST- LL had a higher percentage of people classified as having a lacunar stoke or posterior circulatory stroke (see fidelity section).

### Fidelity to trial protocol

All participants received intervention as allocated except one participant who withdrew from the FST-LL group as he wanted FST-UL. The content of FST-UL and FST-LL was consistent with the protocol (Table 2) and the amount of therapy was essentially the same in the two groups (Table 3).

For the participants recruited via referral from therapists it was not possible to access the clinical neuroimaging information in a timely way to confirm stroke location. Inclusion or otherwise was, therefore, based on clinical presentation. This resulted in the inclusion of four participants who were subsequently identified to have a stroke affecting the posterior circulation (Table 1).

## Adverse reactions

No adverse reactions were experienced by any participant in this trial.

## Efficacy of Functional Strength Training

Table 4 displays the results for the primary and secondary outcomes. There was a significant difference in the ARAT scores (primary outcome) between the groups with the lower limb group having a lower score at both outcome ($p=0.042$) and follow-up ($p=0.019$). There was no difference in the FAC scores between the groups at either outcome ($p=0.654$) or follow-up ($p=0.925$). The proportional odds assumption for FAC was tested and no reason was identified to reject the fit of the model (outcome: $p=0.964$; follow-up: $p=0.821$). The only secondary outcome to show a significant difference was the TUG at outcome ($p=0.047$) with the lower-limb group completing the test in a shorter time. However, that analysis only includes individuals who were able to complete the TUG and fewer individuals in the lower-limb group could complete this.

The results of the imputed data, in terms of the effect sizes and significance levels, are similar to those of the observed and are therefore not presented.

Using actual standard deviation data from ARAT and FAC scores from this trial and the drop-out rate, the estimated sample size to provide 90% power at 5% significance for a subsequent multi-centre trial is 150 participants per group to detect a 5.7 unit change in ARAT and 57 per group to detect a 1.0 unit change in FAC.

## Discussion

This trial found that FST provided to people between six months and five years after stroke improved motor function of the upper limb but not the lower limb immediately after a six-week period of therapy and that these results were maintained at follow-up six weeks thereafter. Safety and feasibility of providing FST to people late after stroke in their own homes has been demonstrated. Furthermore the results add to evidence which questions the notion of a recovery "plateau" for upper limb function six months or more after stroke[7]. The sample size for a subsequent definitive pragmatic trial is estimated, based on actual data from this trial, as 150 participants per group.

The present findings of benefit from FST-UL but not FST-LL are similar to those of earlier randomised trials with participants within three months of stroke [3,4]. Combining this evidence is, however, inadvisable because of the different populations of stroke survivors sampled. Interpretation of the present findings also needs to consider that the differences found in earlier trials were not statistically significant [3,4] and that a related intervention called task-orientated progressive resistance strength training enhanced lower limb motor function in people at least one year after stroke[18]. It is possible therefore that earlier observational finding of benefit for FST-LL early after stroke[5] could be replicated in the so-called chronic stroke population. Arguing against this possibility is that the randomisation procedures used in the present trial avoid deficiencies of earlier studies namely: risk of randomisation bias[5,] and comparison with a no-intervention condition[18].

Another strong design aspect of the present trial is avoidance of the potential confounder of comparing experimental treatment to no treatment or to a conventional treatment of lower dose[19]. Participants were randomised to equal doses of either FST-LL or FST-UL. Although the amount of therapy delivered was smaller than planned, the present trial shows that the positive result for the upper limb is unlikely to have been confounded by intensity of therapy as the lower limb group received essentially the same amount (Table 3).

It is possible, however, that improvement potential differs between the upper limb and lower limb irrespective of the amount of therapy. The baseline data (Table 1) show that the median (IQR) ARAT scores were 16.7 (13.5) and 14.8 (12.9) for the upper limb and lower limb groups respectively. The total possible ARAT score is 57 so the percentage of total score for the upper limb group was 29% and for the lower limb group was 26%. Whereas 44% of all randomized participants had a baseline FAC score of 3 or more of the highest possible score of 5. This possible difference in improvement potential could be greater in the upper limb as: (a) there is a tendency for rehabilitation to focus on lower limb rather than upper limb function[20]; (b) the lower limb is used during everyday activity such as moving in and out of a chair; and (c) stroke survivors may exhibit a learned non-use for the upper limb. The present results could therefore have been influenced by differences between the upper and lower limbs in potential for improvement in the so-called chronic phase after stroke.

The recruitment rate of 5% to the present trial was lower than the 9% and 10% of the two earlier trials of FST[3,4]. The present trial recruited people who were living at home a mean of two years after stroke compared with people in an in-patient rehabilitation facility a mean of 20[3] and 34[4] days after stroke. As these studies[3,4] used face-to-face recruitment methods whereas we contacted most people via a letter[10] this suggests that recruitment to a subsequent trial might be higher if face-to-face screening could be conducted

A potential disadvantage of randomising participants to either FST-UL or FST-LL was the clinical expectation of a cross-training effect between the upper and lower limbs mediated by inter-limb coupling mechanisms. Some experimental evidence supports this possibility[22,23] and some does not[24,25]. More pertinent is that clinical research data indicate that stroke survivors who receive upper limb therapy may improve upper limb function but not lower limb and vice versa[25]. The results of the present trial also question the clinical expectation of a cross-training effect between the upper and lower limbs. Randomisation to either FST-LL or FST-UL in a subsequent multi-centre definitive trial is justified.

## Study Limitations

A challenge encountered during the present trial was to ensure timely access by research therapists to neuroimaging data held in the hospital hosting the acute stroke unit. This challenge arose when participants were recruited through referral from community-based therapists who did not have access to neuroimaging data or detailed medical notes. As this was a pragmatic trial the process adopted was that used in clinical community practice whereby therapists make assessments based mainly on behavioural clinical presentation. This procedure resulted in the inclusion of four participants who were subsequently found to have stroke in the posterior not anterior circulation territory. However, this protocol deviation has arguably increased the applicability of these findings to clinical practice. From a pragmatic viewpoint, and learning from the experience of conducting the present trial, it seems sensible to recommend that any subsequent trials of FST in community settings should recruit participants using study criteria that can be replicated in clinical practice[27] whilst also then obtaining the neuroimaging data required for detailed characterisation.

## Conclusions

In summary, a subsequent multicentre trial of FST-UL and FST-LL upper and lower limb function of people 6 months to five years after stroke is justified and informed by the results of the present first-ever trial. The findings of this present trial erode the notion of a recovery plateau after stroke.

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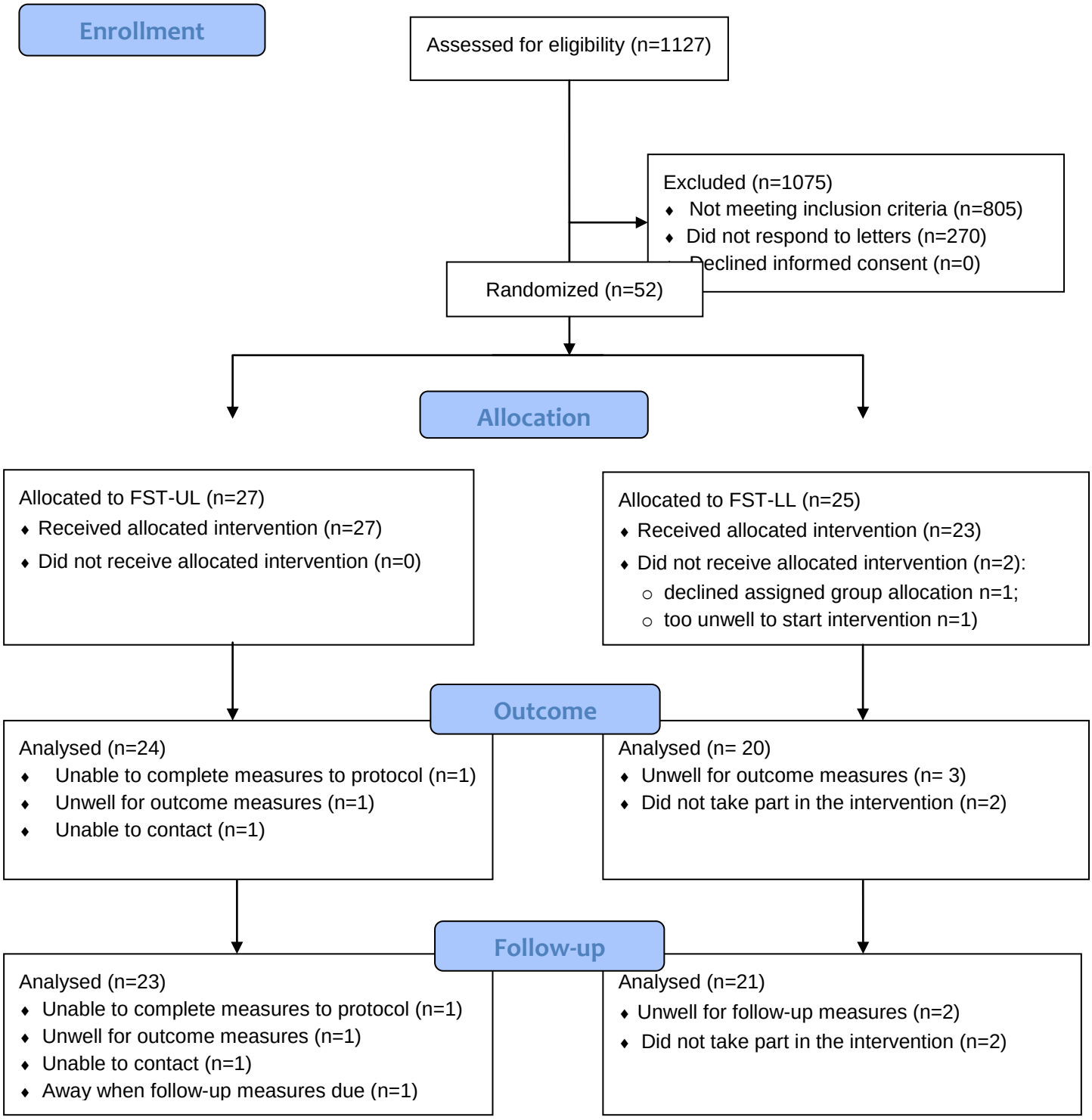
Figure

**Fig 1. Trial Flowchart**
(FST-UL = functional strength training for the upper limb;
FST-LL = functional strength training for the lower limb)



## Table 1. Baseline characteristics of all randomized participants

| | FST-UL (n = 27) | FST-LL (n = 25) |
|---|---|---|
| Age in years * | 67.6 (12.9) | 69.0 (13.7) |
| Months since stroke * | 24.4 (16.6) | 24.4 (13.7) |
| Gender # | | |
| Male | 18 (66.7) | 17 (68.0) |
| Female | 9 (33.3) | 8 (32.0) |
| Hemiside # | | |
| Right | 15 (55.6) | 12 (48.0) |
| left | 12 (44.4) | 13 (52.0) |
| Stroke classification # | | |
| LACS | 6 (22.2) | 9 (36.0) |
| PACS | 12 (44.5) | 9 (36.0) |
| TACS | 3 (11.1) | 6 (24.0) |
| POCS | 3 (11.1) | 1 (4.0) |
| haemorrhage | 3 (11.1) | 0 (0) |
| Action Research Arm Test + | 16.7 (13.5) | 14.8 (12.9) |
| Able to complete Nine Hole Peg Test # | 1 (3.9) | 0 (0) |
| Functional Ambulation Categories # | | |
| 0 | 3 (11.1) | 2 (8.0) |
| 1 | 4 (14.8) | 5 (20.0) |
| 2 | 8 (29.6) | 7 (28.0) |
| 3 | 1 (3.7) | 2 (8.0) |
| 4 | 11 (40.7) | 9 (36.0) |
| 5 | 0 | 0 |
| Modified Rivermead Mobility Index + | 26.8 (3.4) | 26.1 (4.4) |
| Timed Up and Go Test * | 42.3 (31.5) | 49.3 (36.8) |

* = mean (standard deviation); # = number of participants (%); + = median (interquartile range); ST-UL = Functional Strength Training for Upper Limb; FST-LL = Functional Strength Training for Lower Limb; LACS = lacunar anterior circulation stroke; PACS = partial anterior circulation stroke; TACS = total anterior circulation stroke.

**Table 2. Content of Functional Strength Training for participants who completed both baseline and outcome measures: percentage of total therapy time**

| | Group allocation | |
|---|---|---|
| | FST-UL | FST-LL |
| FST-UL provided | | |
| Functional movement training – upper limb | 54.5 | 0 |
| Focus primarily on resistance during function | 26.0 | 0 |
| Facilitation upper limb activity from another body part | 8.7 | 0 |
| Focus on cueing | 5.6 | 0 |
| Gravity-neutral repetitive movement | 5.2 | 0 |
| FST-LL provided | | |
| Functional movement training – lower limb | 0 | 67.8 |
| Focus primarily on resistance during function | 0 | 13.8 |
| Performance of specific movement patterns | 0 | 10.9 |
| Promotion muscle activity and joint movement during function | 0 | 7.5 |

**Table 3. Functional Strength Training for participants who completed both baseline and outcome measures: time-duration and reasons for "missed" intervention**

| | Allocated group | |
|---|---|---|
| | FST-UL | FST-LL |
| Hours of FST-UL for 24 participants | | |
| Total delivered | 410.2 | |
| Total planned | 576.0 | |
| Percentage of planned that was delivered | 71.3% | |
| Mean delivered per participant | 17.1 | |
| Hours of FST-LL for 19 participants | | |
| Total delivered | | 325.7 |
| Total planned | | 504.0 |
| Percentage of planned that was delivered | | 64.6 % |
| Mean delivered per participant | | 17.1 |
| Reasons for "missed" intervention (% of planned time) | | |
| Participant unwell | 2.8 % | 2.4 % |
| Participant cancelled | 5.4 % | 7.5 % |
| Therapist unavailable | 2.8 % | 3.6 % |
| Annual leave/bank holiday | 0.7 % | 1.1 % |
| Data unavailable | 0 % | 0.8 % |

FST-UL = Functional Strength Training for Upper Limb; FST-LL = Functional Strength Training for Lower Limb.

## Table 4. Outcome scores over time for both groups

| | Outcome | | | | | | Follow-up | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | FST-UL | | FST-LL | | Effect size For difference between groups | p-value[+] | FST-UL | | FST-LL | | Effect size | p-value |
| | N | Mean (SD)/ N (%) | N | Mean (SD)/ N(%) | | | N | Mean (SD)/ N(%) | N | Mean (SD)/ N(%) | | |
| **Primary outcomes** | | | | | | | | | | | | |
| ARAT | 24 | 22.9 (14.2) | 19 | 14.2 (14.0) | -5.06 (-9.93,-0.18) * | 0.042 | 24 | 20.3 (15.1) | 20 | 15.6 (14.2) | -5.91 (-10.85,-0.97)* | 0.019 |
| FAC | 24 | | 20 | | | | 24 | | 21 | | | |
| 0 | | 3 (12.5) | | 1 (5.0) | | | | 4 (16.7) | | 2 (9.5) | | |
| 1 | | 2 (8.3) | | 6 (30.0) | | | | 4 (16.7) | | 5 (23.8) | | |
| 2 | | 5 (20.8) | | 4 (20.0) | 0.73 (0.18,2.89) # | 0.654 | | 4 (16.7) | | 4 (19.1) | 0.94 (0.24,3.69) # | 0.925 |
| 3 | | 1 (4.2) | | 0 (0.0) | | | | 0 ( 0.0) | | 2 (9.5) | | |
| 4 | | 13 (54.2) | | 9 (45.0) | | | | 12 (50.0) | | 8 (38.1) | | |
| **Secondary outcomes** | | | | | | | | | | | | |
| MRMI* | 19 | 26.5 (4.7) | 19 | 26.4 (2.0) | -3.2 (-10.0,3.7)* | 0.367 | 18 | 27.2 (3.0) | 20 | 26.5 (3.9) | 0.49 (-4.75,5.72)* | 0.856 |
| TUG - time[1] | 20 | 26.1 (17.1) | 19 | 47.1 (35.0) | 1.61 (1.01,2.59) | 0.047 | 19 | 38.6 (30.2) | 18 | 39.8 (28.3) | 0.93 (0.72,1.21) | 0.592 |
| TUG - ability to complete [2] | 25 | 20 (80.0) | 21 | 19 (90.5) | 3.14 (0.40,39.69) | 0.389 | 26 | 19 (76.0) | 22 | 17 (77.3) | 1.27 (0.23,7.25) | 1.000 |
| 9HPT – ability to complete[2] | 24 | 1 (4.2) | 17 | 0 (0.00) | NA | 1.000[3] | 23 | 1 (4.4) | 0 | 0(0.00) | NA | 1.000[3] |

[+] = p-value for difference between treatment groups * = mean difference in rank; [#] = common odds ratio for a one unit increase; ARAT = Action Research Arm Test; FAC = Functional Ambulation Categories; TUG = Time Up and Go Test; 9HPT = ( Hole Peg Test; [1] the average of those times taken to complete the task; [2] the ability to complete the task at least once; [3] based on Fisher's exact test ignoring factors used in minimisation.

## Appendix II

Mares K, Cross J, Clark A, Barton G, Poland F, Watson W, McGlashan K, Myint PK and Pomeroy VM. The FeSTivaLs trial protocol: A randomized evaluation of the efficacy of functional strength training on enhancing walking and upper limb function later post stroke. International Journal of Stroke, 2012; 8, 374-382

# The FeSTivaLS trial protocol: A randomized evaluation of the efficacy of functional strength training on enhancing walking and upper limb function later post stroke

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***Rationale*** **Functional Strength Training may enhance motor function of people who are more than six months post stroke.**

***Aims*** **to evaluate the clinical efficacy of enhancing upper and lower limb motor function with FST to explore participants' views (expectations and experiences) of FST, and to determine what cost-effectiveness data to collect in a subsequent Phase III trial.**

***Design*** **Randomized, observer-blind trial with embedded qualitative investigation of participants' views of FST ($n = 6$, purposive sampling).**

***Study*** **Participants ($n = 58$), six months to five years after stroke with difficulty using their paretic upper (UL) and lower limbs (LL) for everyday functional activity. All will be randomized to either FST-UL or FST-LL delivered in their own homes for fours days each week for six weeks. FST involves repetitive progressive resisted exercise during goal directed functional activities. The therapist's main input is to provide verbal prompting and feedback.**

***Outcomes*** **Measures will be undertaken before randomization (baseline), after the six-week intervention (outcome) and six weeks thereafter (follow-up). Primary outcomes for clinical efficacy will be the Functional Ambulation Categories (FAC) and the Action Research Arm Test (ARAT). Clinical efficacy analysis will use the proportional odds model for FAC and a Mann-Whitney test for ARAT. Participants' views of FST will be explored at baseline and outcome through audio-taped, semi-structured, narrative approach, interviews. The analytic process for interviews will sort transcribed data thematically and seek categories to inform conceptualization (theory-building). A purpose-designed cost questionnaire will identify what cost resource items are likely to be affected by FST.**

Key words: exercise, physical therapy, rehabilitation, stroke, upper extremity, walking

## Introduction

Many stroke survivors are left with permanent disability. To improve current rehabilitation outcomes the rehabilitation therapy provided might need to be task-specific re-training of functional activity (1). A prerequisite for participation in such repetitive functional re-training is the ability to produce sufficient voluntary activation of paretic muscle to achieve the muscle strength threshold required (2). Indeed, decreased muscle strength may contribute more to loss of functional activity than impaired dexterity, muscle tone, sensation or pain (3). A systematic review suggests that there is capacity for improvement in muscle strength (4). This may not, however, translate into improvements in functional activity unless the strengthening program incorporates that activity (2). Findings of early phase trials of Functional Strength Training (FST) offers evidence of efficacy in people who are within 3 months of stroke (5,6) but it is unclear as to whether these results can be generalized to people who are at least 6 months after stroke.

There are potential clinical differences between the sub-acute and chronic phase populations as spontaneous recovery

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occurs mainly in the first three months after stroke (7). Stroke survivors in the chronic phase have often been perceived to have 'plateaued' in terms of potential for further motor improvement. This assumption is being questioned as many stroke survivors continue to show substantial motor improvement late after stroke because of continued spontaneous recovery and/or rehabilitation interventions (8). It is possible, therefore, that participation in FST after stroke will result in better motor function. However, participation in FST requires stroke survivors to commit time and energy. This commitment has been found early after stroke (5,6) when both physiotherapy and the recovery that can be achieved is valued (8). In the chronic phase, people may cease or reduce ongoing activity (9), even though further motor improvement is possible (7,10).

## Aims

The *hypothesis* is that providing FST to people who are at least 6 months after stroke will improve motor function and ability to perform everyday functional activities. The first steps toward testing this hypothesis in a definitive clinical trial are:

- to find whether there is sufficient efficacy to justify a subsequent trial of FST for upper and lower limb motor recovery in people between 6 months and 5 years after stroke
- to explore participants' expectations and experiences of undertaking FST in their own homes
- to estimate the probable recruitment rate to a subsequent clinical trial
- to estimate the sample size required for a subsequent definitive clinical trial (considering effect size, attrition rate and response variation), and
- to determine what cost-effectiveness data should be collected in a subsequent clinical trial.

This trial adheres to the UK Medical Research Council guidance for evaluation of complex interventions (11) and the need for progressive staging of pilot studies of motor interventions in stroke rehabilitation (12).

## Methods

### Ethics, design and setting

Ethical approval was granted by the Cambridgeshire 2 Research Ethics Committee (ref: 09 H0308 147). The trial is registered on the Current Controlled Trials database (ISRCTN71632550).

This is a two-group, randomized, observer-blind, trial with an embedded qualitative investigation of participants' expectations and experiences of undertaking FST in their own homes (Fig. 1).

The design of this trial considers the potential confounder of comparing experimental treatment to no treatment or to a conventional treatment of lower dose (13) by randomizing participants to equal doses of either FST for the lower limb (FST-LL) or the upper limb (FST-UL). This strategy increases value for money above that provided by an alternative design of a three-group trial, where one group receives either no treatment or, preferably, a placebo. If a placebo were used for FST, it would need to match therapy time, therapist attention and appear to have potential for improving functional ability despite evidence of no effect. Devising such a credible placebo is challenging, if not impossible, because even passive movements and observing a picture of another person's action have excitatory effects on the motor execution system (14). Therefore, the present trial has been designed with two intervention groups (FST-LL and FST-UL). Each group will act as the control for the other.

Allocation of participants to either FST-UL or FST-LL could, however, create a difficulty, as there is a clinical expectation of a cross-training effect. Some experimental evidence supports this clinical expectation of cross-training between the upper and lower limbs during functional tasks (15–17). Although, this effect was absent in lower limbs when they were kept motionless during rhythmic upper limb cycling (18). Furthermore, cross training may be inhibited when the relationship between the upper and lower limb movement is not functionally related (19). In summary, there are inter-limb coupling neuronal mechanisms, but it is unclear from experimental evidence whether or not a cross-training effect may or may not occur during either FST-LL or FST-UL. We have therefore used clinical research findings that stroke survivors who received upper limb therapy statistically improved upper limb but not lower limb and vice versa (20). All participants in this trial will therefore undertake both upper and lower limb measures irrespective of group allocation. In the unexpected event of both groups showing statistically important improvement in the upper and lower limbs, i.e. a cross-training effect is found, then this strategy will not be used in subsequent trials. The two-group design, however, is suitable for initial evaluation of efficacy as spontaneous motor recovery is not expected at this time-point after stroke and clinical research evidence indicates no cross-training effect between upper and lower limb therapy (20).

### Procedure (Fig. 1)

After providing informed consent all participants will undertake the clinical efficacy and cost-effectiveness measurement battery (baseline) conducted by an assessor who is blinded to group allocation throughout the trial. Those participants who have given additional informed consent for participation in the embedded qualitative investigation will undertake a semi-structured interview (A) with a qualitative researcher. This interview is conducted before the participant is aware of their group allocation. Following baseline measures, participants are randomized to either FST-UL or FST-LL and receive their allocated intervention for 1 hour each day, 4 days a week for 6 weeks. On completion of the intervention phase of the

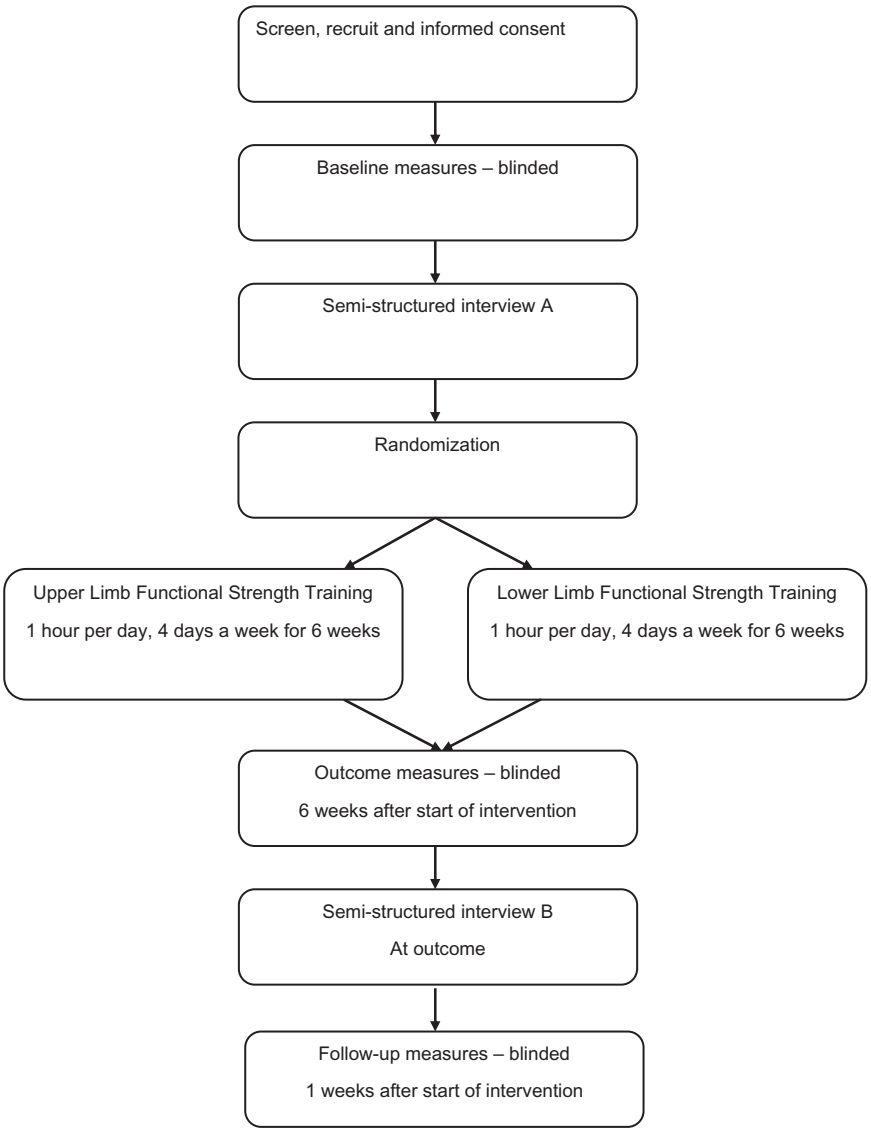


**Fig. 1** Flowchart to illustrate trial design.

trial all participants will undertake the clinical efficacy and cost-effectiveness measurement battery (outcome) conducted by the blinded assessor. Those participants involved in the embedded qualitative investigation will subsequently undertake another semi-structured interview (B) with a qualitative researcher. Six weeks after the last of the 24 intervention sessions, all of the participants will undertake the clinical efficacy and cost-effectiveness measurement battery (follow-up) conducted by the blinded assessor.

## Study population

All participants in this trial will:

- be adults aged 18+ years, 6 months to 5 years after a stroke in the territory of the anterior or middle cerebral artery (infarct or hemorrhage)
- be able to walk four steps with continuous support from one person and/or assistive devices, but unable to step on and off a 7·5 cm high block more than 14 times in 15 s with either their paretic or non-paretic leg [Step test (21)]
- have sufficient voluntary activity in the paretic upper limb to move the paretic hand from position on lap to table top in front, but unable to pick up four £1 coins individually from a tabletop and stack them evenly in a pile
- be able to follow a one-stage command with the non-paretic upper limb, i.e. sufficient communication/orientation to participate in FST
- not have a known pathology which excludes participation in the low intensity exercise training involved in functional strength training, and
- not be receiving formal therapy for their upper or lower limb.

## Sample size

### Clinical efficacy and cost-effectiveness

This study will provide data for a power calculation for a subsequent definitive trial. A formal power calculation is not yet possible but we estimate that 26 participants per group would have 90% power at 5% significance (two-tailed) to detect a change of 1 point on the Functional Ambulation Categories (FAC) (22) assuming a standard deviation (SD) of 1 and 5·7 points on the Action Research Arm Test (ARAT) (23) assuming a SD of 5·7. To allow for an attrition rate of 10% (estimated from our earlier studies) we will recruit 58 stroke survivors.

### Participants' expectations and experiences of undertaking FST

We will use purposive selection to identify six of the participants recruited to the trial. Sample selection aims to maximize diversity in participants' characteristics to increase the validity and transferability of research findings to other settings. The sample will include:

- people taking part in FST-UL and FST-LL
- men and women
- people of ages crossing the age range of the main sample, and
- people of varying levels of functional independence (measured in terms of mild, moderate or severe UL or LL disability).

## Recruitment (Fig. 2)

Potential participants will be recruited from three sources:

- A clinical database of people discharged from the acute stroke service. A clinical team member will check the names of discharged stroke survivors against other hospital records to remove the names of those who have since died. The remaining potential participants will be sent a letter providing information about the trial with a reply slip and stamped addressed envelope (recruitment letter). Potential participants will be asked to return the reply slip to the research team to indicate whether or not they would be interested in taking part in the trial. If this reply slip is not returned within 2 weeks, then one follow-up letter will be sent.
- The 6-month follow-up clinic for all stroke survivors. The Stroke Specialist Nurse will give recruitment letters to all those people likely to meet the trial criteria. If an individual is interested in taking part, they will send the reply slip to the research team.
- Therapy staff will be informed about the trial by the research team and by posters. They will give recruitment letters to all patients likely to meet the inclusion criteria. If individuals are interested in taking part they will return the reply slip to the research team.

Following receipt of a reply slip, the research team will arrange a home visit to complete screening and to provide a Participant Information Sheet. Those interested in taking part in the trial will receive a phone call to confirm this at least 1 week after the date of the home visit. This ensures sufficient time to consider the implications of taking part in the trial. During this time, the potential participant's general practitioner is contacted to confirm that for that individual there is no medical reason precluding performing exercises. Written informed consent is obtained by the blinded assessor carrying out the baseline measures.

## Randomization

Group allocation to either FST-UL or FST-LL will be determined by telephone call to an independent automated system within the Norwich Clinical Trials Unit. Minimization of baseline imbalance between treatment groups will be based on the Pocock and Simon's range method and used to determine the allocation for each participant by Functional Ambulation category (FAC) (22) and Action Research Arm Test (ARAT) (23). The FAC is categorized as: mild, score 4 + (able to walk independently on level ground but needs help on stairs, slopes etc); moderate, score 3 (needs verbal supervision/stand-by help from one person); severe, score 2 or less (needs continuous/intermittent support of one person). The ARAT is categorized as: mild, score 39–57 (57 = able to complete all items normally); moderate, score 20–38 (38 = able to complete all items albeit slowly/abnormally); severe, score 0–19 (19 = able to complete all items partially).

## Service user involvement

This protocol was reviewed by the Norfolk Stroke Service Patients Forum who said they had no concerns. They welcomed the idea of therapy delivered at home and felt that the amount proposed was acceptable and achievable. They expressed a preference for choosing whether they worked on their arm or leg, but reported that if this choice was not available, this would not stop them from being a participant. Ongoing user involvement is provided by the Patient and Public Involvement in Research Group (PPIRES: norfolk-healthresearch.nhs.uk) in the design of information sheets for potential participants. The content and structure of the semi-structured interviews are also informed by Connect guidelines to support participation of people with aphasia.

## Interventions

The research therapists will provide FST to participants for either their paretic upper or lower limb, according to group allocation, for an hour a day, 4 days a week for 6 weeks. This intensity of therapy is planned because repetition of activity may be important for outcome and can be tolerated by people

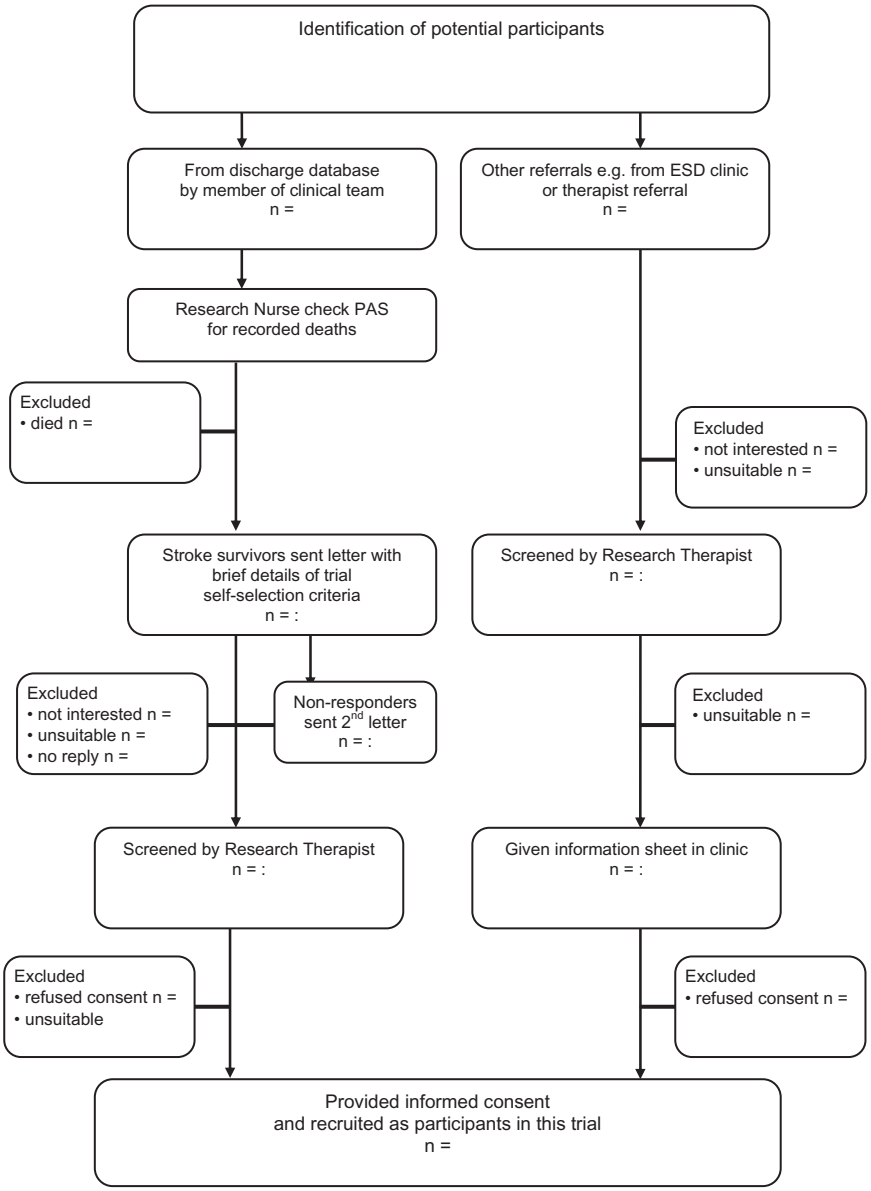


**Fig. 2** Flowchart to illustrate participant recruitment process.

late post stroke (24). There is a possibility, however, that participants could become fatigued so sessions will be paced to give sufficient rest periods.

FST involves repetitive progressive resistive exercise during goal-directed functional activity with the therapist: directing participants' attention to the activity being performed; providing verbal prompting to enhance performance; and providing appropriate verbal feedback to enhance knowledge of performance (5,6). FST is designed to increase ability to produce voluntary muscle force throughout joint range, increase ability to modulate force in muscles/muscle groups appropriate for the activity being trained and improve functional ability (5,6). The first session will identify the specific activities particularly affected by muscle weakness, thus FST will be individually adapted to each participant. Activities are progressed systematically, increasing the amount of resistance and number of repetitions. Resistance can be varied using external resistance bands/weights and also increasing task difficulty through strategies such as decreasing seat height for sit/stand activities and increasing/decreasing the requirement for hand grip span. If participants become fatigued, presenting as increasing difficulty in performing the activities, the therapist will initially change activities or offer a rest period until either 1 hour of therapy has been completed or it becomes apparent that the participant is unable to continue with the intervention that day.

Standardized treatment schedules will be used to record the amount and type of intervention provided. This approach has

been used in earlier trials (5,6). This recording should provide sufficient description of therapy to enable replication of findings and implementation into clinical practice (25).

As this trial intervention is likely to be carried out by different therapists over the time that it will run, adherence to the intervention will be monitored by the lead research therapist. Training for each new therapist who participates in the study will take place before they start any interventions. During the trial, the lead research therapist will monitor how and what therapy is recorded and will also visit all participants at least once during their intervention phase to ensure consistency.

**Functional strength training for the lower limb (FST-LL)**
FST-LL will focus on functional activities involving the lower limbs. Exercises may include variations of:

- standing up and sitting down
- stepping on and off a block
- going up and down stairs
- balance exercises such as standing on one leg, and
- obstacle negotiation.

**Functional strength training for the upper limb (FST-UL)**
FST-UL is based on the key elements of normal upper limb function, i.e. moving the hand into a position and then using it to manipulate objects. The focus is on: improving the power of shoulder/elbow muscles to enable appropriate placing of the hand; improving the production of appropriate force in arm and hand muscles to achieve the specific grasp; and specific interventions for the wrist and finger muscles to maximize ability to manipulate objects. Exercises may include:

- reaching for a jug and then pouring water from it
- picking up a jar and unscrewing the lid
- reaching to the foot to lace up a shoe using both hands, and
- moving everyday objects of different weights to locations of different heights.

## Outcomes

### Primary outcomes

**Clinical efficacy**
These will be the Functional Ambulation Categories (FAC) (22) for lower limb function and the Action Research Arm Test (ARAT) (23) for upper limb function.

### Secondary outcomes

**Clinical efficacy**
For lower limb function we will use the Modified Rivermead Mobility Index (26) and the Timed Up and Go Test (27). The Nine Hole Peg Test (28) will be used for upper limb function.

**Participants' expectations and experiences of undertaking FST**
The subset of six purposively sampled participants will each be interviewed in their homes at baseline and outcome (Fig. 1) by a researcher with expertise in qualitative methodology. Any of this subset of participants withdrawing from the study will still be interviewed at outcome if this is appropriate and they agree. These interviews use a semi-structured format and a narrative approach (29,30). All will be audio recorded. Interview guides (Table 1) will ask participants to share their experiences and views. These will elicit rich detailed data by actively and sensitively probing issues identified during the interviews as having particular importance for the participant. This longer-term approach will facilitate respondents to convey their own story of their stroke experiences, including participation in FST, and to raise issues they see as pertinent, independently of the researcher's initial questions, while still enabling collection of some pre-set broad categories of information across all participants.

**Adverse event monitoring**
Adverse events are not expected but there is a small possibility of an overuse syndrome resulting in limb pain. This will be considered to have occurred if a participant reports or exhibits limb pain (behavioral signs) to the Research Physiotherapist on four consecutive treatment days. If pain occurs then participants will be withdrawn from their allocated treatment but included in the measurement battery according to the intention to treat principle.

**Cost effectiveness**
For costs, we will seek to identify what resource items should be monitored in a future study as likely to be affected by FST and those items about which we are most uncertain. These will be monitored using a purpose-designed cost questionnaire. For effectiveness, we will seek to test the suitability of using the EuroQuol EQ-5D (31) in subsequent trials by using baseline and follow-up data to estimate the validity and responsiveness (32) of the EQ-5D in stroke survivors. Finally, the information on the costs and effects will be used to give an indication of the likely cost-effectiveness of FST, the level of uncertainty associated with these estimates, and to conduct a value-of-information analysis to provide an indication of the expected value of future research (33). Both the cost questionnaire and the EQ-5D will also be carried out at baseline, outcome and at follow-up by the same assessor who carries out the clinical outcome measures (Fig. 1).

### Data monitoring body

Because this is an early phase trial a formal Data Monitoring Committee will not be convened. This function will be provided by the Trial Management Group.

**Table 1** Interview schedules

Interview 1 (Baseline) to capture participants' own stories of their lives before their stroke, at the time of stroke, their post-stroke experience of managing their condition and initial expectations of rehabilitation. This will help contextualise views and expectations of rehabilitation generally and FST specifically.

Indicative questions (all to be probed)

Introduction and checks on convenience and continued willingness to be interviewed

1. Could you please tell me something about your life before you had your stroke?
2. Could you please tell me a bit about your life just before you had your stroke?
3. Can you please tell me what happened when you had your stroke?
4. What about any things done to help you manage things for yourself after the stroke while you were in hospital?
5. Can you tell me about your thoughts about your recovery and things done to help you recover?
6. What kinds of things do you hope to get from the FST that you are taking part in for this research?
7. Can you tell me a bit about any home or family arrangements which help you to get on with your life since you had your stroke?
8. Is there anything else you would like to tell me about your experience of managing your recovery since your stroke?

Interview 2 (Outcome) to access participants' subsequent experiences of taking part in FST, to further contextualise and collect data on their views on the acceptability of FST delivered in a community setting, in relation to specific features of FST.

Indicative questions (all to be probed)

Introduction to say this is to find out how the participant found the FST and about life since last interviewed; checks on convenience and continued willingness to be interviewed

1. Could you please tell me what has been happening in your life since the last time we met?
2. What was it like taking part in the FST exercise?
3. Is there anything you have enjoyed about taking part, and if so, please tell me about it. What was it? Why did you enjoy it?
4. Is there anything you have not liked about taking part, and if so, can you tell me about it? What was it? Why didn't you like it?
5. Are there any ways in which you think it has helped you?
6. Are there any ways in which you feel your life may have changed since taking part in FST?
7. How do you feel about keeping up any of the exercises yourself?
8. How do you feel about the idea of now going on to get other referrals/treatments for yourself?
9. Is there anything else you would like to tell me about your experience of FST?

## Analysis

### Clinical efficacy

In accordance with the intention-to-treat principle all participants will be analyzed according to the group to which they were randomly allocated. Statistical analysis will use a Mann-Whitney test for ARAT, Modified Rivermead Mobility Index, Timed Up and Go and the Nine Hole Peg Test, although if imbalance occurs at baseline, a rank-based analysis of covariance will be used. FAC will be analyzed using the proportional odds model. Secondary analyses will focus on a per-protocol analysis and the analysis of the secondary outcome measures. Adverse events will be recorded and using a Poisson regression model a comparison of the event rate will be carried out. The main aim of the analysis is to estimate the parameters, which will be needed for a formal sample size calculation for a subsequent Phase III trial. To inform subsequent trials the variation in outcome measure will be estimated from the primary analysis and the recruitment and drop-outs rates predicted from those in this trial. Statistical analyses will be carried out using Stata. The analysis will also estimate recruitment and attrition rates to inform subsequent trials (aims 3 and 4).

### Cost effectiveness

A model will be constructed in order to estimate both the mean overall cost and mean overall effect of i) FST-LL and ii) FST-UL, compared to no provision of FST (assuming that outcomes without FST provision would have been the same as at baseline). In both cases, if either FST or no FST were shown to be less costly and more effective then this would suggest that it 'dominates' the other, and represents a cost-effective use of scarce resources. Alternatively, the incremental cost-effectiveness ratio (ICER) associated with FST will be estimated and assessed in relation to a range of cost-effectiveness thresholds, e.g. a threshold of £20 000 to £30 000 per QALY is recommended by NICE (34) in order to estimate the likely cost-effectiveness of the intervention. The associated level of uncertainty will also be characterized by estimating the cost-effectiveness acceptability curve (CEAC). Value of information analysis will also be used to estimate the value of further research (32). Finally, sensitivity analysis will also be undertaken to assess the robustness of conclusions to changes in key assumptions.

### Participants' expectations and experiences of undertaking FST

All audio-recorded interview data will be transcribed verbatim and analyzed using a framework analytic approach, which will elucidate participants' expectations and experiences of undertaking FST. Analysis may be additionally supported by the use of appropriate software such as NVivo 9. This will be used to build more fully conceptualized understandings of experience-based reasons for possible differences in

acceptability of the interventions for different participants and to highlight potential challenges to researchers' assumptions about what may be acceptable and feasible.

The analytic process will sort the data thematically and seek categories to inform conceptualization (theory-building). Such conceptualization will be developed iteratively, so as to emerge from the beginning of the interview data collection process and be completed within the timescale indicated for the wider project. The qualitative analytical approach will draw on narrative analysis approaches to identify meaningful categories and structures in participants' stories. It will combine 'top down' scrutiny of the data (seeking views about acceptability of specific features of FST and specific aspects of delivery of the program in the community) and 'bottom up' scrutiny of the data (seeking and charting categories, concepts and themes which emerge from the narratives presented, about participants' approach to and engagement in the program). It is expected that initial analysis will guide the development of questions in Interview 2. The longitudinal analysis will help establish links between reasons, interactions, experiences and potentially changing views of respondents in relation to the FST program and its acceptability to them. Such findings can be used to inform options in developing the intervention intended to follow this study.

## Summary

This mixed methods protocol describes an early phase trial designed primarily to evaluate whether delivery of FST is acceptable to people living in the community who are at least 6 months after stroke and whether there is sufficient evidence of clinical efficacy to justify a subsequent definitive clinical trial. This trial is congruent with the need to undertake progressive evaluation of stroke rehabilitation therapies to enhance the design of Phase III trials (12,13).

## Acknowledgements

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## Appendix III

Cooke E, Mares K, Clark A, Tallis RC and Pomeroy VM. The effects of increased dose of exercise-based therapies to enhance motor recovery after stroke: A systematic review and meta-analysis, BMC Medicine, 2010, 8: 60

# The effects of increased dose of exercise-based therapies to enhance motor recovery after stroke: a systematic review and meta-analysis

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## ABSTRACT

**Background:**To determine the strength of current evidence for provision of a higher dose of the same types of exercise-based therapy to enhance motor recovery after stroke.

**Methods:** An electronic search of: MEDLINE, EMBASE, CINHAL, AMED, and CENTRAL was undertaken. Two independent reviewers selected studies using predetermined inclusion criteria: randomised or quasi randomised controlled trials with or without blinding of assessors; adults, 18+ years, with a clinical diagnosis of stroke; experimental and control group interventions identical except for dose; exercise-based interventions investigated; and outcome measures of motor impairment, movement control or functional activity. Two reviewers independently extracted outcome and follow-up data. Effect sizes and 95% confidence intervals were interpreted with reference to risk of bias in included studies.

**Results:** 9 papers reporting 7 studies were included. The risk of bias was assessed as low predominantly. Intensity of the control intervention ranged from a mean of 9 to 28 hours. Experimental groups received between 14 and 92 hours of therapy. The included studies were heterogeneous with respect to types of therapy, outcome measures and time-points for outcome and follow-up. Consequently, most effect sizes relate to one study only. Single study effect sizes suggest a trend for better recovery with increased dose at the end of therapy but this trend was less evident at follow-up Meta-analysis was possible at outcome for: hand-grip strength, -10.1 [-19.1,-1.2]; Action Research Arm Test (ARAT), 0.1 [-5.7,6.0]; and comfortable walking speed, 0.3 [0.1,0.5]. At follow-up, between 12 and 26 weeks after start of therapy, meta-analysis findings were: Motricity Arm, 10.7 [1.7,19.8]; ARAT, 2.2 [-6.0,10.4]; Rivermead Mobility, 1.0 [-0.6, 2.5]; and comfortable walking speed, 0.2 [0.0,0.4].

**Conclusions:** Current evidence provides some, but limited, support for the hypothesis that a higher dose of the same type of exercised–based therapy enhances motor recovery after stroke. Prospective dose-finding studies are required.

## BACKGROUND

Exercise-based therapy is known to enhance motor recovery after stroke but the most appropriate amount, i.e. the dose, of therapy is unknown. There is strong clinical opinion that if higher doses of exercise-based therapy could be provided then motor outcome would be improved.

The possibility of a dose-response relationship between exercise-based therapy and motor recovery is supported by the findings of several systematic reviews [1-5] . However, some of the included trials in all of the published systematic reviews were not designed primarily to evaluate different doses of the same therapy. Rather, they were designed to evaluate either different types of therapy, augmentation of one therapy with another or even the effects of a therapy compared with no treatment. Consequently, the results of these systematic reviews are confounded by examination of different types as well as different intensities of therapies. Differentiation of the effects of different types and different intensities of exercise-based therapies is required.

In contrast to widely-held clinical opinion and conclusions of systematic reviews an increased dose of constraint-induced movement therapy (CIMT) resulted in a worse outcome than either a smaller dose of CMIT or a smaller dose of conventional therapy [6]. This unexpected finding echoes those from animal model studies which indicate that a high usage of a paretic forelimb early after experimental stroke is associated with a poorer motor outcome and an increase in size of the brain lesion [7-9] if it is provided early after stroke [10]. It is possible, therefore, that high doses of exercise-based therapy could be detrimental for motor recovery after stroke. This is not the only possibility, however, as experimental animal model studies indicate that more activity, provided in enriched environments, enhances motor recovery more than a standard housing environment [11].. In addition, preliminary investigation suggests the existence of a moderate relationship ($r = 0.45$, $p<0.01$) between the number of repetitions of an exercise and improvement in motor function[12] and post-hoc analysis of three separate research studies of the same therapy suggests greater benefit for a higher dose [13].

Whether an increased dose of exercise-based therapy is beneficial, detrimental or makes no difference to motor recovery after stroke needs to be elucidated. Well designed studies of different doses of the same therapy at different times after stroke in well characterised groups of stroke survivors are required. Before undertaking such studies it will be beneficial to update and refine published systematic reviews to ensure that current evidence informs their design. This paper reports a systematic review and meta-analysis designed to determine the strength of current evidence for providing a higher intensity of the same types of exercise-based therapy to enhance motor recovery after stroke.

## METHODS

### *Design*

The design of this systematic review followed recommendations of the Cochane Collaboration. The review protocol was not published prior to this report other than as part of a PhD thesis [14].

### *Search strategy*

The following databases were searched electronically; US National Library of Medicine Database (MEDLINE); European Medical Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINHAL); Allied and Complementary Medicine Database (AMED); and Cochrane Central Register of Controlled Trials (CENTRAL). An example of the search strategy used is given in Box 1. The initial search was conducted to cover the time period from induction of the databases to November 2008 and this was updated in a subsequent search to include the period up to October 2009. The updated search (December 2008 to October 2009) did not include CINHAL because the host had changed from OVID. A decision was made not to update the CINHAL search because records identified through it in the initial search were also found in other databases.

Reference lists of all articles reporting included trials were searched for any extra possibly relevant records. If any records were identified from the hand searching of reference lists and they came from journals not included on the CENTRAL data base, the contents pages of those journals were hand searched. A hand search of our own private databases of references was also undertaken. In addition authors of included articles were contacted for any unpublished data.

### *Criteria for inclusion of trials*

Types of trial

Randomised or quasi randomised controlled trials with or without blinding of assessors;

Types of participants

Adults, aged over 18 years, with a clinical diagnosis of stroke

Types of interventions

- Experimental and control group interventions identical except for dose. Therapy dose can be described in terms of time spent in therapy and/or of effort expended [15]. Description of time includes: minutes per session; sessions per day/week; and number of days/weeks [15]. Description of effort can be made in terms of the work or power required to perform an exercise for example, resistance training and the amount of weight used [15]. For this systematic review dose refers to the total time spent in exercise-based therapy.
- Interventions investigated were exercise-based (no electrostimulation, splinting or orthotics) to facilitate muscle activity or functional ability;

Types of outcome measures

- Measure of motor impairment – muscle function e.g. Motricity Index, muscle tone, joint range of motion;
- Measures of motor impairment – movement control e.g. co-ordination, dexterity, reaction time;
- Measure of motor activity e.g. Modified Rivermead Mobility Index, Action Research Arm Test, Functional Ambulation Categories, 9 Hole Peg Test.

### *Trial selection.*

The identification of relevant trials was undertaken by two reviewers independently using the pre-set inclusion criteria set out on a predesigned form. Reviewers assessed the record titles and categorised each as 'definitely relevant', 'possibly relevant' or 'definitely irrelevant'. Any title that both reviewers ranked 'definitely irrelevant' was excluded. The reviewers repeated the categorisation process for abstracts and full papers in turn. They did not use the category 'possibly relevant for the full papers. Any disagreements between the reviewers were resolved through referral to full papers and discussion. Trials reported in full papers which were categorised as 'definitely irrelevant' by both reviewers were excluded and reasons documented. Trials which both reviewers categorised as 'definitely relevant' were classified as included trials for evaluation in this systematic review.

### *Assessment of risk of bias*

Assessment of the risk of bias in included trials was undertaken by two reviewers independently for design features using the tool developed by the Cochrane Collaboration [16]. Any disagreements between reviewers were resolved by discussion, referral to full papers and contact with authors for clarification where necessary. A risk of bias plot was produced for the review using categories of low, unclear or high risk.

### *Data Extraction*

Data extraction was undertaken by two reviewers independently using a predesigned form. Any disagreements were resolved by discussion and referral to the original full papers. Trial authors were contacted to clarify results when this was necessary and possible. Data was extracted on:

- Trial design, sample size and attrition;
- Participant characteristics' e.g. age, gender, site of lesion, stroke classification;
- Type of interventions;

- Dose of interventions (sum of treatment hours);
- Measures made at outcome (end of intervention period) and follow-up time-points in terms of average scores for trial groups.

***Statistical analysis of outcome and follow-up data***
Analysis was undertaken, where possible, on an intention- to-treat basis. Trials were not excluded if data was unavailable for subjects who did not complete all the outcome measures. Data analysis was undertaken using the Cochrane statistical package RevMan 4.2.

Effect sizes were calculated as odds ratios (OR) and 95% confidence interval (CI) for dichotomous outcomes and as weighted mean differences (WMD and 95% CI) for continuous outcomes. WMDs were determined initially using a Fixed Effect Model. Where two or more trials had used the same outcome measure, however, and if there was evidence of heterogeneity, the WMDs were estimated from a Random Effects Model. Where it was not possible to combine and compare the outcome measures reported in different trials, then statistical results were described and tabulated individually. Sub-groups were formed by each follow-up time point. No overall analysis was done since this would involve combining subgroups based on the same individuals and could bias the results.

***Synthesis and interpretation***
The results of the statistical analysis were interpreted with reference to the risk of bias in trials, and comparability of participants, types of interventions and dose of interventions.

## RESULTS
Full details of the number of records screened and studies included in this review are given in Figure 1. In summary, 940 potentially relevant records were screened and 31 potentially relevant records were identified. Twenty-two records did not meet the inclusion criteria and are listed in Table 1 alongside the reasons for their omission from this review. The remaining nine records were articles reporting seven studies (three articles reported different aspects of the same study [17-19]. Therefore nine articles reporting seven studies have been included in this review [17-25] (Fig 1).

***Study designs***
Of the 7 included studies three used a multi-centre, observer-blind randomised controlled design. The remaining four studies used a single-centre, observer-blind randomised controlled design (Table 2)

***Participants***
The seven studies included 680 participants (range 20-189) who completed baseline measurements (Table 2). One trial provided additional therapy from a qualified therapist and an assistant, but only the subjects treated by the qualified therapist are included in this review to ensure comparability with the other studies [21]. The mean age of participants in the seven studies ranged from 65.9 years [17-19] to 76.5 years [22] and time since stroke on admission to studies ranged from a median of 5 days [23] to a mean of 35 days [25](Table 2). Full details of participant characteristics are provided in Table 2.

***Interventions***
Four of the studies described the intervention as a 'normal movement' (Bobath) approach [20-23], two studies investigated conventional physical therapy as used in the UK [24,25] and one study based the intervention on an eclectic approach involving task specific training regime following stroke [17-19] (Table 3). The dose of the exercise-based intervention was described in terms of intensity (minutes per day), frequency (times per week), duration (number of weeks). From this the total dose was calculated. The dose of the control intervention was not provided in two studies [21,22]. The dose of the control intervention in the remaining five studies ranged from a mean of 9.2 hours [25] to 27.5 hours [17-19]. The mean dose received by the experimental groups (control plus extra) ranged from 13.8 hours [24] [D] to 91.8 hours [17-19]. Details are provided in Table 3.

***Assessment of potential bias***

The results of the assessment of potential bias are presented in Table 4. In summary, the majority of design elements for included studies were assessed as likely to present a low risk of bias. The exceptions were:

1. The blinding procedure used in one study [23] was assessed as presenting a potential high risk of bias because in the discussion section of the paper it is stated that clinical therapists were not blind to treatment allocation and therefore gave more uni-disciplinary treatment to those participants who were receiving less therapy in the trial.
2. Allocation concealment procedures used in two studies [17-19, 21]were unclear as there were no specific statements about this aspect of randomisation procedure e.g. use of sealed opaque envelopes
3. Incomplete outcome data is possibly present in two studies [21,22] but this is unclear from information presented in the papers. In one trial [21] it was reported that a number of participants died yet there was no reference to the process used for analysis for drop outs. Indeed the results tables suggest that all participants were included in the outcome analysis. One trial [22] provided no reasons for withdrawals and no methods for dealing with participants who withdrew before measurement time-points.
4. One trial appeared to report outcomes selectively [22]. Specifically step-time ratio was included in list of outcomes to be measured yet was not reported in the results section. Also sit-to-stand time, timed walk and functional reach were not measured at baseline yet there was no explanation as to why these were omitted.

***Outcomes***

Extraction of data for one study [17-19] was undertaken considering its 3-group design of placebo, extra arm therapy and extra leg therapy and that all participants undertook all measures. In this present review we considered that the placebo group would act as a control for both experimental groups but that data extracted for the arm group would be that specific to the upper limb and data extracted for the leg group would be that specific to the lower limb. Consequently data analysed in this present review does not include upper limb measures reported for the leg group and vice versa. Two other studies also used a 3-group design [24,25] to compare different types and different doses of physical therapy. The data extracted from these for this review consists of that for the groups receiving the routine amount and extra amount of conventional physical therapy.

The time-points for outcome measures were mostly comparable as they were made between 4 and 6 weeks after the start of therapy except for one study where treatment was provided for 20 weeks [17-19] (Table 3) At follow-up 1 there was more variety between studies with time-points ranging from 12 to 26 weeks after the start of treatment and also 3 months after stroke (Table 3). Follow-up 2 time-points were either 6 months after start of treatment, 52 weeks after start of treatment or 6 months after stroke (Table 3)

1. Motor impairment – muscle function (Table 5)
   Heterogeneity between studies in use of specific measures limited meta-analysis. At outcome there was a trend towards benefit for a higher dose of therapy but effect sizes for 5 of the 10 comparisons were not statistically significant. Significant effect sizes found for individual comparisons were: Motricity Index Leg score, 23.0 [10.0,35.9]; Motricity Index Arm score, 24.1 [9.2,33.1]; knee extension torque, 17.5 [1.1,33.9], knee flexion torque, 15.0 [3.7,26.3]; and hand grip strength, -11.0 [-20.2,-1.8]. Meta-analysis was only possible for hand grip force/strength (2 studies) and this found a benefit for the standard dose of therapy, -10.1 [-19.1,1.2].

   At follow-up 1 the trend toward benefit for a higher dose of therapy remained but only two of the seven individual effects sizes were significant. These were both from the same study [17-19] Motricity Index Leg score, 41.0 [27.7,54.3]; and Motricity Index Arm score, 17.5 [2.3,32.7]. Meta-

analysis was only possible for Motricity Index Arm score (two studies) and the effect size was 10.7 [1.7,19.8].,

No significant differences were found between the two doses of therapy at follow-up 2 (three studies). Meta-analysis was not possible.

2. Motor impairment – movement control (Table 6)
   All of the outcome measures were made at 5 or 6 weeks after the start of therapy but heterogeneity in measures used between studies prevented meta-analysis. Effect sizes were insignificant for all individual comparisons and no trends were discernable in the data.

3. Functional activity (Table 7)
   At outcome, data from one trial relating to Rivermead Mobility Index was omitted because only 3 of 35 participants in the extra therapy group appear to have been included in the outcome data compared to all participants in the control group [21]. Therefore values provided may not have been representative of the entire group. Meta-analysis was undertaken for Action Research Arm Test (3 studies) and comfortable walking speed (2 studies) with effect sizes of 0.1 (-5.7,6.0] and 0.3 [0.1,0.5] respectively. For other measures, the individual study comparisons found a trend towards a better outcome with higher dose for most comparisons but this was weaker than for motor impairment- muscle function. Significance was only found in individual study comparisons in favour of extra therapy for: ability to walk at 0.8m/sec or more with an odds ratio of 3.9 [1.1,13.9] and maximal walking speed effect size, 0.4 [0.1,0.7]. A significant benefit for standard dose therapy was found for one individual study comparison for the Rivermead Gross Function score with effect size -2.0 [-3.4,-0.6].

   At follow-up-1 meta-analysis was undertaken for Action Research Arm Test (2 studies), Rivermead Mobility Score (2 studies) and comfortable walking speed (2 studies) with non-significant effect sizes of 2.2 [-6.0,10.4], 1.0 [-0.6,2.5] and 0.2 [-0.1,0.4] respectively. For other measures the significant effect sizes from individual studies were: Rivermead Arm score, -2.0 [-3.7,-0.3]; 5 metre walk time, -13.6 [-26.2,-1.0]; Functional Ambulation Categories, 1.0 [0.2,1.8]; and ability to walk at 0.8 m/sec or more, 2.8 [0.8,10.6].

   The follow-up-2 meta-analysis (3 studies) found a significant benefit for standard dose therapy for ARAT, subtotal of -6.4 [-12.8,0.00]. A significant benefit in favour of standard dose therapy was also found from an individual study in respect of the Rivermead Arm score with an effect size of -2.00 [-4.0,-0.1]. The benefit for higher dose therapy was, however, maintained for Functional Ambulation Category, 1.0 [0.4,1.6].

## DISCUSSION

Unlike the findings of earlier meta-analyses this present systematic review is not confounded by the inclusion of primary studies which compared both different types as well as intensities of exercise-based therapy. Consequently the present findings refine and also update the results of earlier systematic reviews and meta-analyses. Essentially, some, but limited, support is provided for the hypothesis that a higher dose of exercise-based therapy enhances motor recovery after stroke. There are some indications from the present meta-analysis for benefit from a higher dose for: comfortable walking speed; maximum walking speed; and upper limb muscle function. Meta-analysis was, however, limited by heterogeneity between studies in the measures used and therefore most estimates of effect size were derived from single studies. Those single study sample estimates that were statistically significant were mostly in favour of a higher dose of therapy. In contrast, there are also some indications from meta-analysis for benefit from a standard dose for hand grip force/strength and upper limb functional ability. Consideration of the mostly low risk of bias within included studies provides assurance for these findings.

The more stringent inclusion criteria for studies in this present review resulted in a smaller number of included studies than in previous reviews. For example, the meta-analysis undertaken by Kwakkel and colleagues [3] included 20 RCTs involving 2686 patients. The systematic review reported here also differs from earlier ones because it did not combine different outcome measures in the same analysis. We were concerned to avoid undertaking analyses of sets of heterogeneous measures in a single meta-analysis.

An earlier systematic review concluded that a 16-hour difference in treatment time between experimental and control groups provided in the first 6 months after stroke is needed to obtain significant differences in activities of daily living" [3]. Investigation of the data reported here for a potential dose-response relationship is limited by the relatively small number of comparisons that can be included in a meta-analysis because of the variation in measures used in included studies. However, visual inspection of outcome time-point data (Tables 5, 6 and 7) and data on dose (Table 3) suggests a trend for better outcome with higher dose. The highest doses, however, were of task-specific interventions [17-19] whereas the smaller doses consisted of UK conventional physical therapy [24,25]. This difference could have influenced the results of the present review. It is also possible that differences in effect sizes between studies could be due to differences in underlying standard care. The study by Kwakkel and colleagues [17-19] was conducted in the Netherlands whereas the other four studies took place in the United Kingdom. This could have influenced the results of the present review because there may be important differences in underlying routine care between centres and countries [26]. There may also be differences in standard therapy over time [27]. Therefore the differences in clinical setting for studies may also be influential on outcome. Consequently, this present review which restricted included studies to those investigating different doses of the same therapy to avoid the confound of different types of therapy may itself be confounded by the inclusion of different types as well as different intensities of therapy. Essentially this systematic review highlights the need for prospective dose-ranging studies of specific interventions before undertaking efficacy studies.

None of the doses investigated in included studies emerged from preliminary dose-finding studies. The same observation emerged from in a systematic review and meta-analysis of electrostimulation [28]. Indeed dose-finding has not featured prominently as a precursor to stroke rehabilitation trials [29,30] Without precursor dose-finding studies it is possible that the studies included in this review investigated sub-optimal doses of exercise-based therapies. The case for prospective dose-finding studies as precursors to Phase II and phase III trials of rehabilitation has been made already [29,30]. Nevertheless, we are aware of only one study designed to investigate the relative efficacy of three or more doses of the same rehabilitation therapy [31]. Dose-finding has not featured prominently as a precursor to phase II and phase III trials of rehabilitation therapies.

It is possible that the present review may be influenced by a publication bias as the literature search excluded studies written in a language other than English. A strong publication bias is, however, unlikely to be present the studies included in this present review were also included in previous meta-analyses. In addition, authors of included studies were contacted for any unpublished data.

## CONCLUSIONS

To the best of our knowledge the present systematic review of the effects of dose of therapy is the first to control for the potential confounder of different types of intervention. It has refined and updated knowledge of the effects on motor recovery of the provision of an increased dose of exercise-based therapy after stroke. The findings indicate that there is limited empirical evidence to inform clinical decisions on how much exercise-based therapy is needed to enhance motor recovery after stroke. Further systematic reviews are unlikely to resolve this clinical uncertainty because of the heterogeneity between exercise-based therapies in included studies and the apparent lack of dose-finding studies undertaken as precursors to robust clinical trials. The results of the present systematic review therefore

indicate a need to undertake dose-finding studies of specific exercise-based interventions as precursors to robust clinical trials.

## COMPETING INTERESTS

We gratefully acknowledge: funding provided by The Healthcare Foundation and St George's Charitable Foundation that enabled us to undertake this study. The authors declare that they have no other competing interests.

## AUTHORS' CONTRIBUTIONS

Dr Cooke has made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, revision of manuscript, and has given final approval of the version to be published.

Kathyrn Mares has made substantial contributions to acquisition of data, analysis and interpretation of data, revision of manuscript and has given final approval of the version to be published.

Dr Clark has made substantial contributions to analysis and interpretation of data, revision of manuscript, and has given final approval of the version to be published.

Professor Tallis has made substantial contributions to conception and design, revision of manuscript, and has given final approval of the version to be published.

Professor Pomeroy has made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, revision of manuscript, and has given final approval of the version to be published.

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30. Pomeroy VM, Tallis RC: **Need to focus research in stroke rehabilitation**. *Lancet* 2000;**355**:836-837.
31. Hunter SM, Hammett L, Ball S, Smith N, Anderson C, Clark A, Tallis R, Rudd A, Pomeroy VM: **Appropriate dose of Mobilisation and Tactile Stimulation to enhance upper limb recovery early after stroke: a randomised controlled trial**. Submitted and under review.

**Box 1. Search strategy for electronic databases**

1. exp Stroke/
2. stroke.mp.
3. cerebrovascular diseas$.mp.
4. cerebral vascular diseas$.mp.
5. cerebral vascular accident$.mp.
6. cerebrovascular accident$.mp.
7. (hemipleg$ or hemipar$).mp.
8. 6 or 4 or 1 or 3 or 7 or 2 or 5
9. exp Physical Therapy Modalities/
10. physiotherapy.mp.
11. physical therapy.mp.
12. 11 or 10 or 9
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomised controlled trials.sh.
16. random allocation.sh.
17. double-blind method.sh.
18. single-blind method.sh.
19. 18 or 16 or 13 or 17 or 12 or 15 or 14
20. clinical trial.pt.
21. exp Clinical Trial/
22. ((singl$ or doubl$ or treb$ or trip$) adj25 (blind$ or mask$)).ti,ab.
23. (clin$ adj25 trial$).ti,ab.
24. placebo$.ti,ab.
25. placebo.sh.
26. random$.ti,ab.
27. research design.sh.
28. 27 or 25 or 21 or 26 or 20 or 22 or 24 or 23
29. comparative study.sh.
30. exp Evaluation Studies/
31. follow up studies.sh.
32. (contro$ or prospectiv$ or volunteer$).ti,ab.
33. 32 or 30 or 31 or 29
34. 33 or 28 or 19
35. exercis$.mp.
36. exercis$.sh.
37. exp Exercise/
38. functional strength train$.mp.
39. activities of daily living.mp.
40. neuro facilitation.mp.
41. bobath therap$.mp.
42. motor relearn$.mp.
43. rehabilitation.mp.
44. rehabilitation.sh.
45. exp Rehabilitation/
46. restoration of function$.mp.
47. 35 or 39 or 40 or 36 or 41 or 38 or 42 or 46 or 45 or 37 or 43 or 44
48. intensit$.mp.
49. intensit$.sh.
50. frequenc$.sh.
51. frequenc$.mp.
52. duration.mp.
53. duration.sh.
54. dose.mp.
55. dosage.mp.
56. amount.mp.
57. quantit$.mp.
58. how much.mp.
59. dos$.mp.
60. dosing.mp.
61. doses.mp.
62. amounts.mp.
63. 63. 50 or 53 or 57 or 61 or 51 or 58 or 48 or 59 or 52 or 60 or 56 or 49 or 62 or 54 or 55
64. 64. 8 and 63 and 34 and 12 and 47

Abbreviations
mp=title, original title, abstract, name of substance word, subject heading word

**Table 1. Excluded Studies**

| Study | Reason for Exclusion |
|---|---|
| Ada 2006 | Not a randomised controlled trial. |
| Barreca 2004 | Treatment interventions between control and experimental group differed in content. |
| Dromerick 2009 | Interventions included different time periods for wearing of mitt (not an exercise based intervention) and different doses of shaping, therefore, unable to determine which aspect of this intervention would contribute to functional outcomes. |
| Duncan 2003 | Treatment interventions between control and experimental group differed in content. |
| Fang 2003 | Control group received no intervention, therefore study investigated effects of physiotherapy rather than an increased intensity of physiotherapy. |
| Feys 1998 | Investigated the effects of an intervention not intensity. |
| Fisher 2001 | Not a randomised controlled trial. |
| Green 2002 | Investigated the effect of an intervention in a specific setting not intensity. |
| Kuys 2008 | Not a randomised controlled trial. |
| Kwakkel 2002 | Examination of a subgroup of the original trial (Kwakkel 1999). |
| Moreland 2003 | Progressive resisted exercise - not the definition of intensity used in this review. |
| Nugent 1994 | Not a controlled or randomised controlled trial. |
| Page 2004 | Investigated the effect of an intervention not intensity. |
| Richards1993 | Treatment interventions between control and experimental group differed in content. |
| Richards 2008 | Not a randomised controlled trial. |
| Sivenius 1985 | Extra therapy incorporated components of physical, occupational and speech therapy. It was not possible to isolate the effects of exercise-based therapy. |
| Slade 2002 | Therapy analysed included physical, perceptual and cognitive, washing and dressing, daily living activities, group treatment, joint treatment and splinting and this was analysed as ‘a package’. It was not possible to isolate the effects of exercise-based therapy. |
| Smith 1981 | No specific treatment techniques described. Intensive therapy involved multi disciplinary treatment and therefore difficult to isolate the effects of exercise-based therapy. Control group also given extra treatment if deemed necessary. |
| Sunderland 1992 | Treatment interventions between control and experimental group differed in content. The experimental group also included EMG biofeedback. |
| Wade 1992 | Subjects received physiotherapy immediately or after three months delay, therefore effectively the first half of a crossover study – physiotherapy versus no treatment. Therefore not different intensities of the same physiotherapy treatment. |
| Werner 2002 | Treatment interventions between control and experimental group differed in content. |
| Wolf 2007 | Not a randomised controlled trial. |

**Table 2. Included studies design, participants and attrition**

| Study | Design | Participants | | | | | | | | | | Attrition (cumulative) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number & gender | | Mean (SD) age (years) | | Stroke lesioned hemisphere | | Stroke classification | | Mean (SD) time after stroke (days) | | | |
| | | Control | Extra | Control | Extra | Control | Extra | Control | Extra | Control | Extra | Control | Extra |
| Cooke 2009 | Multi-centre Observer-blind RCT | 38 (21 M) | 35 (22 M) | 66.4 (13.7) | 67.5 (11.3) | 17 right | 13 right | All anterior circulation stroke | | 36.8 (22.5) | 32.4 (21.3) | 7 by 6 weeks 21 by 6 weeks | 3 by 6 weeks 10 by 12 weeks |
| Donaldson 2009 | Single centre Observer-blind RCT | 10 (5M) | 10 (5 M) | 72.7 (14.5) | 73.0 (8.6) | 5 right | 4 right | All anterior circulation stroke | | 13.4 (4.4) | 25.6 (15.5) | 2 by 6 weeks 7 by 12 weeks | 0 by 6 weeks 4 by 12 weeks |
| GAPS 2004 | Multi-centre Observer-blind RCT | 35 (17 M) | 35 (24 M) | 67 (10) | 68 (11) | 15 right | 15 right | TACI = 7<br>PACI = 18<br>LACI = 8<br>POCI = 1<br>unsure = 1 | TACI = 6<br>PACI = 15<br>LACI = 10<br>POCI = 2<br>unsure = 2 | 25 days (range 6-71) | | 0 by 4 weeks 1 by 3 months 1 by 6 months | 1 by 4 weeks 3 by 3 months 4 by 6 months |
| Lincoln 1999 | Single centre Observer-blind RCT | 95 (45 M) | 94 (51 M) | Median 73 (IQR 64-80) | Median 73 (IQR 65-81) | 38 right | 47 right | TACI = 7<br>PACI = 29<br>LACI = 13<br>POCI = 0<br>unsure = 46 | TACI = 9<br>PACI = 31<br>LACI = 11<br>POCI = 0<br>unsure = 43 | 1-5 weeks after stroke | | 5 by 5 weeks 11 by 3 months 14 by 6 months | 7 by 5 weeks 10 by 3 months 13 by 6 months |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kwakkel 1999 & 2002 | Multi-centre Observer-blind RCT | | *Arm group* 33 (16M) | | *Arm group* 69 (9.8) | | *Arm group* 19 right | TACI = 25 PACI = 9 LACI = 3 POCI = 0 unsure =0 | *Arm group* TACI = 19 PACI = 11 LACI = 3 POCI = 0 unsure = 0 | | *Arm group* 7.2 (2.8) | *Arm group* 4 by 20 weeks 4 by 26 weeks 5 by 52 weeks |
| | | 37 (14 M) | *Leg group* 21 (13 M) | 64.1 (15) | *Leg group* 64.5 (9.7) | 24 right | *Leg group* 18 right | | *Leg group* TACI = 17 PACI = 13 LACI = 1 POCI = 0 unsure =0 | 7.5 (2.9) | *Leg group* 7.0 (2.5) | 3 by 20 weeks 3 by 26 weeks 4 by 52 weeks | *Leg group* 5 by 20 weeks 5 by 26 weeks 6 by 52 weeks |
| Partridge 2000 | Single centre Observer-blind RCT | 60 | 54 (52 M) | 76.5 (range 60 – 90) | | 53 right | | No data provided in paper | | No data provided in paper | | 4 by 6 weeks 11 by 6 months | 2 by 6 weeks 10 by 6 months |
| Rodgers 2003 | Single centre Observer-blind RCT | 61 (30 M) | 62 (28 M) | Median 75 (no range provided) | Median 74 (no range provided) | 35 right | 34 right | TACI = 13 PACI = 17 LACI = 29 POCI = 2 unsure = 0 | TACI = 8 PACI = 17 LACI = 34 POCI = 3 unsure =0 | Median of 5 days after stroke | | 10 by 3 months 13 by 6 months | 8 by 3 months 14 by 6 months |

**Table 3. Included studies interventions, intensity and outcome measures**

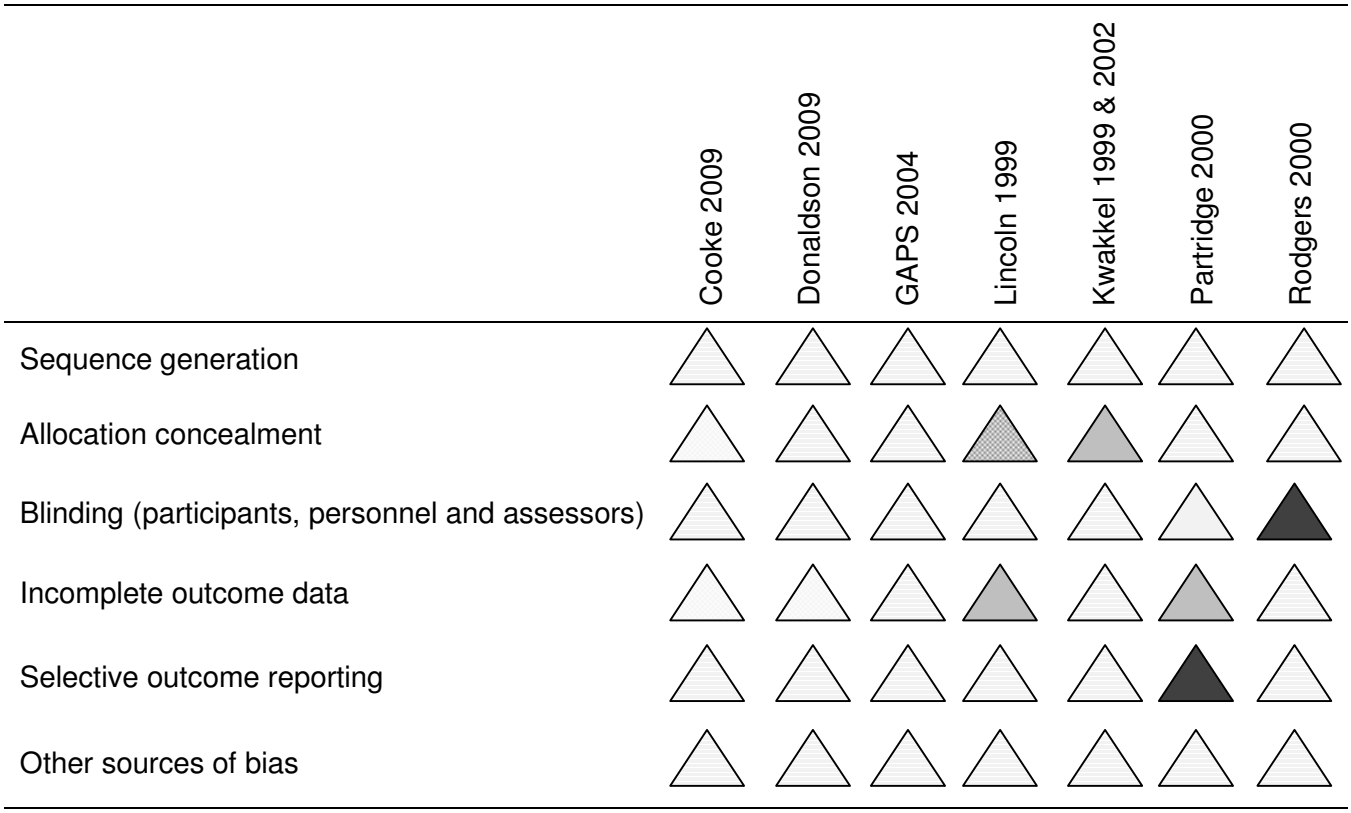
| Study | Intervention | | Intensity - mean hours delivered (SD) | | Measurement time points | | | | Outcome measures |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Extra | Control | Extra | Baseline | Outcome | Follow-up 1 | Follow-up 2 | |
| Cooke 2009 | Conventional physical therapy – lower limb from usual staff | Extra from research staff | 9.2 (6.9) | 23.0 (10.4) | Pre-intervention | After 6 weeks of intervention | 12 weeks after end treatment | NA | ▪ Walking speed<br>▪ Ability to walk at 0.8 m/s or more<br>▪ Modified Rivermead Mobility Index<br>▪ Knee flexion peak torque<br>▪ Knee extension peak torque |
| Donaldson 2009 | Conventional physical therapy – upper limb from usual staff | Extra from research staff | 2.81 (3.7) | 13.8 (27.1) | Pre-intervention | After 6 weeks of intervention | 12 weeks after end treatment | | ▪ Action Research Arm Test<br>▪ 9 hole peg test<br>▪ Hand grip force<br>▪ Pinch grip force<br>▪ Elbow flexion force – isometric<br>▪ Elbow extension force - isometric |
| GAPS 2004 | Treatment broadly based on 'normal movement' (Bobath approach) from usual staff. | | Average 21 (no data) | Average 34 (no data) | Pre-intervention | After 4 weeks of intervention | 3 months after start treatment | 6 months after start treatment | ▪ Rivermead Mobility Index<br>▪ Motricty Index |
| Lincoln 1999 | Treatment based on the Bobath approach from usual staff | Extra from research staff | No data | Median 9.58 extra to control (IQR 4.7-10) | Pre-intervention | After 5 weeks of intervention | 3 months after start treatment | 6 months after start treatment | ▪ Rivermead Arm Assessment<br>▪ Action Research Arm Test<br>▪ Rivermead Motor Assess – gross function<br>▪ 10-hole Peg Teat<br>▪ Maximum grip strength |
| Kwakkel 1999 & 2002 | Routine arm & leg training using evidenced-based guidelines from usual staff<br>*Arm group*<br>Arm training from usual staff<br>*Leg group*<br>Leg training from usual staff | | 27.5 arm & 23.2 leg* | *Arm group* 91.8*<br>*Leg group* 84.2* | Pre-intervention | After 20 weeks treatment | 26 weeks after start treatment | 52 weeks after start treatment | *Arm group*<br>▪ Action Research Arm Test<br>▪ Frenchay Activities Index<br>*Leg group*<br>▪ Comfortable walking speed<br>▪ Maximum walking speed<br>▪ Functional Ambulation Categories |
| Partridge 2000 | Bobath method of treatment from usual staff | | No data | No data | Pre-intervention | After 6 weeks of intervention | 6 months after start treatment | NA | ▪ Functional reach<br>▪ 5-metre timed walk<br>▪ Timed sit-to-stand |
| Rodgers 2003 | Normal movement approach (Bobath) within meaningful activity and task analysis from | | 17.4 | 24.9 | Pre-intervention | None | 3 months after stroke | 6 months after stroke | ▪ Action Research Arm Test<br>▪ Upper Limb Motricity Index<br>▪ Frenchay Arm Test |

usual staff

* calculated using minutes/day data 20 weeks each with 5 treatment days

$ calculated using median 30 days with 0.58 hours a day for control and 0.83 hours a day for extra

**Table 4. Risk of bias for included studies**



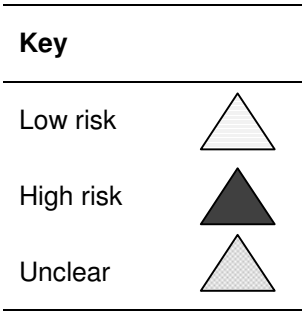



**Table 5 motor impairment – muscle function**

| Time-point | Study | Measure used | Augmented therapy | | Standard therapy | | Mean difference | |
|---|---|---|---|---|---|---|---|---|
| | | | Number subjects | Mean (SD) | Number subjects | Mean (SD) | Effect size | [95% CI] |
| **Outcome** | | | | | | | | |
| 4 weeks after start therapy | GAPS | Motricity arm + leg | 33 | 119.0 (46.0) | 34 | 111.0 (45.0) | 8.0 | [-13.8,29.8] |
| 20 weeks after start therapy | Kwakkel | Motricity leg | 26 | 68.2 (25.8) | 34 | 45.2 (24.8) | **23.0** | **[10.0,35.9]** |
| 20 weeks after start therapy | Kwakkel | Motricity arm | 29 | 53.1 (32.0) | 34 | 28.9 (28.5) | **24.2** | **[9.2,33.1]** |
| 6 weeks after start therapy | Donaldson | Hand grip force | 10 | 71.9 (49.5) | 8 | 64.8 (39.3) | 7.1 | [-34.0,48.1] |
| 5 weeks after start therapy | Lincoln | Hand grip strength | 87 | 0 (25.19) | 90 | 11.0 (36.3) | **-11.0** | **[-20.2,-1.8]** |
| | ***Subtotal – hand grip force/strength*** | | 97 | | 98 | | **-10.1** | **[-19.1,-1.2]** |
| 6 weeks after start therapy | Donaldson | Pinch grip force | 10 | 31.5 (23.1) | 8 | 24.5 (19.7) | 7.0 | [-12.8,26.8] |
| 6 weeks after start therapy | Donaldson | Elbow extend force | 10 | 64.5 (44.6) | 8 | 68.6 (39.6) | -4.1 | [-43.1,34.8] |
| 6 weeks after start therapy | Donaldson | Elbow flexion force | 10 | 76.1 (58.7) | 8 | 75.0 (38.7) | 1.1 | [-44.1,46.3] |
| 6 weeks after start therapy | Cooke | Knee extend torque | 26 | 45.3 (33.2) | 25 | 27.8 (26.3) | **17.5**[a] | **[1.1, 33.9]** |
| 6 weeks after start therapy | Cooke | Knee flexion torque | 26 | 34.0 (23.1) | 25 | 19.0 (17.8) | **15.0**[a] | **[3.7, 26.3]** |
| **Follow-up 1** | | | | | | | | |
| 3 months after start therapy | GAPS | Motricity arm + leg | 32 | 130.0 (44.0) | 33 | 120.0 (42.0) | 10.0 | [-10.9,30.9] |
| 26 weeks after start therapy | Kwakkel | Motricity leg | 26 | 68.2 (25.3) | 34 | 27.2 (26.8) | **41.0** | **[27.7,54.3]** |
| 26 weeks after start therapy | Kwakkel | Motricity arm | 29 | 48.6 (31.1) | 34 | 31.1 (30.1) | **17.5** | **[2.3,32.7]** |
| 3 months after stroke | Rodgers | Motricity arm | 54 | 85.0 (20.0) | 51 | 78.0 (36.3) | 7.0 | [-4.3,18.3] |
| | ***Subtotal – Motricity arm*** | | 83 | | 85 | | **10.7** | **[1.7,19.8]** |
| 18 weeks after start therapy | Cooke | Knee extend torque | 19 | 56.4 (36.3) | 18 | 37.9 (27.8) | 18.5[a] | [-2.3, 39.3] |
| 18 weeks after start therapy | Cooke | Knee flexion torque | 19 | 41.7 (28.8) | 18 | 25.2 (22.9) | 16.5[a] | [-0.2, 33.2] |
| 3 months after start therapy | Lincoln | Hand grip strength | 84 | 9.0 (28.2) | 84 | 19.0 (43.0) | -10.0 | [-19.5,1.8] |
| **Follow-up 2** | | | | | | | | |
| 6 months after start therapy | Lincoln | Hand grip strength | 81 | 23.0 (40.7) | 81 | 25.0 (45.2) | -2.0 | [-15.3,11.3] |
| 6 months after stroke | Rodgers | Motricity arm | 48 | 83.0 (28.2) | 48 | 77.0 (25.9) | 6.0 | [-4.8,16.8] |
| 6 months after start therapy | GAPS | Motricity arm + leg | 30 | 124.0 (42.0) | 34 | 121.0 (51.0) | 3.0 | [-19.8,25.8] |

[a] = fixed effect model used; [b] = random effect model used; FU = Follow-up; * = < 0.05

**Table 6 Motor impairment - movement control**

| Time-point | Study | Measure used | Augmented therapy | | Standard therapy | | Mean difference | |
|---|---|---|---|---|---|---|---|---|
| | | | Number subjects | Mean (SD) | Number subjects | Mean (SD) | Effect size | [95% CI] |
| **Outcome** | | | | | | | | |
| 6 weeks after start therapy | Cooke | Symmetry step time | 19 | 18.8 (35.6) | 15 | 28.6 (33.1) | 9.7[a] | [-32.9, 13.5] |
| 6 weeks after start therapy | Cooke | Symmetry step length | 19 | 13.5 (15.8) | 15 | 25.0 (36.6) | 11.5[a] | [-31.3, 8.3] |
| 6 weeks after start therapy | Donaldson | 9 Hole Peg Test | 10 | 0.2 (0.2) | 8 | 0.2 (0.1) | 0.0[a] | [-0.1, 0.1] |
| 5 weeks after start therapy | Lincoln | 10 Hole Peg Test | 87 | 0.0 (19.3) | 90 | 0.0 (41.5) | 0.0[a] | [-9.5,9.5] |
| **Follow-up 1** | | | | | | | | |
| 18 weeks after start therapy | Cooke | Symmetry step time | 19 | 19.4 (29.9) | 14 | 23.0 (23.5) | 3.6[a] | [-21.9, 14.6] |
| 18 weeks after start therapy | Cooke | Symmetry step length | 19 | 23.7 (49.9) | 14 | 12.3 (11.0) | -11.4[a] | [-11.8, 34.6] |
| **Follow-up 2** | | | | | | | | |
| 6 months after start therapy | Lincoln | 10 Hole Peg Test | 81 | 0 (40.7) | 81 | 0 (45.2) | 0.0 | [-13.3,13.3] |

[a] = fixed effect model used; [b] = random effect model used; FU = Follow-up; * = = < 0.05

Note: symmetry values represent difference from total symmetry therefore a higher value indicates a worse outcome.

**Table 7 Effect sizes for functional activity**

| Time-point | Study | Measure used | Augmented therapy | | Standard therapy | | Mean difference | |
|---|---|---|---|---|---|---|---|---|
| | | | No. subjects | Mean (SD) | No. subjects | Mean (SD) | Effect size | [95% CI] |
| **Outcome** | | | | | | | | |
| 6 weeks after start therapy | Donaldson | ARAT | 10 | 41.8 (17.8) | 8 | 45.0 (14.0) | 3.2 | [-17.9,11.5] |
| 20 weeks after start therapy | Kwakkel | ARAT | 29 | 9.0 (28.9) | 34 | 0.0 (1.5) | 9.0 | [-1.5,19.5] |
| 5 weeks after start therapy | Lincoln | ARAT | 87 | 1.0 (25.9) | 90 | 5.0 (28.2) | -4.0 | [-12.0,4.0] |
| | ***Subtotal - ARAT*** | | 126 | | 132 | | 0.1 | [-5.7,6.0] |
| 5 weeks after start therapy | Lincoln | Rivermead arm | 87 | 3.0 (5.9) | 90 | 4.0 (5.2) | -1.0 | [-2.6,0.6] |
| 6 weeks after start therapy | Cooke | Rivermead mobility | 31 | 36.6 (10.4) | 32 | 34.6 (10.8) | 2.0 | [-3.2,7.2] |
| 6 weeks after start therapy | Cooke | Walk 0.8m/s or more | 31 | 11 | 32 | 4 | **3.9[c]** | **[1.1,13.9]** |
| 6 weeks after start therapy | Cooke | Comfort walk speed | 32 | 0.6 (0.5) | 31 | 0.3 (0.4) | **0.3** | **[0.1,0.5]** |
| 20 weeks after start therapy | Kwakkel | Comfort walk speed | 26 | 0.7 (0.5) | 34 | 0.4 (0.4) | **0.3** | **[0.1,0.5]** |
| | ***Subtotal – comfort walk speed*** | | 58 | | 65 | | **0.3** | **[0.1,0.5]** |
| 20 weeks after start therapy | Kwakkel | Max walk speed | 26 | 0.9 (0.7) | 34 | 0.5 (0.6) | **0.4** | **[0.1,0.7]** |
| 20 weeks after start therapy | Kwakkel | FAC | 29 | 4 (1.5) | 34 | 3 (2.2) | **1.0** | **[0.1,2.0]** |
| 6 weeks after start therapy | Partridge | 5 metre walk time | 33 | 49.2 (32.0) | 22 | 39.9 (29.9) | 9.3 | [-7.3,25.9] |
| 5 weeks after start therapy | Lincoln | Rivermead Gross Function | 87 | 3.0 (4.4) | 87 | 5.0 (5.2) | **-2.0** | **[-3.4,-0.6]** |
| **Follow-up 1** | | | | | | | | |
| 26 weeks after start therapy | Kwakkel | ARAT | 29 | 4.0 (28.2) | 34 | 0.0 (1.85) | **4.0** | **[-6.3,14.3]** |
| 3 months after stroke | Rodgers | ARAT | 54 | 53.0 (27.4) | 51 | 54.0 (41.5) | -1.0 | [-14.5,12.5] |
| | ***Subtotal - ARAT*** | | 83 | | 85 | | 2.2 | [-6.0, 10.4] |
| 18 weeks after start therapy | Cooke | Rivermead mobility | 28 | 36.6 (9.8) | 23 | 39.7 (5.7) | -3.1 | [-7.4,1.2] |
| 3 months after start therapy | GAPS | Rivermead mobility | 32 | 9.7 (3.3) | 34 | 8.1 (3.6) | 1.6 | [-0.1,3.3] |
| | ***Subtotal – Rivermead mobility*** | | 60 | | 57 | | 1.0 | [-0.6,2.5] |
| 18 weeks after start therapy | Cooke | Comfort walk speed | 27 | 0.6 (0.5) | 23 | 0.4 (0.4) | 0.2 | [-0.1,0.5] |
| 26 weeks after start therapy | Kwakkel | Comfort walk speed | 26 | 0.6 (0.5) | 34 | 0.4 (0.4) | 0.2 | [-0.0,0.4] |
| | ***Subtotal – Comfort walk speed*** | | 59 | | 61 | | 0.2 | [-0.1,0.4] |
| 3 months after stroke | Rodgers | Frenchay Arm Test | 54 | 4.0 (2.2) | 51 | 4.0 (3.7) | 0.0 | [-1.2,1.2] |
| 3 months after start therapy | Lincoln | Rivermead arm | 84 | 3.0 (5.9) | 84 | 5.0 (5.2) | **-2.0** | **[-3.7,-0.3]** |
| 6 months after start therapy | Partridge | 5 metre walk time | 27 | 35.8 (16.5) | 33 | 49.4 (32.1) | **-13.6** | **[-26.2,-1.0]** |
| 3 months after start therapy | Lincoln | Rivermead Gross Function | 84 | 5.0 (5.2) | 84 | 6.0 (5.9) | -1.0 | [-2.7,0.7] |
| 26 weeks after start therapy | Kwakkel | FAC | 26 | 5.0 (0.7) | 34 | 4.0 (2.2) | **1.0** | **[0.2,1.8]** |
| 18 weeks after start therapy | Cooke | Walk 0.8m/s or more | 27 | 10 | 23 | 4 | **2.8** | **[0.8,10.6]** |
| 26 weeks after start therapy | Kwakkel | Max walk speed | 26 | 0.9 (0.7) | 34 | 0.6 (0.6) | 0.3 | [-0.0,0.6] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Follow-up 2** | | | | | | | | |
| 6 months after start therapy | Lincoln | ARAT | 81 | 3.0 (28.9) | 81 | 19.0 (33.3) | **-16.0** | **[-25.6,-6.4]** |
| 52 weeks after start therapy | Kwakkel | ARAT | 28 | 6.0 (31.3) | 33 | 1.0 (21.1) | 5.00 | [-8.6,18.7] |
| 6 months after stroke | Rodgers | ARAT | 48 | 55.0 (31.9) | 48 | 56.0 (23.7) | -1.0 | [-12.2,10.2] |
| | ***Subtotal - ARAT*** | | 157 | | 162 | | -6.4 | [-12.8,0.0] |
| 6 months after stroke | Rodgers | Frenchay Arm Test | 48 | 5.0 (3.0) | 48 | 4 (3.0) | 1.0 | [-0.2,2.2] |
| 6 months after start therapy | Lincoln | Rivermead arm | 81 | 4.0 (6.7) | 81 | 6.0 (5.9) | **-2.0** | **[-4.0,-0.1]** |
| 6 months after start therapy | Lincoln | Rivermead Gross Function | 81 | 6.0 (5.9) | 81 | 7.0 (3.7) | -1.0 | [-2.5,0.5] |
| 52 weeks after start therapy | Kwakkel | Max walk speed | 25 | 0.9 (0.6) | 33 | 0.7 (0.6) | 0.2 | [-0.1,0.5] |
| 52 weeks after start therapy | Kwakkel | FAC | 25 | 5 (0.7) | 33 | 4 (1.48) | **1.0** | **[0.4,1.6]** |
| 6 months after start therapy | GAPS | Rivermead mobility | 30 | 10.2 (3.1) | 34 | 9.1 (4.0) | 1.1 | [-0.6,2.8] |
| 52 weeks after start therapy | Kwakkel | Comfort walk speed | 25 | 0.6 (0.5) | 33 | 0.5 (0.4) | 0.1 | [-0.1,0.3] |

[a] = fixed effect model used; [b] = random effect model used; [c] = odds ratio used; FU = Follow-up; * = = < 0.05; ARAT = Action Research Arm Test; FAC = Functional Ambulation Category

**Fig 1. Flow Diagram for this systematic review (note: 3 full-text articles reported the same study)**

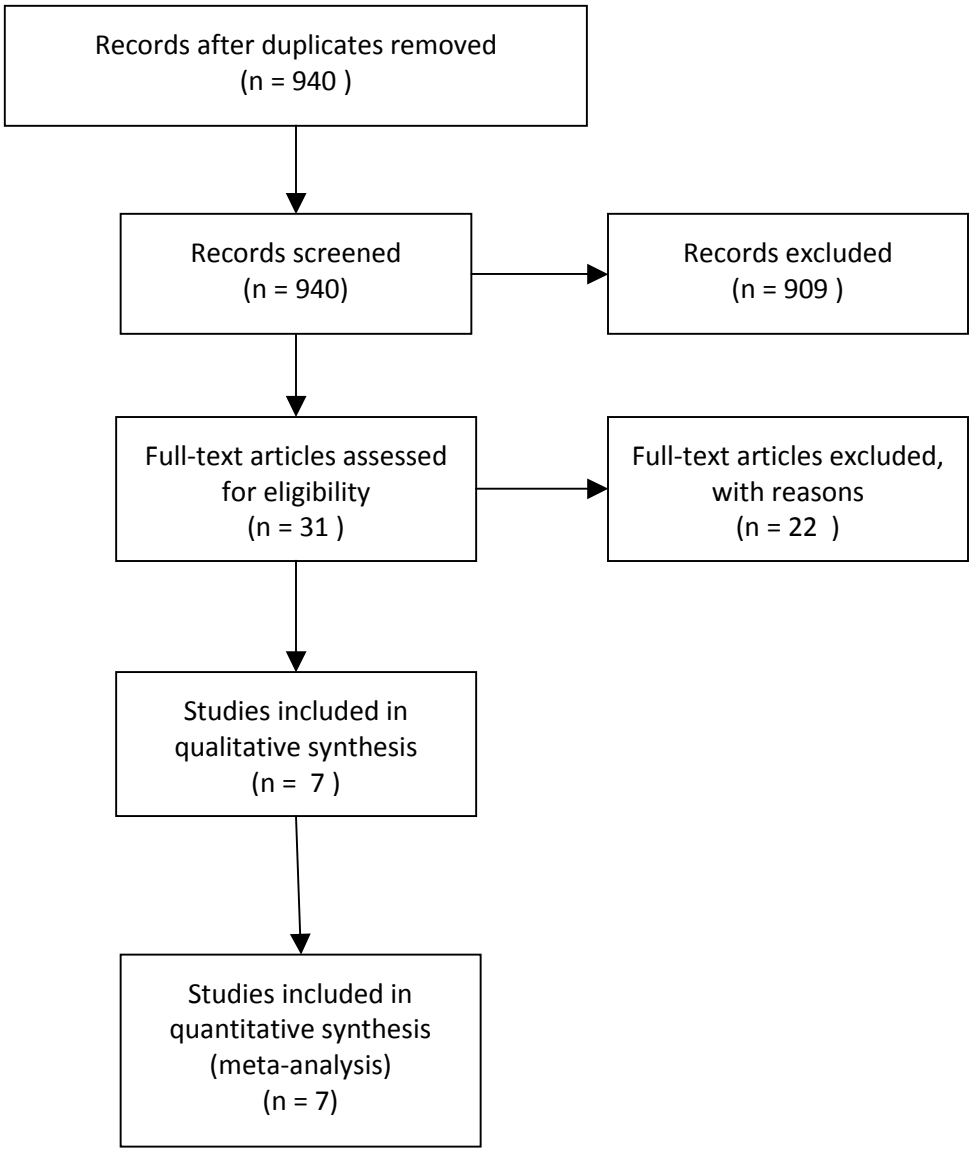


**Fig 1. Flow Diagram for this systematic review (note: 3 full-text articles reported the same study)**

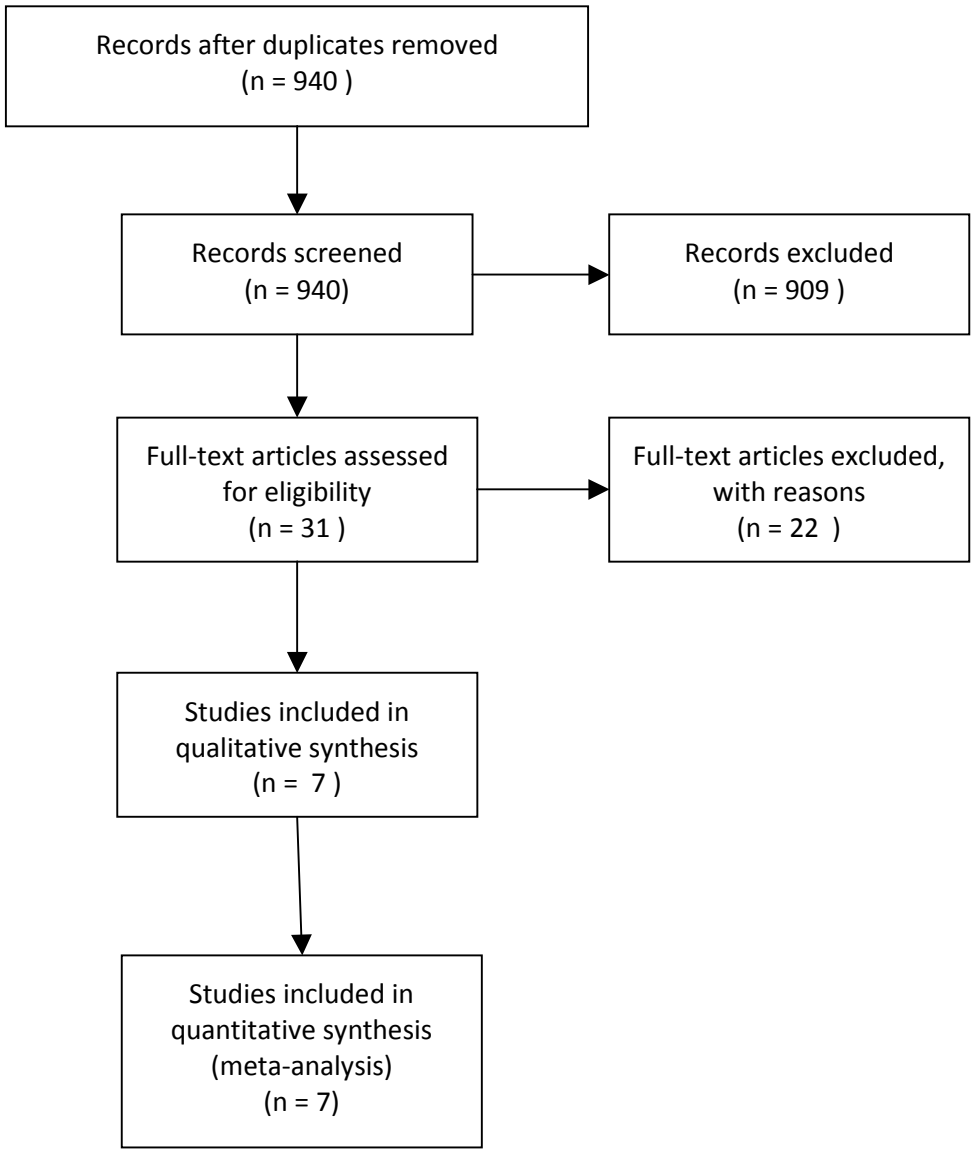



Figure 1

# Appendix IV

Data extraction form

## Appendix IV: Data Extraction form

| First author | Journal/Conference Proceedings etc | Year |
|---|---|---|
| | | |
| | Intervention (n= ) | Control (n= ) |
| **Intervention** | | |
| **Age (mean, median, range, etc.)** | | |
| **Sex of participants (numbers / %, etc)** | | |
| **Type of stroke** | | |
| **Side of weakness** | | |
| **Time since stroke** | | |

| | | |
|---|---|---|
| **Number of participants who received intended treatment** | | |
| **Number of participants who were analysed** | | |
| **Median (range) length of follow-up reported in this paper (state weeks, months or years or if not stated)** | | |
| **Duration of treatment (State weeks / months, etc, if cross-over trial give length of time in each arm)** | | |
| **Time-points when measurements were taken during the study** | | |
| **Time-points reported in the study** | | |
| **Trial design (e.g. parallel / cross-over*)** | | |
| **Other** | | |

| For Continuous data | | | | | | |
|---|---|---|---|---|---|---|
| Outcomes | Unit of measurement | Intervention group | | Control group | | Details if outcome only described in text |
| | | n | Mean (SD) | n | Mean (SD) | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

| For Dichotomous data | | |
|---|---|---|
| Outcomes (rename) | Intervention group (n)<br>n = number of participants, not number of events | Control group (n)<br>n = number of participants, not number of events |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

## Appendix V

Risk of bias assessment form

# Appendix 5: Risk of bias assessment form adapted from Cochrane Handbook version 5.1.0 (Higgins and Green, 2011).

Author (year): _____

Reviewer: _____

| Quality Criteria | High risk | Low risk | Unclear |
|---|---|---|---|
| **Random Sequence Generation** | | | |
| **Allocation concealment** | | | |
| **Blinding of participants and personnel** | | | |
| **Blinding of outcome assessment** | | | |
| **Incomplete outcome data** | | | |
| **Other sources of bias** | | | |

## Appendix VI

Recruitment form

Norfolk and Norwich University Hospital NHS
NHS Trust

Recipients address

**Norfolk and Norwich University Hospital**
Colney Lane
Norwich
NR4 7UY

Date

Dear

I am writing to tell you about **research** being carried out in Norfolk by **Dr Jane Cross and a team of researchers at The University of East Anglia**.
Dr Cross and her team are **seeing whether a new physiotherapy treatment is effective** for people who have a stroke. They want to find out whether doing **6 weeks of a new therapy** called “Functional Strength Training” can **help people** to **use their arm and leg better for daily activities** such as walking and getting dressed.

The Research team **are asking people who have had a stroke within the last 5 years** to take part. In all the researchers are **looking for 58 people** who have weakness in their **arm and leg** caused by their stroke. **Your details** were identified from your **in-patient stay** after having your stroke.

**What would I have to do?**

Taking part in the study would mean having **physiotherapy for your arm or leg** for **4 days a week for 6 weeks**. Each training session will be **an hour** long. You might practise **tasks for the arm** such as **reaching for objects**, **unscrewing lids** and **pouring water**; or **tasks for the leg** such as **climbing stairs**, **standing**, and **walking**. We would need to **assess your arm and leg** before and after the 6 weeks of therapy.
**All the therapy and assessments would be in your home** with a research physiotherapist. We may also **ask questions** about how you found the therapy and whether it was what you were hoping for.

**Am I the right person for this research?**

**Are you walking as well as you had done before the stroke?**

**Are you able to use your arm as well as you had done before the stroke?**

If your answer is **NO** to both these questions then **you may be able to be included in this research.**

Taking part in this research is **entirely voluntary**. You **will not be out of pocket** if you decide you would like to take part.

Please return the **reply slip** in the **stamped address envelope** to show whether or not you would like to have **more information about the study.**

If you would like to talk to somebody before deciding, please contact Kath Mares on 01603 593099 or 07827 840497.

If the research team has not heard from you within 2 weeks we will send you one reminder by post.

Thank you for taking the time to consider this invitation

Yours sincerely

**Dr Phyo Myint**
Consultant in Elderly Medicine
Norfolk and Norwich University Hospital

**Dr Kneale Metcalf**
Consultant in Elderly Medicine
Norfolk and Norwich University Hospital

## Appendix VII

Expression of interest form

**Functional Strength Training to improve walking and upper limb function in people later after stroke**

**EXPRESSION OF INTEREST FORM**

**Thank you for filling in this form and expressing an interest in being part of this research. Following receipt of this form we will contact you by telephone to arrange to come and visit you to discuss the research further.**

**Information about you**

| |
|---|
| **Name:** |
| **Address:** |
| **Postcode:** |
| **Tel:** |

**Thank you for filling in this form. Please do not hesitate to contact me if you have any questions about the study or filling in the form.**

**Please return the form in the envelope provided to: Kath Mares, School of Allied Health Professions, Queen's Building, University of East Anglia, Norwich NR4 7TJ**

**Tel: (01603) 593099 – if no reply please leave a message and I will call back**
**Email: k.mares@uea.ac.uk**

# Appendix VIII

Participant information sheet


# Participant Information sheet

**Study Title:**
**Functional Strength Training to improve walking and upper limb function in people later after stroke: a phase II Trial** (Protocol, version 5)

You are invited to take part in a **research study.** Before you decide whether you would like to take part you **need to understand why** the research is being done and **what would be involved**. Please take time to **read the following information carefully**.

Talk to others about the study if you wish. If you have **any questions** or would like **further information** there are some **contact numbers on page 10 and 11 of this information pack.**

- **Part 1** describes the **purpose of this study** and **what will happen** if you decide to take part.

- **Part 2** gives **detailed information** about **how the study will be carried out**

## Part 1

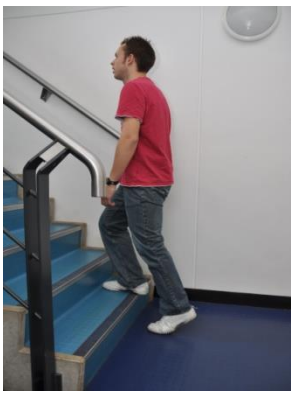
### What is the purpose of this study?

**Weakness** in the **arm and leg** is common **after stroke** and this can affect people's ability to walk and carry out daily activities.
Many people think that there is little chance of further improvement a year after stroke. Most people do not receive therapy at this time. We want to find out whether a **new therapy called Functional Strength Training (FST)** is effective for people **at least six months after their stroke**. We also want to find out what people **think about FST** and whether it is **suitable to be provided to people in their own homes**

### What is Functional Strength Training (FST)?

**Functional Training** involves **practising activities** that you do every day such as walking and reaching for objects. Adding **'Strength' Training** means increasing **the number of times the activity is practised or making the activity harder bit by bit.**

**FST for the leg**



**Activities could include:**

**Standing up** from chairs at different heights

**Climbing steps** or **stairs**

**Exercises** with **weights sitting down**

**FST for the arm**

**Activities could include:**

**Reaching** for objects from cupboards

**Lifting** objects of different weights.

**Tying** shoelaces, undoing buttons

## Why have I been asked to take part?

You have been chosen because you have had a **stroke within the last 5 years**. If you decide to take part you will be one of **58 participants** in this study.

**We are looking for people who;**

- Have weakness in their **arm and leg** following a stroke;
- Are **not receiving physiotherapy** for their arm and leg;
- But who **are able** to **participate in physiotherapy**.

## Do I have to take part?

**No.** It is **up to you to decide**. Taking part in the research study is **entirely voluntary**. If you want to you can **speak to a member of the research team before you decide**.

You are **free to withdraw from the study at any time** and you do not have to give a reason.

## What will happen if I decide to take part?

Once you are happy that you **want to take part** in the study, one of the **research team will visit you at home**.

On your home visit a member of the research team will **assess** your **arm and leg** to see whether or not **you are suitable to participate** in the study.

If you are **not suitable** to participate in the study, you will be told by the Research team and you will **not be asked to take any further part** in the study.

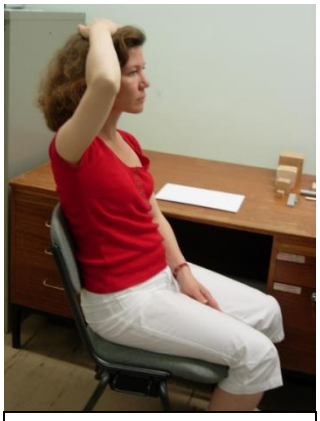
If you are you will be asked to **sign a consent form** to show you **agree to take part.** We will leave the consent form with you for 1 week so that you can think about becoming part of the study. If you still wish to take part in the study a Researcher will come and visit you at home and will take some **more measurements** of your arm and leg. They will also help you complete a **questionnaire** about **your health** and **use of health services**

This will take approximately **30-40 minutes**.

**In order to do this we will**:

- Assess your ability to **stand** and **walk**
- Assess your ability to **use your stroke arm in every day activities**. For example, lift different sized objects from the table onto a box in front of you

Examples of activities the researcher will use to assess your arm:



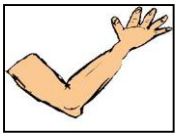
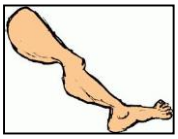
Touch your head

9 Hole Peg Test

With your consent the **Research Team** will tell your **GP** that you are **taking part** in the study and check that there are **no medical reasons** why you can't take part.

**After the home visit**

**If you are suitable for the study** you will be allocated to **group 1 or group 2 at random**.

- **Group 1** will receive 6 weeks of FST training for their **arm** 
- **Group 2** will receive 6 weeks of FST training for their **leg** 

You will be **identified by a number**. None of your personal details are given. The research therapist giving the FST training will **tell you which group you are in.**

**Can I choose which group I get allocated?**

**No**. Participants have to be **randomly allocated** to either of the groups to allow us to find out **whether this treatment is effective or not**. The researcher who does the **assessments** at the **start and end** of the study **will not know which group you are in** and therefore will not be able to influence the findings. This is called a **'blind trial**'. You must **not tell the assessor which group you are in** or anything about **your FST training**.

**Outcome and follow- up assessments**

**After the 6 weeks of FST training** the researcher will **assess your arm and leg again**, using the same assessments as before.

This will also happen **6 weeks after the FST training** has stopped so we can see if **any improvements** in your arm and leg have **been maintained**.

You will also be asked to complete the **same questionnaire** about your **health** and **use of health services**.

**Weekly measures of arm and leg function**

**Once a week** (usually the first visit each week) **the therapist who is visiting you to carry out the intervention will carry out a brief assessment of your arm and leg movement.** This information will be used to tell us whether 6 weeks of therapy is enough, too little or too much. This assessment should only take about **20 minutes and won't impact on the time you have for the intervention.**

**Interviews**

A small number of participants **(6 out of the 58)** will be chosen to take part in **two interviews** as **well as the FST therapy**.

There will be **two interviews** conducted by an **Independent Researcher**. These will take place in your **home before** and **after** the FST therapy period.

The **purpose** of the interviews is to help us find out whether or not you find this level of training **acceptable** and whether it is suitable to be provided in **people's homes**

**Interview 1**

Will take place **before you start the FST** Training

You will be asked questions about what life was like **before your stroke**.

We want to find out what **difficulties you now have because of your stroke** and **what you are hoping to achieve** by participating in the FST

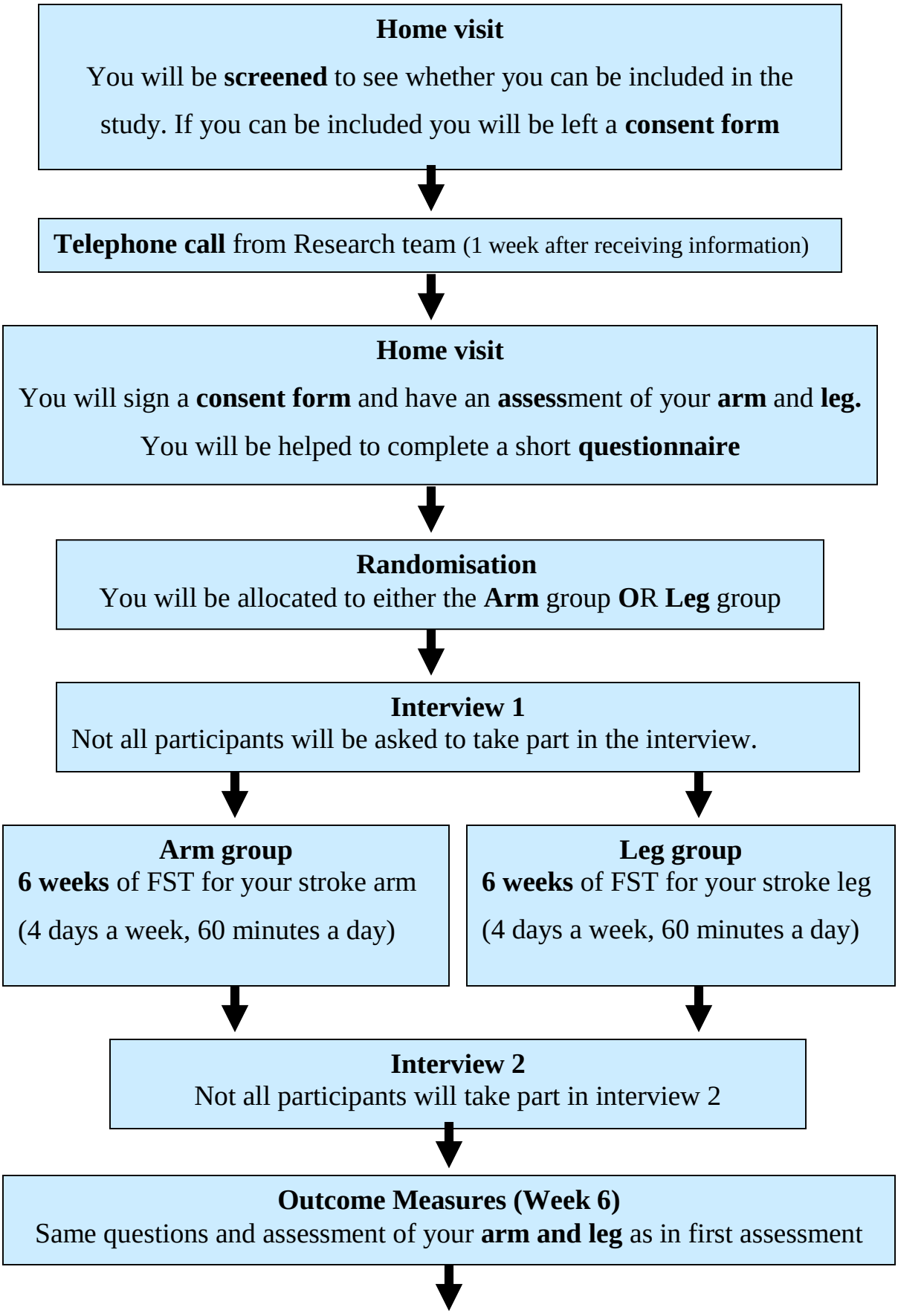
**Interview 2**

Will take place **after the 6 weeks of FST** Training

You will be asked for **feedback** about what you thought of the FST training.

For example if it was too tiring and whether you saw any benefits.

# Diagram to show the procedure for the study



**Follow-up measures (Week 12)**
Same questions and assessments of your **arm and leg**

£

**Expenses**

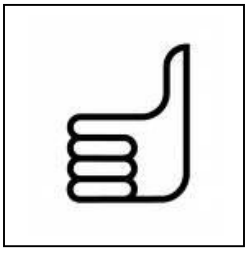
The study will take place **entirely within your own home** and therefore there will be **no travel expenses**.

You will not be out of pocket if you take part in the study.

**Are there any possible risks with this study?**

There is a **small risk** that you may experience some pain or discomfort if you overwork your arm or leg in therapy. This will be **closely monitored** and we will pace therapy to your level of ability. **Therapy can be stopped at any time**. If you want to stop being involved you simply tell us.

If there are any **questions** during the study that you **do not want to answer**, **you do not have to answer them**.



**What are the possible benefits of taking part in the study?**

Previous studies have shown that functional strength training improved recovery of people early after stroke. However we do not know if the therapy is effective for people at least a year after stroke.

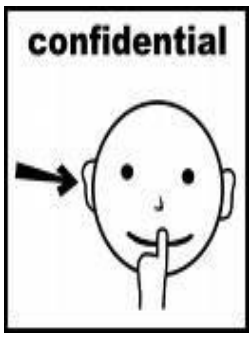
**What happens when the study stops?**

This is the first study of FST at 1 year after stroke. The



**What if there is a problem?**

If you have **any complaints** about the way you have been dealt with or any harm is caused during the study this will be addressed. Detailed information relating to this is outlined in **Part 2** (p.11).




**Will my taking part in the study be kept confidential?**

**Yes**, all the **information about you** and **your participation** in the study will be **kept strictly confidential**. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in **Part 2** (p.12).

This completes Part 1 of the information sheet.

If this information interests you and you are considering taking part, please continue to read additional information in Part 2 before making any decision.

If you have **any queries** you can contact the Research Physiotherapist, **Kath Mares or Jane Cross** the Principal Investigator.

**Contact details:**


**Kath Mares**
Research Physiotherapist

The Queens Building
University of East Anglia
Norwich
NR4 7TJ

k.mares@uea.ac.uk

01603 593099/ 07827 840497

**Dr Jane Cross**
Principle Investigator

The Queens Building
University of East Anglia
Norwich
NR4 7TJ

j.cross@uea.ac.uk

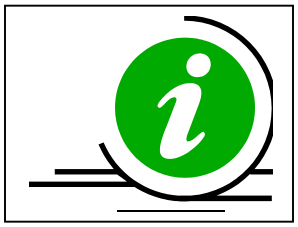
01603 593636


**Independent Contact Details:**
If you wish to discuss this study with someone who is not involved in the research then you can contact the
Research and Development Office, Norfolk and Norwich University Hospital:

**http://www.nnuh.nhs.uk/Dept.asp?ID=60**

**01603 286611**

## Part 2



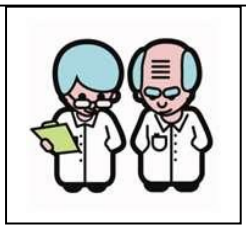
### What happens if new information about the research therapy comes along?

Sometimes in research, new things are found out about new therapies. Very few studies have been done about this therapy (FST) and this study is to find evidence to justify a larger study. If however, new information is published then you will be told.


### What happens if I no longer wish to continue with the study?

**You may withdraw** from the study **at any time** without giving a reason. If you withdraw from the study, we will need to use the data collected up to when you withdrew.

**Withdrawing** from the study **will not affect your treatment** now or at any time in the future **by any healthcare team**



### Will anyone else know I am doing this?

With your consent the research team will contact your **GP** to inform them you are **taking part in the study**.

If the Research Team are concerned at any time about your health during your participation in this study they will **report these concerns** to your **GP** or the appropriate **health care professional**.


**What if there is a problem or something goes wrong?**

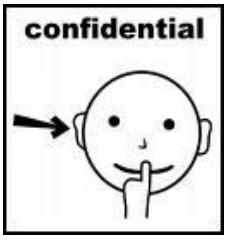
If you have any **concerns** about this study, you should first contact **Kath Mares** or **Jane Cross**, who will do their best to **answer your questions** or **resolve the problem**. (Contact details given at end of Part 1).

If you are still unhappy or wish to make a **formal complaint** you may do this through the **NHS Complaints Procedure**. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research study there are **no special compensation arrangements**.
If you are harmed due to someone's negligence then you may have grounds for legal action for compensation against the University of East Anglia, but you may have to pay your legal costs.

**Who is organising/funding the research?**

**The Stroke Association** have awarded a **grant** to enable the trial to be funded. The Research Team at the **University of East Anglia** are responsible for **organising** and **running** the trial.




**Will my taking part in this study be kept confidential?**

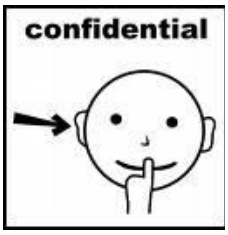
The research team will only have access to information about you that is relevant to the study. All information will be kept **strictly confidential**.

Information may include details such as your **date of birth** and the **date** and **diagnosis of your stroke**. Personal information such as your **address** will also be required to allow us to visit you at home.

You will be given a **trial number** for the purpose of **collecting and analysing data**. This means you will remain anonymous

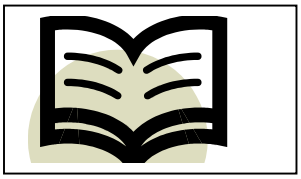

The data will only **be accessed by authorised persons** within the **Research Teams** and the **Research and Development Office** of the **NHS Trust**, who ensure the **quality of the research** carried out.

**How will my information be stored?**




Data will be **stored securely** in the **research office** during the study and for **5 years** after the study. Long term data is then stored in a secure room in the **NHS Clinical trials Research Unit** at UEA for **25 years**.

All procedures for **handling, processing, storage** and **destruction of data** are compliant with the Data Protection Act 1998.



**What will happen to the results of the research study?**

The results of the trial will be **analysed** and used to justify **whether or not a larger scale study** is required to prove effectiveness of this therapy.

The results will be **published in an academic journal** but individual participants will **not be identifiable**. Participants can be sent trial report at the end of the study. Part of this study will contribute to a PhD for Kath Mares (Research Physiotherapist).

**Who has reviewed the study?**

The Trial has been reviewed by **The Stroke Association** and **Stroke Survivors at our Patient Forum**. All were **positive** about the proposed trial and **feedback** has been incorporated into this **research plan**.

The **Cambridgeshire 2 Research Ethics Committee** has approved the study and it will be monitored by a **Trial Management Group**.

**End of Part 2**

**Thank you** for taking the time to **read this information**. If you choose to participate, you will **keep a copy** of this **participant information sheet** and the **signed consent form**.

## Appendix IX

Consent form

Participant Name:

Participant Identification Number for this trial:

# Consent Form

**Title of Project**: Functional Strength Training to improve walking and upper limb function in people later after stroke: a phase II Trial

**Name of Researcher:**

**1)**


I confirm that I have **read and understood** the information sheet dated 15/3/2012, Version 6 for the above study.

I have had the opportunity to consider the information, ask questions and have had these questions answered to my satisfaction.

**I have read and understood the information sheet**

**Yes**

**No**

Please initial or tick the relevant box as able

**2)**

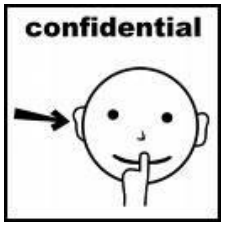

I understand that my **participation is voluntary** and that I am **free to withdraw** at **any time**, without giving any reason, without any future medical care or legal rights being affected.

**I understand I can stop at any time**

**Yes**

**No**

**3)**




I understand that **some information about my stroke may be held by** individuals from the **University of East Anglia**. These may be people outside of the research team who may need to see the information for audit and monitoring.

**My information can be seen**

**Yes**

**No**

**4)**

I agree that my **GP** can be **informed of my participation** in the study. I agree for my GP to be asked **whether or not I am fit** to take part in this study. I agree that my GP can **be informed** if there are any **concerns about my health** during the study

**My GP can be told I am in the study**

**Yes**

**No**

**5)**

**I consent to the use of audio visual equipment for the purposes of recording my interviews if I am selected for that part of this project.**

**I consent for my interviews to be recorded**

**Yes**

**No**

**6)**  I **agree to take part** in the study

**I agree**

| Yes | No |
|---|---|

| Name of participant | Date | Signature |
|---|---|---|
| Researcher (Person taking consent) | Date | Signature |

When completed; 1 for patient; 1 for researcher site file; 1 (original)

## Appendix X

GP letter

Faculty of Medicine and Health Sciences
School of Allied Health Professions
University of East Anglia
Norwich Research Park
Norwich
NR4 7TJ

Date:

Dear Dr ……..

I am writing to inform you that you patient …… (DOB……) has consented to take part in a trial that is currently underway at the University of East Anglia. This trial is called Functional Strength Training Later after Stroke (FeSTIvAlS) and has been funded by the Stroke Association. We are aiming to recruit 58 participants who have had a stroke between 6 months and 5 years ago to take part in a functional strength training programme which will target either their upper or lower limb, depending on group allocation.
Please find a one page copy of the protocol on the reverse of this letter.

**We would be grateful if you could let us know of any medical reason why this patient may not be included in this study. If we have not heard from you within 10 working days from the receipt of this letter, then we will go ahead and included the patient named above ion the study.**

If you require any further information about the study then please contact either myself (Kath Mares) or the Principal Investigator, Dr Jane Cross.

Kath Mares
k.mares@uea.ac.uk
01603 593099

Dr Jane Cross
j.cross@uea.ac.uk
01603 593315

Yours sincerely

Kath Mares (Research Physiotherapist)

## Appendix XI

GP protocol

# Functional Strength Training Later After Stroke (FeSTIvAIS)

Description of Intervention:
Functional Strength Training (FST) is a 'hands-off' progressive, resistive low intensity exercise during functional activity. FST is designed to increase ability to produce voluntary muscle force throughout joint range and increase ability to modulate force in muscles/muscle groups appropriate for the activity being trained and improve functional ability. Activities are progressed by increasing the number of repetitions, increasing range of joint motion required and increasing the load to be moved. The intervention will be carried out in people's homes by a Research Physiotherapist four times a week for six weeks. Portable equipment (e.g. free weights and steppers) will be used as appropriate. Participants will be encouraged to use the paretic limb (upper or lower as allocated) in everyday functional activity.

Research study primary objective:

- To estimate if there is sufficient efficacy to justify subsequent trials of Functional Strength Training (FST) for upper and lower limb motor recovery in people who are between six months and five years after stroke.

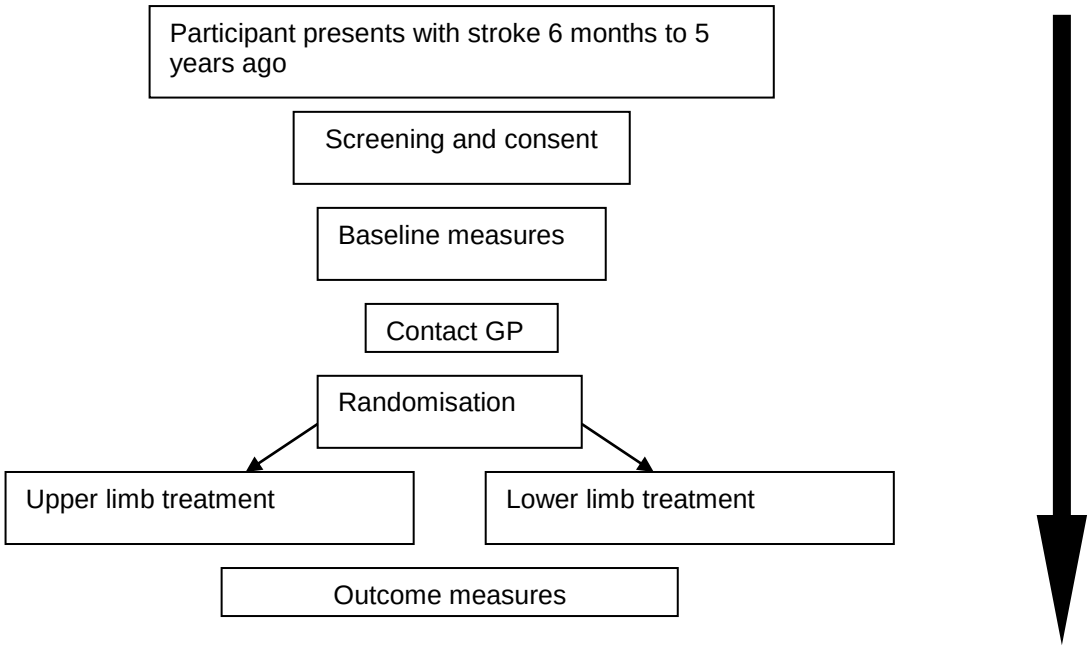
Inclusion criteria:

- adults aged 18+ years, 6 months to 5 years after stroke in anterior circulation (infarct or haemorrhage)
- be able to walk 4 steps with continuous support from one person and/or assistive devices, but unable to step on and off a block with either the affected or unaffected leg more than 14 times in 15 seconds.
- be able to take paretic hand from position on lap and place on table top in front, but unable to pick up four £1 coins individually from a tabletop and stack them evenly in a pile.
- can follow a 1-stage command i.e. sufficient communication/orientation for interventions in this trial

**Exclusion criteria:**

- **known pathology which excludes participation in the low intensity exercise training involved in functional strength training.**

Study design:




Adverse events are not expected in this intervention but there is a small possibility of an overuse syndrome resulting in limb pain. This will be considered to have occurred if a participant reports or exhibits limb pain (behavioural signs) to the Research Physiotherapist on 4 consecutive treatment days. If pain occurs then participants will be withdrawn from their allocated treatment.

Kath Mares
Research Physiotherapist FeST1vAIS (ISRCTN71632550)
Ethics reference: 09/H0308/147
k.mares@uea.ac.uk
01603 593099

## Appendix XII

Lower limb treatment schedule

**Appendix 12: Lower limb physiotherapy treatment record for patients in FST trial**
(Items in bold refer to components of Functional Strength Training)

**Date ……..  Patient ID ……..…  Therapist ID .....……..**

**No. Physiotherapists used ..……  No. Rehabilitation Assistants used …..….  Estimated duration of session ……**

***Aims***

| | | | | | |
|---|---|---|---|---|---|
| 1. To reduce pain | | 3. To improve muscle activity/function | | 5. To improve gross mobility | |
| 2. To improve sensory awareness | | 4. To improve postural control | | 6. To improve endurance | |

***Gross position of patient during activities used – what about kneeling postures?***

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1. Supine lying | | 4. non-paretic side lying | | 7. 4 pt kneeling | | 10. Standing | |
| 2. Crook lying | | 5. Sitting - $90^0$ | | 8. 2 pt kneeling | | 11. Walking | |
| 3. Paretic side lying | | 6. Sitting – perch | | 9. ½ kneeling | | 12. Other | |

***Equipment used***

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1. High hold/surface | | 4. Perching stool | | 7. Walking aid | | 10. Other | |
| 2. Low hold/surface | | 5. Rolled up towel | | 8. Tilt table | | | |
| 3. Hip high hold/surface | | 6. Gym ball | | 9. Standing frame | | | |

## Specific Physical Therapy interventions

***Function – in lying towards sitting***

*1. Soft tissue mobilisation*

| | |
|---|---|
| 1.1 Specific soft tissue mobilisation | |
| 1.2 Passive movement | |
| 1.3 Muscle stretching | |

***2. Facilitation of activity in specific muscles***

| | |
|---|---|
| 2.1 Imagery of specific muscle activity | |
| 2.2 Specific muscle activation | |
| 2.3 Activation of muscle activity during function | |

***3. Facilitation of isolated (selective) joint movement***

| | |
|---|---|
| 3.1 Imagery specific joint movement | |
| 3.2 Active assisted isolated joint movement | |
| 3.3 Facilitate specific joint movement during function | |

*4. Facilitation of co-ordinated (combined) movement*

| | |
|---|---|
| 4.1. Imagery of co-ordinated patterns of movement | |
| 4.2 Active assisted co-ordinated patterns of movement | |
| 4.3 Facilitate co-ordinated movement during function | |
| 4.4 Facilitate leg/foot activity from another body part | |

***5. Resistive exercise***

| | |
|---|---|
| 5.1 Resistance from therapist | |
| 5.2 Resistance from patient's bodyweight | |
| 5.3 Resistance from equipment | |

*6. Specific sensory (tactile & proprioceptive) input*

| | |
|---|---|
| 6.1 "Hands-on" techniques | |
| 6.2 Provision of environmental surface | |

7. *Splinting techniques*

| | |
|---|---|
| 7.1 Strapping | |
| 7.2 Splinting | |

***8. Function – in lying towards sitting***

| | |
|---|---|
| 8.1 PT "hands-on" techniques to re-ed posture | |
| 8.2 Re-ed of funct act through specific mvmnt patterns | |
| 8.3 Rolling – functional activity training | |
| 8.4. Bridging - functional activity training | |
| 8.5 Lying to sitting – functional activity training | |
| 8.6 Sitting to lying - functional activity training | |
| 8.7 Static sitting balance training | |

***9. Function – In sitting towards standing***

| | |
|---|---|
| 9.1 PT "hands-on" techniques to re-ed posture | |
| 9.2 Re-ed of funct act through specific mvmnt patterns | |
| 9.3 Dynamic sitting balance training | |
| 9.4 Transfers training | |
| 9.5 Sit to standing – functional activity training | |
| 9.6 Stand to sit – functional activity training | |

***10. Function – In standing towards walking***

| | |
|---|---|
| 10.1 PT "hands-on" techniques to re-ed posture | |
| 10.2 Re-ed of funct act through specific mvmnt patterns | |
| 10.3 Static standing balance training | |
| 10.4 Dynamic standing balance training | |
| 10.5 One leg stand activities – functional training | |

***11. Function – Walking and onwards***

| | |
|---|---|
| 11.1 PT "hands-on" techniques to re-ed posture | |
| 11.2 Re-ed of funct act through specific mvmnt patterns | |
| 11.3 Overground indoor walking training | |
| 11.4 Overground outdoor walking training | |
| 11.5 Treadmill walking/bicycle training | |
| 11.6 Obstacle negotiation training | |
| 11.7 Ascending/descending stair training | |

## Instructions for completion of recording form overleaf

1. ONE FORM FOR EACH TREATMENT SESSION
   Please complete one form for each treatment session given to patients included as subjects in the Functional Strength Training lower limb clinical trial
2. TO COMPLETE THE AIMS SECTION
   Please place a tick in the box which best describes the aims relevant to the particular treatment session being recorded
3. TO COMPLETE THE GROSS POSITION SECTION
   Please place a tick in the box for every gross position used to deliver physiotherapy treatment during the treatment session being recorded
4. TO COMPLETE THE EQUIPMENT SECTION
   Please place a tick in the boxes which best describes the equipment used during the particular treatment session being recorded
5. TO COMPLETE THE SECTION "SPECIFIC PHYSICAL THERAPY INTERVENTIONS"
   Please place a tick in the boxes which best describe the treatment that was given to the patient during the particular treatment session being recorded.
6. FOR FURTHER DESCRIPTION OF ITEMS ON RECORDING FORM OVERLEAF
   Please refer to the accompanying document "Description of Lower Limb Treatment for Patients in FST Trial"

## Abbreviations for and glossary of terms used in recording form overleaf

| | |
|---|---|
| Act | Activity/activities |
| Environmental surface | A surface to enhance sensory input during functional activity e.g. sitting on a block of foam, walking on an exercise mat, walking on uneven ground |
| Facilitation | The application of an appropriate mode and dose (frequency, duration and intensity) of sensory stimulus provided by the therapist to access a desired active response from the patient |
| Funct | Function/functional |
| High hold/surface | A surface level with at least the mid-thoracic point of the patient to provide a hold and/or security during physical therapy intervention |
| Imagery | Mental rehearsal of a motor act that occurs in the absence of overt motor output |
| Low hold/surface | A surface level between the hip and mid-thoracic point of the patient to provide a hold and/or security during physical therapy intervention |
| Mvmnt | Movement |
| Physiotherapist | Person with professional Physiotherapy qualification |
| PT | Physical Therapy |
| Re-ed | Re-education |
| Rehabilitation Assistant | Person assisting the physiotherapist but who is not a qualified physiotherapiest (e.g. student, nurse, technician, carer) |

## Appendix XIII

Upper limb treatment schedule

## Appendix 13: Upper Limb Treatment Recording Form (Items in bold refer to components of Functional Strength Training)

Date:…….. Patient ID:…… Therapist ID:…….
No. physiotherapists used: …… No rehab assistants used……. Est duration of upper limb Rx……..

### Aims:

1. Postural Control ☐
2. Musculo-skeletal range of motion ☐
3. Oedema management ☐
4. Alignment ☐
5. Manipulative ability of the hand ☐
6 Sensory ability ☐
7. Muscle activity Paretic limb ☐
8. Transport ability of the arm ☐
9. Prevent/ reduce pain ☐
10. Muscle activity Non paretic limb ☐
11. Incorporate arm into balance and mobility activity ☐
12. Awareness of 2° complications ☐

### Gross position of patient during activities used:

1. Supine ☐
2. Prone ☐
3. Sidelying on unaffected side ☐
4. Side lying on affected side ☐
5. 4-point kneeling ☐
6. 2-point kneeling ☐
7. Unsupported sitting ☐
8. Supported sitting ☐
9. Asymmetrical sitting ☐
10. Perch Sitting ☐
11. Standing ☐
12. Prone standing ☐

### Setting

1. Gym ☐
2. Ward ☐
3. Hydrotherapy pool ☐
4. Other (please state)……..

**Equipment Used**:……

### Treatment Activities.

**1.** *Soft tissue mobilisation*

*1.1* Stroking ☐
*1.2* Effleurage ☐
*1.3* Lymph drainage techniques ☐
*1.4* Petrissage (kneading/wringing/picking-up/rolling) ☐
*1.5* Specific compression (trigger points) ☐
*1.6* Myofascial release ☐
*1.7* Frictions ☐

**2.** *Joint mobilisation*

*1.1* Accessory Movements ☐
*1.2* Passive Movements ☐
*1.3* Active Movements ☐

**3.** ***Facilitation of muscle activity/movement***

*3.1* Mental Imagery ☐
*3.2* Patient Generated Cueing ☐
*3.3* Therapist Generated Cueing ☐
*3.4* 'Hand on' to induce a desired motor response ☐
*3.5* Active Assisted ☐
*3.6* Facilitated Arm/Hand Activity from another body part ☐
*3.7* Restricted use of non-paretic limb ☐

**4.** *Positioning*

*4.1* Side lying hemiplegic side ☐
*4.2* Side lying non-hemiplegic side ☐
*4.3* Supine lying ☐
*4.4* Half lying ☐
*4.5* Sitting in armchair ☐
*4.6* Forwards lean sitting ☐
*4.7* Sitting in wheelchair ☐

**5.** *Specific sensory input*

*5.1* Tactile Stimulation ☐
*5.2* Proprioceptive Stimulation ☐
*5.3* Electrical stimulation ☐

**6.** *Splinting techniques*

*6.1* Shoulder support ☐
*6.2* Elbow support ☐
*6.3* Wrist/hand support ☐

Splinting material used ……..

**7.** ***Exercise to increase strength***

*7.1* Resistance from the therapist ☐
*7.2* Resistance from body weight ☐
*7.3* Resistance from equipment ☐
*7.4* Gravity neutral repetitive movement ☐

**8.** ***Balance and mobility incorporating upper limb activity***

*8.1* In, or from, lying ☐
*8.2* In, or from, kneeling ☐
*8.3* In, or from, sitting ☐
*8.4* In, or from, standing ☐
*8.5* In walking ☐

**9.** ***Upper limb functional tasks***

*9.1* Bilateral functional activities ☐
*9.2* Unilateral reaching activities that are object directed ☐
*9.3* Unilateral reaching activities that are spatially directed ☐
*9.4* Dexterity exercises ☐

**10.** *Education for patient and/or carer*

*10.1* To encourage self monitoring of upper limb ☐
*10.2* Transfers training ☐
*10.3* Limb handling and positioning skills ☐
*10.4* Written/ visual/ photo exercise programme ☐

***11.*** *Other interventions / techniques*

*11.1* Acupuncture ☐
*11.2* Ultrasound ☐
*11.3* Compression ☐

# Instructions for completion of recording form

1. ONE FORM FOR EACH TREATMENT SESSION
   Please complete one form for each treatment session given to patients included as subjects in the Functional Strength Training upper limb clinical trial
2. TO COMPLETE THE AIMS SECTION
   Please place a tick in the box that best describes the aims relevant to the particular treatment session being recorded. Unless stated otherwise, it is assumed that the aim is to 'Improve/ Optimise' in each case.
3. TO COMPLETE THE GROSS POSITION SECTION
   Place a tick in the box for every gross position used to deliver physiotherapy treatment during treatment sessions being recorded
4. TO COMPLETE THE EQUIPMENT SECTION
   Please write the name of any equipment used during the particular treatment session being recorded. Please refer to the booklet for further details of equipment.
5. TO COMPLETE THE SECTION "TREATMENT ACTIVITIES"
   Please place a tick in the boxes which best describe the treatment that was given to the patient during the particular treatment session being recorded.
6. FOR FURTHER DESCRIPTION OF ITEMS ON RECORDING FORM OVERLEAF
   Please refer to the accompanying document "Upper Limb Treatment Schedule Booklet: to accompany the Upper Limb Treatment Recording Form"

# Abbreviations for and glossary of terms used in recording form overleaf

| | |
|---|---|
| Effleurage | A gliding manipulation performed with light centripetal pressure that deforms subcutaneous tissue down to the investing layer of the deep fascia * |
| Est duration of upper limb Rx | Estimated duration of upper limb treatment session. If the treatment session does not involve the upper limb the therapist should place a '0' in this section. |
| Facilitation | The application of an appropriate mode and dose (frequency, duration and intensity) of sensory stimulus provided by the therapist to access a desired active response from the patient ** |
| Friction | A repetitive, specific, nongliding technique that produces movement between the fibres of connective tissue, increasing tissue extensibility, and promoting ordered alignment of collagen within the tissues. * |
| Lymph drainage techniques | A nongliding technique performed in the direction of lymphatic flow, using short, rhythmical strokes with minimal to light pressure, which deforms subcutaneous tissue without engaging muscle * |
| Mental Imagery | Mental rehearsal of a motor act that occurs in the absence of overt motor output |
| Myofascial Release | A technique that combines a nongliding fascial traction with varying amounts of orthopaedic stretch to produce a moderate, sustained tensional force on the muscle and its associated fascia, which results in palpable viscoelastic lengthening and plastic deformation of the fascia * |
| Petrissage | A group of related techniques that repetitively compress, shear, and release muscle tissue with varying amounts of drag, lift, and glide * |
| Physiotherapist | Person with professional Physiotherapy qualification |
| Rx | Treatment |
| Specific compression | A non-gliding technique that is applied with a specific contact surface to muscle, tendon, or connective tissue; the compression and release is applied in a direction that is perpendicular to the target tissue, and the compression is often sustained * |
| Stroking | Gliding over the patient's skin (unidirectionally) with minimal deformation of subcutaneous tissues.* |
| Rehabilitation Assistant | Person assisting the physiotherapist but who is not a qualified physiotherapist |

*References:*


* Andrade C-K, Clifford P. Outcome-Based Massage. Lippencott Williams and Wilkins, London 2001.

** Hunter S M, Crome P, Sim J, Pomeroy V M. Formulation of a schedule of 'mobilization and tactile stimulation' for the upper limb after stroke: a precursor to evaluation. In press July 2006

## Appendix XIV

Field notes

# Field Notes



| | | |
|---|---|---|
| **Participant ID:** | **FSTXXX** | **Group Allocation: LL** |
| **Date:** | XXXXX | |
| **Length of session:** | 45 minutes / 15 minutes rest | |

| | |
|---|---|
| **Adverse Events**:<br><br>None | |
| **Notes**:<br>In sitting (dining room chair): | Toe tapping x10 (x3)<br>Lifting left foot on and off step x 10 (x 3)<br>Repeated with 1lb ankle weight x 10 (x 3)<br>Kicking football to targets - 10 minutes |
| High stool | Sit to stand and return x10 (x3) using hands<br>Sit to stand in right step standing x 10 (x2) using hands<br>Sit to stand and return x10 (x3) no hands<br>Repeat in right step standing x10 (x3) no hands |
| Standing | Dynamic balance activity throwing ball (10 minutes)<br>Dynamic balance activity kicking ball, holding on to stick (10 minutes)<br>Dynamic balance activity kicking ball without stick (5 mins) |

# Field Notes



| | | |
|---|---|---|
| **Participant ID:** | **FSTXXX** | **Group Allocation: LL** |
| **Date:** | XXXXX | |
| **Length of session:** | 50 minutes / 10 minutes rest | |

| | |
|---|---|
| **Adverse Events**:<br><br>None | |
| **Notes**:<br>In sitting (dining room chair): | Lifting left foot on and off step x 10 (x 3)<br>Repeated with 1lb ankle weight x 10 (x 3)<br>Repeated with 2lb ankle weight x10 (x 1) |
| High stool | Sit to stand and return x10 (x 3) no hands<br>Sit to stand in right step standing x 10 (x 2) using hands<br>Sit to stand and return x10 (x 2) right foot on step using hands<br>Repeat in right step standing x10 (x 3) no hands |
| From dining room chair | Sit to stand and return x10 (x 2)<br>Sit to stand and return x 10 (x 2) in right step stand |
| Standing | Dynamic balance activity throwing ball (10 minutes)<br>Dynamic balance activity kicking ball with alternating legs (10 minutes) no stick |
| Overground walking practice | Walking practice using bean bags to increase step length and hip, knee and dorsiflexion during walking (10 mins) |

# Field Notes



| | | |
|---|---|---|
| **Participant ID:** | **FSTXXX** | **Group Allocation: LL** |
| **Date:** | XXXXX | |
| **Length of session:** | 30 minutes / 5 minutes rest | |

| | |
|---|---|
| **Adverse Events**:<br><br>No adverse events reported but had been out for the day yesterday and was complaining of feeling tired today. | |
| **Notes**:<br>In sitting (dining room chair): | Lifting left foot on and off step with 2lb ankle weight x 10 (x 3) |
| From dining room chair | Sit to stand and return x10 (x3) using hands<br>Sit to stand in right step standing x 10 (x2) using hands<br>Sit to stand and return x10 (x3) no hands<br>Repeat in right step standing x10 (x3) no hands |
| Standing | Dynamic balance activity throwing ball (10 minutes)<br><br>Stopped treatment at participants request as complaining of feeling too tired. |

# Field Notes



| | | |
|---|---|---|
| **Participant ID:** | **FSTXXX** | **Group Allocation: LL** |
| **Date:** | XXXXX | |
| **Length of session:** | 0 mins | |

**Adverse Events**:

None

**Notes:**
Participant telephoned to cancel appointment as was feeling too tired, expressed continued wish to participate in study, arranged appointments for the following week.

## Appendix XV

Ethics form

## Welcome to the Integrated Research Application System

## IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

**Please enter a short title for this project** (maximum 70 characters)
Functional strength training one year after stroke -FeST1vAIS

**1. Is your project an audit or service evaluation?**

○ Yes ◉ No

**2. Select one category from the list below:**

○ Clinical trial of an investigational medicinal product
○ Clinical investigation or other study of a medical device
○ Combined trial of an investigational medicinal product and an investigational medical device
◉ Other clinical trial or clinical investigation
○ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
○ Study involving qualitative methods only
○ Study limited to working with human tissue samples, other human biological samples and/or data *(specific project only)*
○ Research tissue bank
○ Research database

**If your work does not fit any of these categories, select the option below:**

○ Other study

**2a. Please answer the following question(s):**

| | | |
|---|---|---|
| a) Does the study involve the use of any ionising radiation? | ○ Yes | ◉ No |
| b) Will you be taking new human tissue samples (or other human biological samples)? | ○ Yes | ◉ No |
| c) Will you be using existing human tissue samples (or other human biological samples)? | ○ Yes | ◉ No |

**3. In which countries of the UK will the research sites be located?***(Tick all that apply)*

☑ England
☐ Scotland
☐ Wales
☐ Northern Ireland

**3a. In which country of the UK will the lead R&D office be located?**

◉ England
○ Scotland

- ○ Wales
- ○ Northern Ireland

**4. Which review bodies are you applying to?**

- ☑ NHS/HSC Research and Development offices
- ☑ Research Ethics Committee
- ☐ National Information Governance Board for Health and Social Care (NIGB)
- ☐ Ministry of Justice (MoJ)

**5. Will any research sites in this study be NHS organisations?**

● Yes ○ No

**5a. Do you want your application to be processed through the NIHR Coordinated System for gaining NHS Permission?**

○ Yes ● No

*If yes, you must complete and submit the Portfolio Adoption Form immediately after completing this project filter, before proceeding with completing and submitting other applications.*

**6. Do you plan to include any participants who are children?**

○ Yes ● No

**7. Do you plan to include any participants who are adults unable to consent for themselves through physical or mental incapacity?** *The guidance notes explain how an adult is defined for this purpose.*

○ Yes ● No

**8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service in England or Wales?**

○ Yes ● No

**9. Is the study, or any part of the study, being undertaken as an educational project?**

○ Yes ● No

**10. Is this project financially supported by the United States Department for Health and Human Services?**

○ Yes ● No

**11. Will identifiable patient data be accessed outside the clinical care team without prior consent at any stage of the project (including identification of potential participants)?**

○ Yes ● No

**Integrated Research Application System**
**Application Form for Other clinical trial or investigation**

National Patient Safety Agency
National Research Ethics Service

## Application to NHS/HSC Research Ethics Committee

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

**Short title and version number:** (maximum 70 characters - this will be inserted as header on all forms)
Functional strength training one year after stroke -FeST1vAIS

*Please complete these details after you have booked the REC application for review.*

**REC Name:**
Cambridgeshire 2 REC

**REC Reference Number:**
09/H0308/147

**Submission date:**
15/07/2009

## PART A: Core study information

### 1. ADMINISTRATIVE DETAILS

**A1. Full title of the research:**

Functional strength training to improve walking and upper limb function in people at least 1 year after stroke. A Phase II Trial.

**A3. Chief Investigator:**

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | Dr | Jane | Cross |
| Post | Senior Lecturer | | |
| Qualifications | 1985-Chartered Physiotherapist,<br>1988-Advanced Post Registration Intensive Respiratory Care<br>1991-Managing Health Services (M-Level 25 credits)<br>1999-MSc Health Sciences<br>2005-Doctor of Education | | |
| Employer | University of East Anglia | | |
| Work Address | Queens Building<br>University of East Anglia<br>Norwich | | |
| Post Code | NR4 7TJ | | |

| | |
|---|---|
| Work E-mail | j.cross@uea.ac.uk |
| * Personal E-mail | j.cross@uea.ac.uk |
| Work Telephone | 01603 593315 |
| * Personal Telephone/Mobile | 01603 593315 |
| Fax | |

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*

*A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.*

**A4. Is there a central study co-ordinator for this research?**

○ Yes ◉ No

**A5-1. Research reference numbers.** *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):
Sponsor's/protocol number: R16844
Protocol Version:
Protocol Date:
Funder's reference number: TSA2008/08
International Standard Randomised Controlled Trial Number (ISRCTN): ISRCTN71632550
ClinicalTrials.gov Identifier (NCT number):
European Clinical Trials Database (EudraCT) number:
Project website: n/a

| Ref.Number Description | Reference Number |
|---|---|

**A5-2. Is this application linked to a previous study or another current application?**

○ Yes ◉ No

*Please give brief details and reference numbers.*

## 2. OVERVIEW OF THE RESEARCH

***To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.***

**A6-1. Summary of the study.** *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. This summary will be published on the website of the National Research Ethics Service following the ethical review.*

Weakness of the leg and arm is common after stroke. This affects peoples' everyday lives. For example, being unable to tie shoe laces or cross the road before the lights change.
In previous studies it was found that adding muscle strengthening to functional training (functional strength training) improved ability to walk and use the weak arm in everyday tasks in people who are within the first three months after stroke. This trial will investigate functional strength training in stroke survivors who are at least 1 year after stroke. At this stage of stroke it is not yet clear whether people can still make improvements.

All participants in this trial will be randomly allocated to receive either leg or arm training. They will receive training in their own homes, from a research physiotherapist for 1 hour a day, 4 days a week for 6 weeks. The measures will be made before the training, after 6 weeks training and again 6 weeks after that. Leg and arm function will be assessed in all participants regardless of group allocation.

The trial also aims to investigate what stroke survivors think about functional strength training, i.e. whether participants found it too tiring or disrupted their daily routine. A number of participants will be interviewed before and after the training.

The final thing the trial will investigate is whether the training provides value for money.

Results from the trial will determine whether there is sufficient benefit to justify undertaking large-scale investigation of functional strength training in people at least 1 year after stroke.

Part of this study will contribute to a PhD undertaken by the Research Physiotherapist, Kath Mares.

**A6-2. Summary of main issues.** *Please summarise the main ethical and design issues arising from the study and say how you have addressed them.*

BACKGROUND TO THIS PHASE II TRIAL
Physical therapy interventions to improve motor function are a large component of organised stroke care which has been shown to reduce disability. Despite this, many stroke survivors are left with permanent disability detrimental to everyday life. For example, at discharge from rehabilitation, stroke survivors have an average walking speed of 5.5metres/second (m/s), well below the 0.8m/s required to cross the road before the lights change, and may be unable to perform simple tasks such as unscrewing a lid from a jar.
The impact is considerable, in England and Wales alone approximately 120,000 people sustain a stroke each year. Rehabilitation therapies are beneficial in enhancing recovery but many stroke survivors are left with permanent disability. This is disappointing and there is an urgent need for therapies that are even more effective than those we have now.

Research evidence suggests that therapy might need to be task-specific and focus on re-training of functional activity. However a prerequisite for participation in repetitive functional re-training is the ability to produce sufficient voluntary activation of paretic muscle to achieve the muscle strength threshold required for functional activities. Indeed, decreased muscle strength may contribute more to loss of functional ability than impaired dexterity, muscle tone, sensation or pain. A systematic review of muscle strength training after stroke has found positive effects on both strength and functional ability. However, increases in muscle strength may not translate into improvements in functional ability unless strengthening is provided as part of activities such as sit-to-stand thus both functional and strength training may be beneficial.
We have therefore developed an intervention called Functional Strength Training (FST).

CLINICAL UNCERTAINTY (EQUIPOISE)
Findings of Phase I (upper limb) and Phase II (lower limb) trials give evidence of efficacy in people within three months of stroke. Multi-centre trials are planned to evaluate the efficacy and cost-effectiveness of FST in the first 3 months after stroke. However it is unclear whether the results of these trials can be generalised to people who are at least 1 year after stroke because of potential clinical differences between these two populations. People in the so called chronic phase after stroke are often perceived to have plateaued in terms of potential for further motor improvement. This is now being questioned by findings that repetitive task-specific practice results in substantial motor improvement later after stroke. The current application therefore is for a Phase II trial to find whether there is sufficient indication of efficacy of FST in people at least 1 year after stroke to justify and inform the design of subsequent Phase III trials.

IDENTIFICATION AND CONFIDENTIALITY OF POTENTIAL PARTICIPANTS
Potential participants will initially be informed about the study by the clinical team. They have access to the stroke records created and held within the acute NHS Trust (Norfolk and Norwich Hospital). Therefore the research team will not be given any details about potential participants until they receive the reply slip giving the research team their contact details. Only members of the research team who require these details due to their direct involvement with the participants will have access to these details, i.e. those members of the research team who need to visit participants at home (Research Associate, Research Physiotherapist and where required 2nd Research Associate).

Appropriate members of the research team will have Research Passports and Honorary Contracts within the NHS Trust hosting this research (most passports are already in place). The Research therapist will be registered with the appropriate section of the Health Professions Council and professional body. Thus subject to the same rules of professional conduct as the clinical team.

All information about stroke survivors obtained during the conduct of this study will be stored in lockable filing cabinets in the research office or research laboratory. Dr Cross will take responsibility for ensuring that only people who need access to this information obtain it and will ensure that all the research team are aware of their responsibilities regarding confidentiality. As soon as a participant is included in the trial they will be given a trial number consisting of study acronym and a number e.g. FSTUL001. Personal details will be kept in a separate database from any results which will be identified by ID number only. No participant will be identifiable in any dissemination of results.

NUMBER OF RESEARCHERS VISITING THE PARTICIPANT AT HOME

Most participants will be directly involved with 2 members of the research team. Participants selected for interviews will have 3 different members of the research team visit them at home.

Those directly involved with the participant will be:

1.Research Associate 1 – required to take informed consent, screen for inclusion, and complete all baseline, outcome and follow-up measurements.

2. Research Physiotherapist – required to randomise and deliver the FST Intervention

3. Research Associate 2 – required to undertake the interviews before and after the intervention period (for 6 out of 58 participants)

The number of different researchers involved is to assure blinding and to preserve the independence of the qualitative aspect of the trial.

These requirements will be clearly stated in the Participant Information Sheet and explained to the participant prior to obtaining consent. The Participant Information Sheet will provide photographs, names and contact numbers so that Participants know who is coming and for what purpose. All researchers visiting the participants home will have research passports and wear Identification Badges.

LONE WORKING (Researcher Safety Checklist)

All researchers will follow and abide by the University of East Anglia's Lone Worker Policy. It is Dr Cross's responsibility to ensure that satisfactory systems are in place to ensure the safety of the research team when visiting participants in their homes.

AVOIDANCE OF UNFAIR EXCLUSION AND INCLUSION

The Research team acknowledge that letters will be sent to a wide range of stroke survivors, some of whom will not meet the inclusion criteria of the study. Therefore the letter and Participant Information sheet will be carefully worded to give some guidance about whether people are likely to be included. To try and give all stroke survivors the opportunity to be included, the guidance given will aim to encourage people to contact the research team for more information, but the final screening for inclusion to the study will completed on the initial visit by the Research Associate 1.

DECISION MAKING CAPACITY

After stroke people can experience two key difficulties which affect decision making capacity. These are language impairment (mostly aphasia – difficulty understanding and/or expressing information) and cognitive communication impairment (e.g. attention, memory). Both language impairment and cognitive communication impairment can affect: ability to understand information about a trial; appreciate the current situation and its consequences; reason about the risks, benefits and alternatives of participation; and make and communicate a choice about participation. It is important to include as many stroke survivors as possible, whilst meeting the study criteria, as this will make findings more applicable to clinical practice and a frequent complaint from stroke survivors with aphasia is that they are not given opportunities to be involved in research.

It is important to distinguish between language and cognitive communication impairment for both clinical practice and for research. However it is not feasible to have input from a Speech and Language Therapist with all potential participants.

Therefore enhanced communication strategies will be used as standard in this trial as appropriate for individual potential participants. All researchers in the team who will be involved in recruiting, treating and measurement are therapists with clinical experiences of using these enhanced communication strategies. These strategies involve using multiple communication modes including: verbal, demonstration, gestures, diagrams, selection of written words/picture by potential participants, pictures, short sentences, repetition, responding to cues from stroke survivors, and using closed questions to check understanding. In our experience these strategies are also useful for people without communication impairment. It is our practice therefore to design letters, information sheets and informed consent forms so that information is given both verbally and pictorially. This ensures that even when the researcher is not present potential participants have information to hand which is more easily understandable.

In our experience stroke survivors residing alone in the community are likely to have some level of language and cognitive ability in order to survive in the community. Those who are more impaired are likely to have a close support networks or live with family members who would therefore be able to understand and explain the contents of the letter

and information sheets and assist the potential participants decision as to whether or no they would like to take part.

We will ensure that all potential participants, whether they have a communication impairment or not, are given sufficient time to assimilate information, understand information and ask questions. Contact numbers for the research team will be clearly given on letters and information sheets to give opportunity for potential participants or carers to ask questions as required. We also check understanding of the information and the consequences of being involved in a trial before asking a potential participant to sign an informed consent form.

All members of the research team involved in recruitment and informed consent have had Good Clinical Practice Training.

POTENTIAL RISKS, BURDENS, AND BENEFITS
The risk of harm for any participant in this trial is low. There is however a small risk that participating in FST might result in an overuse syndrome which presents as pain in the arm or leg. We will therefore check regularly for the onset of pain in the weaker arm and hand in participants allocated to either group. Throughout we will monitor participants for behavioural signs of fatigue and discomfort and allow adequate rest periods or stop the session as appropriate for individuals.
All participants will be told that they are free to withdraw from the trial at any time, without giving a reason and without any effect on their current or future healthcare.

All participants will have the benefit of a comprehensive assessment of their upper limb and lower limb function which is not widely available to them in the community. All participants will be given 6 weeks of therapy that they would not have received as part of routine community therapy. Patients will consent to the research team being able to communicate with the clinical team should any concerns be highlighted during the participant's involvement in the trial. As participants included in the trial will not be receiving therapy, the research team may identify difficulties that participants are having and be able to refer these difficulties onto the appropriate Health Care Professional.

Involvement in the study will mean being available for 1 hour a day, 4 days a week for 6 weeks. This may disrupt participant's daily routine. However this aspect is one of the questions being investigated in the trial, i.e. whether or not this intensity of therapy is acceptable in people's homes. Therefore the findings from this trial will help us answer this question and inform subsequent trials.

The issue of intensity was also reviewed by our Stroke Patients Forum. The feedback we received about the protocol was that stroke survivors welcomed the therapy being delivered at home and felt that the intensity was acceptable 1 year after stroke.

USER INVOLVEMENT
The protocol for this trial was reviewed by our Stroke Patients Forum. In addition to the above feedback they would have preferred to be able able to choose whether they worked on their arm or leg in training but understood the need for randomisation and reported that this would not stop them from taking part in the trial. In summary the Stroke Patients Forum were positive about the trial and gave some useful suggestions about what would aid understanding about conduct of the trial. These suggestions were incorporated into the final protocol.
Further service user involvement will be provided in the research by members of The Patient and Public Involvement in Research group (PPIRES: www.norfolkhealthresearch.nhs.uk) who have been involved in the Trial Management Group (TMG). In addition the content and structure of the interviews in the qualitative sub-study will be informed by working with user members of the TMG and using CONNECT guidelines on including stroke survivors with aphasia. User members of the TMG will also be involved in the analysis and interpretation of data. Finally, dissemination to user groups will be assisted by user members of the TMG, PPIRES and the Stroke Patient Forum.

Part of this study will contribute to a PhD undertaken by the Research Physiotherapist, Kath Mares.

**A10. What is the principal research question/objective?** *Please put this in language comprehensible to a lay person.*

Objective / Question 1: Clinical Efficacy
Is there sufficient efficacy to justify subsequent larger trials for functional strength training (FST) to improve paretic limb recovery in people at least 1 year after stroke?

**A11. What are the secondary research questions/objectives if applicable?** *Please put this in language comprehensible to a lay person.*

Objective / Question 2-5:
2. Acceptability of Intervention to participants:
Is FST delivered in the community acceptable to stroke survivors 1 year+ after stroke?

3. Recruitment rate:
What is the probable recruitment rate to a subsequent phase III trial?
4. Sample size:
What sample size is needed for a subsequent phase III trial (effect size, attrition rate, response variation)?
5. Cost Effectiveness
What cost-effectiveness data should be collected in subsequent trials? Does FST provide value for money; are costs reduced by improvements resulting from training?

**A12. What is the scientific justification for the research?** *Please put this in language comprehensible to a lay person.*

Physical therapy interventions to improve motor function are a large component of organised stroke care which has been shown to reduce disability. Despite this, many stroke survivors are left with permanent, disability detrimental to everyday life.

Research evidence suggests that therapy might need to be task-specific and focus on re-training of functional activity. However, participation in repetitive functional re-training requires the ability to produce sufficient voluntary activation of paretic muscles to achieve the muscle strength threshold required for functional activities. Indeed, decreased muscle strength may contribute more to loss of functional ability than impaired dexterity, muscle tone, sensation or pain.

A systematic review of muscle strength training after stroke has found positive effects on both strength and functional activity. However, increases in muscle strength may not translate into improvements in functional ability unless strengthening is provided as part of activities such as sit-to-stand, thus both functional and strength training may be beneficial.

We have therefore developed an intervention called Functional Strength Training (FST). Findings of Phase I (upper limb) and phase II (lower limb) trials give evidence in people within 3 months of stroke. However, it is unclear whether results of these clinical trials will be generalisable to people who are at least 1 year post stroke because of the potential clinical differences between these two populations. People in the so-called chronic phase after stroke are often perceived to have plateaued in terms of potential for further motor improvement. This clinical tenet is now being questioned by the findings that repetitive task-specific practice results in substantial motor improvement late after stroke.

**A13. Please give a full summary of your design and methodology.** *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

Identification of Potential Participants
Potential participants will be identified by the clinical team at the Norfolk and Norwich University Hospital NHS Trust (NNUH).
Dr Phyo Myint, Honorary Consultant Physician in Medicine for the Elderly and Stroke Medicine at the NNUH will lead the identification of patients from the stroke admissions records in the acute trust. From this the Stroke Research Nurses as members of the clinical team will select patients who were discharged home after suffering an anterior circulatory stroke, from 2006 onwards, who were unable to walk more than 50 meters on discharge. The Stroke Research Nurses will ensure patients are not deceased by looking up patients on the PAS (Patient Administration System)then telephoning their GP surgery. This process is necessary so that stroke survivors are not inappropriately selected or families receive letters for deceased relatives potentially causing unnecessary upset.

Approaching Potential Participants
The Stroke Research Nurses will then send a letter to potential participants. The letter will be signed by Dr Myint and Dr Kneale Metcalfe (Consultant in Medicine for the Elderly). The letter will inform potential participants about the research, give a brief summary about what would be involved and some guidance about whether or not people would be suitable to participate (i.e. meet trial inclusion criteria).
A reply slip and stamped addressed envelope will accompany the letter. Potential participants will be asked to return this to the research team to show that they are interested in learning more about the study. This will confirm permission to receiving a Participant Information Sheet and a telephone call from the research team.

Information to Potential Participants
Following return of the reply slip, the research team (Research Associate) will send out a participant information sheet providing more detailed information about the study. This information sheet has been designed with specialist Speech and Language Therapy (SALT)input and follows CONNECT guidelines to make it suitable for people with communication and cognitive deficits following their stroke.
Potential participants will be given at least a week to read the information before the RA contacts them by telephone. The telephone call will answer any questions, ascertain if the person would like to take part and if so arrange a home visit. Prior to the visit a letter will be sent to confirm the appointment date and time.

If the reply slip is not returned within two weeks, one follow up letter will be sent out as a reminder. This will be documented in the first letter.

Obtaining informed consent, screening and baseline measurements
Potential Participants will be visited at home by the RA. The purpose of the home visit will be to complete screening for inclusion to trial, obtain informed consent and carry out baseline assessments. If participants do not meet the inclusion criteria they will be thanked for their time and take no further part in the trial.

Baseline measurements will take approximately 30-40mins. The RA will make measures of how strong the muscles are in the weaker arm and leg. This will involve assessing ability to walk and straighten / bend the knee against resistance. The arm tests will assess how well participants are able to use their weaker arm and hand in everyday functional activity. Tasks include picking up a 5cm wooden block and placing it on a shoulder-height shelf, pouring water from one plastic container to another and placing the weaker hand on the top of the head. The RA will also assist the participant with the questionnaires.

The consent form will ask the participant to consent to their GP being contacted by the Research Team. Following this visit the particpant's GP will be contacted to let them know that the particpant wishes to take part in the study. The letter will ask the GP to inform the Research team within 10 working days whether there is any medical reason why the participant cannot be included. If there is no contact from the GP then the particpant will be invited to take part in the trial.

Randomisation
Independent of the RA the Research Physiotherapist (Kath Mares) will telephone the automated randomisation service and be given the group allocation for the participant. She will then telephone the participant to tell them which group they are in, e.g. whether they will get arm (FSTUL) or leg (FSTLL) training. The treatment start date and time will be negotiated with the participant.

First Interview
After randomisation, a sub-set of six participants will be purposively selected from the main trial sample (6/58) to be interviewed twice (before and after the treatment period). Purposive selection of the sub-sample will ensure maximum variation across key areas of conceptual relevance. The proposed sample of six respondents will therefore include people taking part in the upper limb programme and lower limb programme, be both men and women, of varying ages and levels of functional independence.

Face-to-face, individual interviews will be conducted by a second RA, experienced in conducting interviews, in the participants home. Interviews will follow a semi-structured format and take a narrative approach. This will allow respondents to convey their own story of their stroke experiences and raise issues they see as pertinent to their experiences whilst still enabling the researcher to collect the pre-set broad categories of information across all participants. An interview guide will be designed to elicit rich detailed data.

Interview 1 is designed to capture the respondent's story of their lives before their stroke, at the time they experienced their stroke, their post-stroke experience of managing their condition and initial expectations of rehabilitation. This will help contextualise their views and expectations of rehabilitation generally and the FST programme specifically. Questions will be focused around expectations of the training.

Intervention Period
The research physiotherapist (Kath Mares) will provide either FSTUL or FSTLL training depending on group allocation. Intervention will be provided in the participant's home for 1 hour a day, 4 days a week for 6 weeks.

FST is a ‘hands off’ progressive resistive exercise during functional activity. Activities are progressed by increasing the number of repetitions, increasing range of joint motion required and increasing the load to be moved. Portable equipment (free weights and steppers) will be used as appropriate. Participants will be encouraged to use the paretic limb (upper or lower) in everyday activity. These treatments are described in a treatment schedule which describes the standardisation of the intervention.

Throughout the intervention period participants will be monitored to make sure that the training is not causing pain or excessive fatigue in their weaker limb. There is a monitoring procedure in the protocol to address this issue.

Outcome Measures
After the 6 weeks of FST training the Research Associate(1) will negotiate an appointment for an outcome measurement session (in participants homes). The same parameters will be collected as at baseline including questionnaires.

Second Interview

The same sub-set of 6 participants will then complete interview 2 for the qualitative part of the study. The RA(2)will complete the second interview on the same day as the Research Associate (1) completes the Outcome Measures. Interview 2 is designed to access participants' subsequent experiences of taking part in the FST programme, to further contextualise and collect data on their views on the acceptability of the programme when delivered in a community setting, in relation to specific features of FST.

Follow up measures
These will take place 6 weeks after the Outcome Measure by the Research Associate in the patients' home during a negotiated appointment. This will be exactly the same as the baseline and outcome measurements.

**A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?**

- [x] Design of the research
- [x] Management of the research
- [x] Undertaking the research
- [x] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

*Give details of involvement, or if none please justify the absence of involvement.*
The protocol for the trial was reviewed by our Stroke Patients Forum. In summary they were positive about the proposed trial and their suggested changes to aid understanding of the protocol have been incorporated into this present version. Furthermore, service user involvement has been be provided in this research by members of the Patient and Public Involvement in Research Group (PPIRES: norfolkhealthresearch.nhs.uk/nhr/309/47.html), who have been involved in activities such as design of information sheets / informed consent forms and the trial management group (TMG). In addition the content and structure of the interviews in the qualitative sub-study will be informed by working with user members of the TMG and using CONNECT guidelines on including stroke survivors with aphasia. User members of the TMG will also be involved in the analysis and interpretation of data. Finally, dissemination to user groups will be assisted by user members of the TMG, PPIRES and the Stroke Patient Forum.

## 4. RISKS AND ETHICAL ISSUES

### RESEARCH PARTICIPANTS

**A17. Please list the principal inclusion and exclusion criteria.**

Combined Inclusion and Exclusion Criteria:
1. Adults aged 18+years, 1 to 5 years after stroke in the anterior circulation (Infarct or haemorrhage)not receiving formal therapy for their upper or lower limb

2. Able to walk 4 steps with continuous support from one person and/or assistive devices, but unable to walk up and down a flight of stairs without going sideways or taking one step at a time. Able to take paretic hand from lap and place on table top in front, but unable to pick up four £1 coins individually from a tabletop and stack them evenly in a pile.

3. Can follow a 1-stage command, i.e. suffient communication and orientation for interventions in this trial

4. Potential participants meeting the above criteria will also require consent from their GP to ensure that any other known pathology should not exclude them from participating in functional strength training. Potential Participants will need to consent to their GP being written to.

### RESEARCH PROCEDURES, RISKS AND BENEFITS

**A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the**

**research protocol.** *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

| Intervention or procedure | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Recruitment | 1 | 0 | 60 mins | 2 letters and 1 phone call from RA1 |
| consent | 1 | 0 | 15-30 mins | RA1 in patients home |
| Baseline measures | 1 | 0 | 60 mins | Independent researcher in Patient's home |
| Semi-structured Interview | 1 | 0 | 60 mins | RA2 in patient's home |
| second interview | 1 | 0 | 60mins | RA2 in patient's home |

**A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol.** *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

| Intervention or procedure | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Baseline Measures | 1 | 0 | 30-40 mins | RA1 in Patient's home |
| Outcome Measures | 1 | 0 | 30-40 mins | RA1 in Patient's home |
| FST including Monitoring adverse effects | 24 | 0 | 1hour | Research Physiotherapist Patient's home |
| Follow up measures | 1 | 0 | 30-40 mins | RA1 in Patient's home |

**A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?**

○ Yes ◉ No

**A21. How long do you expect each participant to be in the study in total?**

The total length of time each participant will be expected to be in the study is 13 weeks.
This includes baseline measures, 6 weeks intervention period, outcome measures then follow up measures 6 weeks later and interviews for the sub group of patients .

**A22. What are the potential risks and burdens for research participants and how will you minimise them?**

*For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.*

The risk of harm for any participant in this trial is low. There is however a small risk that participating in FST might result in an overuse syndrome which presents as pain in the paretic limb. This will be considered to have occurred if a participant reports or exhibits limb pain (behavioural signs) to the research physiotherapist on 4 consecutive treatment days. If pain occurs then participants will be withdrawn from their allocated treatment but included in the measurement battery (intention -to-treat principle).

An earlier version of this protocol was reviewed by the UK Stroke Research Network who raised concerns about participants becoming fatigued. The present treatment intervention protocol has been revised to address their concerns so that the length and intensity of treatment sessions can be carefully tailored to individual ability and stamina to ensure that participants do not become too fatigued. The research therapist will monitor any discomfort in the weaker limb during treatment interventions and signs of fatigue. Treatment sessions can be reduced, and / or greater rest periods can be introduced if necessary to reduce these potential effects.

All participants will be told that they are free to withdraw from the trial at any time, without giving a reason and without any effect on their current and future healthcare.

**A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?**

○ Yes ◉ No

**A24. What is the potential for benefit to research participants?**

All participants will have the benefit of a comprehensive assessment of both their upper and lower limb.
Participants will receive 6 weeks of a therapeutic intervention that they would not normally be offered at this stage after stroke (1 year+ post stroke).

**A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished?** *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

This is a phase II trial which will enable the researchers to begin the process of evaluating possible clinical effectiveness. At the end of this research provision of this service will not be adequately evidence based and thus not continued. It is however anticipated that if this research indicates a positive effect research into clinical effectiveness will continue via a phase III randomised controlled trial.
It will be made clear to participants before consent that continuation of this service is not possible at this stage.

**A26. What are the potential risks for the researchers themselves?** *(if any)*

Lone working in the community - this will be undertaken following the lone working policy of the university (Researcher safety Checklist).

## RECRUITMENT AND INFORMED CONSENT

***In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.***

**A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?***For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants will be identified by the clinical team at the Norfolk and Norwich University Hospital NHS Trust (NNUH).
Dr Phyo Myint, Honorary Consultant Physician in Care of the Elderly and Stroke Medicine at the NNUH will lead the identification of patients from the stroke admissions records in the acute trust. From this the Stroke Research Nurses will select patients who were discharged home after suffering an anterior circulatory stroke, from 2006 onwards, who were unable to walk more than 50 meters on discharge. The stroke research nurses will ensure patients are not deceased by looking up patients on the PAS (Patient Administration System) then telephoning their GP surgery.

A letter will be sent to potential participants about the research, including the purpose, an outline of what it would involve and a description of suitable participants. The letter will be sent from Dr Myint and Dr Kneale Metcalfe. Included with the letter will be a stamped addressed envelope for people to return if they are interested in receiving more information about the study. The letter will include a telephone number so that people can ask any questions about the research before they decide whether to return the slip or not.
If they do return the slip they will be sent a Participant Information sheet which provides detailed explanation of the study. Some potential participants may have language or cognitive deficits that make understanding written language difficult, thus this information has been designed in accordance to the CONNECT guidelines and with specialist advice from a speech and language therapist.

After a minimum of a week, for reading and consideration of the information, potential participants will receive a telephone call, from the RA to arrange a visit for screening purposes and consent. These details, including date, time and purpose of visit will be confirmed in a letter.

The potential participants will be visited by the researcher who will be able to clarify any queries in person. The particpants will be screened by the RA1, then, if they are eligible for inclusion informed consent will be obtained.

**A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?**

○ Yes ◉ No

*Please give details below:*

**A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?**

○ Yes ◉ No

**A29. How and by whom will potential participants first be approached?**

A letter will be sent to potential participants from 2 consultants from the health care team. Two consultants from the acute unit where patients would have had their acute stay in hospital.
(Dr Phyo Myint and Dr Kneale Metcalf)

**A30-1. Will you obtain informed consent from or on behalf of research participants?**

◉ Yes ○ No

*If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.*

*If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.*

After stroke people can experience two key difficulties which affect decision making capacity. Both language impairment and cognitive communication impairment (e.g. attention, memory) can affect: ability to understand information about a trial; appreciate the current situation and its consequences; reason about the risks, benefits and alternatives of participation; and make and communicate a choice about participation. It is important to include as many stroke survivors as possible, whilst meeting the study criteria, as this will make findings more applicable to clinical practice and a frequent complaint from stroke survivors with aphasia is that they are not given opportunities to be involved in research.

It is important to distinguish between language and cognitive communication impairment for both clinical practice and for research. Enhanced communication strategies will therefore be used, as appropriate for individual potential participants, as standard in this trial . All researchers in the team involved in recruiting, treating and measurement have experience of using these enhanced communication strategies.
Strategies that may be used involve using multiple communication modes including: verbal, demonstration, gestures, diagrams, selection of written words/picture by potential participants, pictures, short sentences, repetition, responding to cues from stroke survivors, and using closed questions to check understanding. In our experience these

strategies are also useful for people without communication impairment. It is our practice therefore to design information sheets and consent forms so that information is given both verbally and pictorially. This ensures that even when the researcher is not present potential participants have information to hand which is more easily understandable.

We will ensure that all potential participants, whether they are known to have have a communication impairment or not, are given sufficient time to assimilate information, understand information and ask questions. We will also check understanding of the information and the consequences of being involved in a trial before asking a potential participant to sign an informed consent form.

*If you are not obtaining consent, please explain why not.*

*Please enclose a copy of the information sheet(s) and consent form(s).*

**A30-2. Will you record informed consent (or advice from consultees) in writing?**

(●) Yes ( ) No

**A31. How long will you allow potential participants to decide whether or not to take part?**

The recruitment process is staged to allow full information to be given and time to consider it. For independent advice the telephone number of the PPIRES will be given to potential participants on the participant information sheet. Once this has been sent at least a week will pass before seeking written consent.

**A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?**

( ) Yes
(●) No
( ) Not Known

**A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?***(e.g. translation, use of interpreters)*

There are no resources in this project for translation or interpreters expenses. However, acknowledging a number of potential participants may have aphasia following their stroke, specialist advice has been sought in designing the letters and information sheets for this research.

**A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?**

The nature of the study will not provide any interim form of analysis. However adverse event rates will be monitored by the trial management group and any appropriate action arising from this will be the responsibility of this group.

**A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study?** *Tick one option only.*

( ) The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
(●) The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
( ) The participant would continue to be included in the study.
( ) Not applicable – informed consent will not be sought from any participants in this research.

*Further details:*

*If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.*

## CONFIDENTIALITY

**In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.**

### Storage and use of personal data during the study

**A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?***(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☑ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☑ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☐ Manual files including X−rays
  - ☐ NHS computers
  - ☐ Home or other personal computers
  - ☑ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

*Further details:*
All personal data stored on the computer will be in a password protected space on the university's hard drive. This will be stored abiding by the Data Protection Act and Good Clinical Practice guidelines

**A38. How will you ensure the confidentiality of personal data?***Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

The NHS Code of Confidentiality will be complied with. Specifically we will keep data that could identify individuals separate from the anonymised data and ensure that the linking information is accessed only by those who need to know. All data by which individuals may be identified will be kept in lockable filing cabinets within the research office or research laboratory. Any electronic data by which individuals can be identified will be placed in a password protected space on university computers.

**A40. Who will have access to participants' personal data during the study?** *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Members of the research team who are directly involved in patient contact. Consent will be ascertained during the identification process as patients will be sending their contact details to the researchers if they wish to be involved.

### Storage and use of data after the end of the study

**A43. How long will personal data be stored or accessed after the study has ended?**

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ◉ 12 months – 3 years
- ○ Over 3 years

*If longer than 12 months, please justify:*
Part of this trial will form a component of a PhD degree and therefore data analysis might be more prolonged than usual.

## INCENTIVES AND PAYMENTS

**A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?**

○ Yes ◉ No

**A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?**

○ Yes ◉ No

**A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?**

○ Yes ◉ No

## NOTIFICATION OF OTHER PROFESSIONALS

**A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?**

◉ Yes ○ No

*If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.*

**A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?**

◉ Yes ○ No

*It should be made clear in the participant's information sheet if the GP/health professional will be informed.*

## PUBLICATION AND DISSEMINATION

**A50. Will the research be registered on a public database?**

◉ Yes ○ No

*Please give details, or justify if not registering the research.*

UK Stroke research Network (UK SRN)
International Standard Randomised Controlled Trial Number Register (ISRCTN)

**A51. How do you intend to report and disseminate the results of the study?** *Tick as appropriate:*

- [x] Peer reviewed scientific journals
- [ ] Internal report
- [x] Conference presentation
- [ ] Publication on website
- [ ] Other publication
- [ ] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [x] Other (please specify)

Through user groups

**A53. Will you inform participants of the results?**

(•) Yes ( ) No

*Please give details of how you will inform participants or justify if not doing so.*
At the last visit for follow up measures participants will be asked if they would be interested in receiving a summary of the final report when it is produced. If so their details will be retained for this purpose.

## 5. Scientific and Statistical Review

**A54. How has the scientific quality of the research been assessed?** *Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi−centre research group
- [ ] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

*Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:*
This work has been peer reviewed as part of the funding application process by the Stroke Association

*For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.*

*For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.*

**A56. How have the statistical aspects of the research been reviewed?** *Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [ ] Review by a statistician within the Chief Investigator’s institution
- [x] Review by a statistician within the research team or multi−centre group

☐ Review by educational supervisor

☐ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

*In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.*


| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | Dr | Allan | Clark |
| Department | Faculty of Health | | |
| Institution | University of East Anglia | | |
| Work Address | Medicine Building | | |
| | University of East Anglia | | |
| | Norwich | | |
| Post Code | NR4 7TJ | | |
| Telephone | 01603593629 | | |
| Fax | 01603593166 | | |
| Mobile | | | |
| E-mail | Allan.Clark@uea.ac.uk | | |


*Please enclose a copy of any available comments or reports from a statistician.*

**A57. What is the primary outcome measure for the study?**

Functional Ambulatory Category (FAC) to measure lower limb functional ability. The test measures walking ability on a 6 point scale, from 0 (non functional ambulation to 5 (independent amubulation over uneven surfaces, stairs and steps. This scale is widely used in research and clinical practice.

Action Research Arm Test (ARAT) to measure functional ability of upper limb
The ARAT is a test of upper limb function with subscales covering grasp, grip, pinch and gross movements. It has good validity and reliability and is widely used in clinical research

**A58. What are the secondary outcome measures?** *(if any)*

Modified Rivermead Mobility Index (MRMI) (to assess lower limb function)
The MRMI is a measure of mobility which concentrates on body mobility.
It comprises a series of 8 tasks which cover a range of functional activities from turning over in bed to walking and is therefore designed for all levels of patients. It is is easy administer, requires no equipment and can be used in the home setting. It is well used and has proved to be a measure that is valid, reliable and sensitive to change.

9 Hole Peg test (for assessing upper limb function)
The Nine Hole Peg Test assessing finger dexterity and ability to manipulate objects. It is a simple, timed test of fine motor coordination. Reliability and validity have been assessed and norms are available. The test involves the subject placing 9 dowels in 9 holes. Subjects are scored on the amount of time it takes to place and remove all 9 pegs.

EQ-5D
EQ-5D is a standardised measure of health status developed by the EuroQoL Group
in order to provide a simple, generic measure of health for clinical and economic
appraisal1. It is applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.
EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics, and in face-to-face interviews.

Custom designed health economics questionnaires

**A59. What is the sample size for the research?** *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 58
Total international sample size (including UK): 58
Total in European Economic Area:

*Further details:*

**A60. How was the sample size decided upon?** *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

An aim of this Phase II trial is to provide data for a power calculation for a subsequent Phase III trial. A formal power calculation is not yet possible but we estimate, assuming a standard deviation (SD) of 1, that 23 participants per group would have 90% power at 5% significance (2-tailed) to detect a change of 1 point on the FAC and 5.7 points on the ARAT (minimal clinically important difference) assuming a SD of 5.7 using the two-sample t-test, however to allow for the non-normal distribution of the outcome we increase this by 10% to 26 particpants per group. To allow for an attrition rate of 10% (estimated from our earlier trials) we will therefore recruit 58 stroke survivors.

**A61. Will participants be allocated to groups at random?**

(●) Yes ( ) No

*If yes, please give details of the intended method of randomisation:*
Remote telephone randomisation provided by the Clinical Research & Trials Unit (Norfolk and Norwich University Hospital)

**A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.**

Objective 1. Clinical efficacy (principle research question)
The effects of FST will be tested by comparing the changes in Primary and Secondary measures (follow-up-outcome, outcome-baseline) between treatment limbs using t-tests.

Objective 3 and 4: recruitment, sample size and attrition rate:
In accordance with the intention-to-treat principle all participants will be analysed according to which group they were randomly allocated. Analysis will use a Mann-Whitney test, although if imbalance occurs at baseline a rank-based analysis-of co-variance will be used.
Adverse events will be compared between two groups using a Poisson regression model, a comparison of the event rate will be carried out. The main aim of the analysis is to estimate the parameters which will be needed for a formal sample size calculation for a subsequent Phase III trial. Analyses will be carried out using Stata. The analysis will also estimate recruitment and attrition rates to inform subsequent trials.

Objective 2. Acceptability of the intervention. The analytic process will sort the data thematically and seek categories to inform conceptualisation (theory-building). Conceptualisation will be developed iteratively, to emerge from the beginning of the interview data collection process. The analytical approach will draw on narrative analysis approaches to identify meaningful categories and structures in participants' stories. It combines top-down and bottom up scrutiny of data.
Analysis of interview 1 will guide the development of questions in Interview 2. The longitudinal analysis will help establish links between reasons, interactions, experiences and potentially-changing views of respondents in relation to the FST programme and its acceptability to them.

Objective 5: Cost effectiveness data
An economic analysis is necessary as the estimation of cost-effectiveness is an iterative process, and early information on costs and effects can be used to inform the design of subsequent trials. For costs we will seek to identify what resource items should be monitored in a future study.
The resources to be monitored will include those associated with input from the research therapist, any re-admission to hospital, and other health and non health care contacts (e.g. further therapy, social services, nursing care). Additionally we will monitor the costs incurred by participants and their families (e.g. transportation, care they receive). Appropriate unit costs will then be assigned to these resource items to provide an indication of the relative costs.

For effectiveness we will seek to test the suitability of using the EQ-5D in subsequent trials by using baseline and follow-up data to estimate the validity and responsiveness of the EQ-5D in stroke survivors.

Finally, the information on the costs and effects will be used to give an indication of the likely cost-effectiveness of FST, the level of uncertainty associated with these estimates, and to conduct a value-of-information analysis to provide an indication of the expected value of future research.

## 6. MANAGEMENT OF THE RESEARCH

**A63. Other key investigators/collaborators.** *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | Professor | Valerie | Pomeroy |
| Post | Professor of Neuro-rehabiliatation | | |
| Qualifications | PhD, BA, GradDipPhys, FCSP | | |
| Employer | Univeristy of East Anglia | | |
| Work Address | Queens Building<br>University of East Anglia<br>Norwich | | |
| Post Code | NR4 7TJ | | |
| Telephone | 01603591724 | | |
| Fax | 01603593133 | | |
| Mobile | | | |
| Work Email | v.pomeroy@uea.ac.uk | | |

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | Dr | Katherine | McGlashan |
| Post | Consultant in Rehabilitation Medicine | | |
| Qualifications | 1989 MBBS London<br>1996 MRCP London<br>2005 FRCP London | | |
| Employer | Norfolk PCT | | |
| Work Address | Colman Centre (Specialist Rehab)<br>Unthank Road<br>Norwich | | |
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| Fax | | | |
| Mobile | | | |
| Work Email | kate.mcglashan@norfolk-pct.nhs.uk | | |

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | Dr | Fiona | Poland |
| Post | Senior Lecturer in Therapy Research | | |

| | |
|---|---|
| Qualifications | 1978 BA Econ (Hons) Social Anthropolgy, University of Manchester<br>1983 MA Econ, Apllied Social Research, University of Manchester<br>1992 PhD, University of Manchester<br>2001 PG Cert in Teaching in Higher Education, University of Wales, Bangor |
| Employer | University of East Anglia |
| Work Address | AHP, Queens Building<br>University of East Anglia<br>Norwich |
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| Mobile | |
| Work Email | f.poland@uea.ac.uk |

| Title | Forename/Initials | Surname |
|---|---|---|
| Dr | Martin | Watson |

| | |
|---|---|
| Post | Senior Lecturer (Physiotherapy) & course Leader MSc Physiotherapy |
| Qualifications | 2007 PhD,Faculty of Health, University of East Anglia<br>1998 MSc, Faculty of Medicine, Univeristy of Southampton<br>1983 GradDipPhys, Leeds School of Physiotherapy |
| Employer | University of East Anglia |
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| Fax | |
| Mobile | |
| Work Email | m.watson@uea.ac.uk |

| Title | Forename/Initials | Surname |
|---|---|---|
| Dr | Marie-Luce | O'Driscoll |

| | |
|---|---|
| Post | Lecturer (Physiotherapy) |
| Qualifications | 2007 PhD, School of Allied Health Professions, UEA<br>1999 AdCertHE Advanced Certificate Higher Education practice:Centre for Staff Education and Develpoment, UEA<br>1999 MSc Health Sciences: School of Occupational Therapy and Physiotherapy, UEA<br>1989 GradDipPhys Graduate Diploma in Physiotherapy: Normanby College, Kings College, London<br>1985 BSC (Hons) Biological Sciences, Kings College, London |
| Employer | University of East Anglia |
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| Telephone | 01603593301 |
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| Mobile | |
| Work Email | m-l.odriscoll@uea.ac.uk |

| Title | Forename/Initials | Surname |
|---|---|---|
| Dr | Allan | Clark |

| | |
|---|---|
| Post | Lecturer in Medical Statistics |

| | |
|---|---|
| Qualifications | 1996 , BSc (Hons) Applicable Mathematics with Computing, First Class, University of Abertay<br>2002 PhD Statistics, University of Aberdeen |
| Employer | University of East Anglia |
| Work Address | Medicine Building<br>University of East Anglia<br>Norwich |
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| Telephone | 01603593629 |
| Fax | 01603593166 |
| Mobile | |
| Work Email | Allan.Clark@uea.ac.uk |

| Title | Forename/Initials | Surname |
|---|---|---|
| Dr | Gary | Barton |

| | |
|---|---|
| Post | Lecturer in Health Economics |
| Qualifications | 2007 PhD Health Economics, University of Nottingham<br>1998 MSc Health Economics, University of York<br>1996 BA Economics and Sociology, University of York |
| Employer | University of East Anglia |
| Work Address | Faculty of Health<br>University of East Anglia<br>Norwich |
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| Work Email | G.Barton@uea.ac.uk |

| Title | Forename/Initials | Surname |
|---|---|---|
| Mrs | Kathryn | Mares |

| | |
|---|---|
| Post | Lecturer in Physiotherapy |
| Qualifications | Grad Dip Phys, Addenbrookes School of Physiotherapy<br>MSc in health Sciences 2002, University of East Anglia |
| Employer | University of East Anglia |
| Work Address | Queens Building<br>University of East Anglia<br>Norwich |
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| Title | Forename/Initials | Surname |
|---|---|---|
| | | |

| | |
|---|---|
| Post | |
| Qualifications | |
| Employer | |
| Work Address | |

Post Code
Telephone
Fax
Mobile
Work Email

## A64. Details of research sponsor(s)

**A64-1. Lead sponsor** *(must be completed in all cases)*

Name of organisation which will act as the lead sponsor for the research:
University of East Anglia

Status:
○ NHS or HSC care organisation ◉ Academic ○ Pharmaceutical industry ○ Medical device industry ○ Other

| | |
|---|---|
| Address | Research and Business Services<br>University of East Anglia<br>Norwich |
| Post Code | NR4 7TJ |
| Country | England |
| Telephone | 01603 456161 |
| Fax | 01603 458553 |
| Mobile | |
| E-mail | rbs@uea.ac.uk |

**A64-2. Sponsor's UK contact point for correspondence** *(must be completed in all cases)*

| Title | Forename/Initials | Surname |
|---|---|---|
| Miss | Tracy | Moulton |

| | |
|---|---|
| Post | Research Contracts Manager |
| Work Address | Research and Business Services<br>University of East Anglia<br>Norwich |
| Post Code | NR4 7TJ |
| Telephone | 01603591482 |
| Fax | 01603591550 |
| Mobile | |
| E-mail | T.moulton@uea.ac.uk |

**A64-3. Are there any co−sponsors for this research?**

○ Yes ◉ No

**A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another**

**country?**

○ Yes ◉ No

*Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.*

**A68. Give details of the lead NHS R&D contact for this research:**

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | Mrs | Kath | Andrews |
| Organisation | Norfolk and Norwich University Hospital NHS Trust | | |
| Address | R&D Office, Level 3 East Block | | |
| | Norfolk & Norwich University Hospit | | |
| | Colney Lane, Norwich | | |
| Post Code | NR4 7UY | | |
| Work Email | kath.andrews@nnuh.nhs.uk | | |
| Telephone | 01603286611 | | |
| Fax | 01603289800 | | |
| Mobile | | | |

*Details can be obtained from the NHS R&D Forum website: www.rdforum.nhs.uk*

**A69. How long do you expect the study to last?**

Planned start date: 01/09/2009
Planned end date: 07/09/2012

Duration:
Years: 3
Months: 0

**A71-1. Is this a single centre study?**

◉ Yes ○ No

**A71-2. Where will the research take place?** *(Tick as appropriate)*

- ☑ England
- ☐ Scotland
- ☐ Wales
- ☐ Northern Ireland
- ☐ Other states in European Union
- ☐ Other countries in European Economic Area
- ☐ USA
- ☐ Other international (please specify)

**A72. What host organisations (NHS or other) in the UK will be responsible for the research sites?** *Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:*

- ☑ NHS organisations in England 1

- ☐ NHS organisations in Wales
- ☐ NHS organisations in Scotland
- ☐ HSC organisations in Northern Ireland
- ☐ GP practices in England
- ☐ GP practices in Wales
- ☐ GP practices in Scotland
- ☐ GP practices in Northern Ireland
- ☐ Social care organisations
- ☐ Phase 1 trial units
- ☐ Prison establishments
- ☐ Probation areas
- ☐ Independent hospitals
- ☐ Educational establishments
- ☐ Independent research units
- ☐ Other (give details)

Total UK sites in study: 1

**A75-1. Will a data monitoring committee (DMC) be convened?**

○ Yes ◉ No

*If Yes, please forward details of the membership of the DMC, its standard operating procedures and summary reports of interim analyses to the Research Ethics Committee which gives a favourable opinion of the study (or to GTAC if applicable).*

**A75-2. What are the criteria for electively stopping the trial or other research prematurely?**

There are no formal stopping roles. Risk will be assessed on a case by case basis by the trial management group following the adverse event procedure

## A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

**A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research?** *Please tick box(es) as applicable.*

*Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.*

- ☐ NHS indemnity scheme will apply (NHS sponsors only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

University of East Anglia

*Please enclose a copy of relevant documents.*

**A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research?** *Please tick box(es) as applicable.*

*Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.*

- [ ] NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- [x] Other insurance or indemnity arrangements will apply (give details below)

University of East Anglia

*Please enclose a copy of relevant documents.*

**A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?**

*Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.*

- [x] NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- [ ] Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

*Please enclose a copy of relevant documents.*

**A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?**

- ○ Yes
- ◉ No

*Please enclose a copy of relevant documents.*

## PART C: Overview of research sites

**Please enter details of the host organisations (NHS or other) in the UK that will be responsible for the research sites.**

| Research site | PI/ local collaborator |
|---|---|
| Norwich and Norfolk University Hospital NHS Tust | Dr Phyo Myint |

## PART D: Declarations

**D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the main REC or the GTAC (as applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the main REC, in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs.
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

**Contact point for publication**

*NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.*

- [x] Chief Investigator
- [ ] Sponsor's UK contact point
- [ ] Study co-ordinator
- [ ] Student
- [ ] Other – please give details
- [ ] None

Title:
Forename / Initials:
Surname:
Post:
Work address:
Work email:
Work telephone:

**Access to application for training purposes**

*Optional – please tick as appropriate:*

- [ ] I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature: .....

Print Name: Dr Jane L Cross

Date: *(dd/mm/yyyy)*

**D2. Declaration by the sponsor's representative**

*If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.*

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

7. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

This section was signed electronically by Miss Tracy Moulton on 15/07/2009 03:37.

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|---|---|
| Job Title/Post: | Research Contracts Manager |
| Organisation: | UEA |
| Email: | t.moulton@uea.ac.uk |

# Appendix XVI

Study Characteristics

Study characteristics of the studies included in the systematic review.

| Study | Base of support feedback in gait rehabilitation<br>Aruin, A.S. et al (2003) | |
|---|---|---|
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Unknown | |
| Inclusion criteria | Participants with a narrow base of support due to recent single unilateral cardiovascular accident.<br>Able to stand and walk up to 4.5-6m with assistance of a physical therapist. | |
| Sample size | 8 | 8 |
| Male % | 68% of whole sample | |
| Age: mean (SD) | 65.34 (3.4) | |
| Time since stroke onset: months (SD) | 0.59 (0.06) | |
| Intervention | Auditory feedback during gait as an adjunct to conventional gait therapy<br>10 days, twice daily for 25 mins | Conventional gait therapy 10 days, twice daily for 25 mins |
| Primary Outcome | Step width (metres) | |
| Measurement time points | Pre intervention and post intervention | |
| Findings | Step width increased from 0.09(0.003) to 0.16(0.008) $p<0.05$. | Step width increased from 0.099(0.004) to 0.13(0.003) $p<0.05$. |
| | Statistically significant difference in step width between the two groups post intervention ($p<0.05$) | |
| Authors conclusion | Authors conclude that auditory biofeedback may have been useful in light of greater improvement seen in the experimental group. | |
| Comments | Lack of detail about blinding of assessors to treatment allocation increases the potential for bias. All patients included in the study completed the intervention but exact details about treatment fidelity are not possible to discern from the reported study. This is a small study with no power calculation therefore at risk of a type II error, however the intervention seems feasible. It was unclear whether participants in this study were inpatients or outpatients but the intervention appeared to be taking place in a clinical location. | |

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|---|---|---|
| Study | HandTutor™ Enhanced Hand Rehabilitation after Stroke<br>Carmeli et al (2011) | |
| Study Design | Observer blind randomised Controlled Trial – Pilot Study | |
| Participant Characteristics | Experimental | Control |
| Sample | Inpatients in a rehabilitation department in one hospital | |
| Inclusion criteria | Minimum of 10° extension of flexion at the wrist or fingers, an ability to extend the wrist joint five times continuously without losing active range of motion. | |
| Sample size (analysed) | 16 | 15 |
| Male % | 69 | 73 |
| Age: Mean (SD) | 57.8 (8.9) | 62.5 (5.0) |
| Time since stroke onset: Months (SD) | 0.28 (0.25) | 0.37(0.27) |
| Intervention | Traditional hand therapy with additional training using the HandTutor™ for extrinsic feedback for 20-30 minutes on each intervention session. Intervention took place over 15 consecutive treatment sessions. | Traditional hand therapy with extra traditional hand therapy for 20-30 minutes. Intervention took place over 15 consecutive treatment sessions. |
| Primary Outcome | Brunnstrom Fugl Meyer (BFM) and Box and Block Test Measurements taken at 4 time points: Baseline, Midway (after 10 days), end of study period (outcome) and 10 days post intervention (follow up). | |
| Findings<br>BFM mean (SD)<br>Outcome<br>Follow up<br>Box and Block Test mean(SD)<br>Outcome<br>Follow up | <br><br>56.6(6.6)<br>56.9(7.0)<br><br>32.0(11.6)<br>35.0(8.8) | <br><br>52.4(8.1) p=0.0417<br>51.9(6.3) p=0.912<br><br>31.4(16.1) p=0.015<br>33.2(17.5) p=0.5 |
| Authors conclusion | Statistically significant improvement in both primary outcome measures in favour of the experimental group. The authors suggest that the intervention could be a useful alternative for providing extra movement practice whilst the feedback mechanism offers control over the 'correct' practice and may serve to motivate the patient. Lack of a statistically significant difference between the outcome and follow up scores lead the authors to conclude that the training effect was maintained for ten days after the intervention. | |
| Comments | 34/134 (25%) patients screened were included based on the inclusion criteria. Two participants in the experimental group dropped out, one died and the | |

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| | other didn't wish to continue taking part. One participant dropped out of the control group as they did not wish to take part. Reasons for this were not given but the authors' assumption that the intervention might motivate the participant may not be appropriate in light of these drop outs. This assertion was also not based on any data obtained from the trial so seems to be speculative. There is no information about what if any intervention was received on completion of the trial therefore the assumption that the effects of the study are carried over may be confounded by other variables. The process for randomisation was not described clearly therefore this study has a potential risk of selection bias. |

| | | |
|---|---|---|
| Study | Facilitation of Sensory and Motor Recovery by Thermal Intervention for the Hemiplegic Upper Limb in Acute Stroke Patients: A Single-Blind Randomized Clinical Trial<br>Chen et al (2005) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Inpatients on wards within rehabilitation medicine and neurology departments in one hospital. | |
| Inclusion Criteria | Presenting with motor deficits of the upper limb under Brunnstrom stage IV. | |
| Sample size (analysed) | 15 | 14 |
| Male % | 40% | 71% |
| Age: Mean (SD) | 58.5(12.9) | 59.6(12.0) |
| Time since stroke onset: Months (SD) | 0.47(0.22) | 0.41(0.22) |
| Intervention | Standard treatment for the upper limb and thermal stimulation to the upper limb. Intervention given 5 times weekly over six weeks. | Standard treatment for the upper limb. |
| Primary Outcome | Brunnstrom stage: Weekly assessments in order to derive temporal changes over the course of the study. | |
| Findings: mean (SD) | Outcome - 0.4(0.2) | Outcome - 0.2(0.1)<br>p=0.0005 |
| Authors conclusion | Thermal stimulation significantly increased the outcomes of the Brunnstrom stage compared to the control group. Acknowledged the high drop out rate and suggested that in future studies an intention to treat analysis would minimise the effects of this on the study outcomes. | |
| Comments | Forty six people were initially recruited but 17 dropped out because of discharge from hospital, pulmonary infection or searching alternative Chinese medicine therapy. Suggestions were given to minimise the effects of this on the analysis but no proposal were discussed for preventing this from occurring again in the future. Reporting of the trial showed a low risk of bias for all categories suggesting that the results of this trial are reliable, although the small sample size may impact on its generalisability and increase the risk of a type II error. | |

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| Study | Facilitation of motor and balance recovery by thermal intervention for the paretic lower limb of acute stroke: a single-blind randomised clinical trial.<br>Chen et al (2011) | |
| Study Design | Single-blind randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Consecutive patients who were admitted to one rehabilitation hospital over a one year period | |
| Inclusion criteria | Motor deficit of the paretic leg at or less than Brunnstrom stage III | |
| Sample size (analysed) | 17 | 16 |
| Male % | 76% | 56% |
| Age: Mean (SD) | 58.0 (11.5) | 62.3 (11.3) |
| Time since stroke onset: Months (SD) | 0.36(9.5-12.0) | 0.36(9.3-14.0) |
| Intervention | Standard therapy and thermal stimulation for 48 minutes five times weekly for six weeks. | Standard therapy and 'discussion of 20 minutes duration at least 3 times a week' for six weeks |
| Primary Outcome | Fugl-Meyer Assessment, Medical Research Council scale for Lower extremity, Functional Ambulation Category (FAC). Measures were taken at baseline, 4 weeks and 6 weeks (outcome). | |
| Findings<br>FM median (range) Outcome<br>MRC median(range) Outcome<br>Functional Ambulation Category median (range) Outcome | <br><br>14.0(10.5-15.5)<br><br>6.0(4.0-7.0)<br><br>20.(2.0-2.0) | <br><br>6.0(3.0-9.8) p<0.001<br><br>3.0(1.3-4.0) p<0.001<br><br>1.0(1.0-1.0) p<0.001 |
| Authors conclusion | Authors reported this to be a pilot study with a relatively small sample of people and suggested larger confirmatory trials were warranted. | |
| Comments | Two people dropped out of the study because they were discharged from hospital. It was not possible to blind either the therapist or participant to group allocation therefore this may have been a source of bias. All other aspects of the risk of bias assessment were reported and seemed to be at low risk. Dose was reported but it is unclear whether this was the intended intensity for this intervention and therefore it is not possible to speculate on treatment fidelity. | |

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| Study | The effectiveness of EMG biofeedback in the treatment of arm function after stroke<br>Crow et al (1989) | |
| Study Design | Single blind randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | All patients admitted to one District Hospital, participants were stratified according to severity of upper limb symptoms. | |
| Inclusion criteria | At least a flicker of activity around the shoulder girdle and had not already spontaneously recovered or did not have near normal movement. | |
| Sample size (analysed) | 20 | 20 |
| Male % | 70% | 55% |
| Age: Mean (SD) | 67.4(10.4) | 68.1(9.5) |
| Time since stroke onset: Months (SD) | 2-8 weeks post stroke | |
| Intervention | EMG biofeedback<br>Intervention was carried out over 6 weeks | Placebo<br>Intervention was carried out over six weeks |
| Primary Outcome | Action Research Arm Test (ARAT) and Brunnstrom Fugl-Meyer (BFM) taken at baseline, 6 weeks (outcome) and 12 weeks (follow up) | |
| Findings<br>BFM mean (SD)<br>Outcome<br>Follow up<br>ARAT mean (SD)<br>Outcome<br>Follow up | <br><br>34.5(22.0)<br>35.2(20.6)<br><br>21.3(22.8)<br>20.5(21.9) | <br><br>22.9(21.1) p=0.02<br>27.0(21.2) p=0.09<br><br>12.5(21.7) p=0.05<br>15.9(22.9) p=0.16 |
| Authors conclusion | EMG biofeedback facilitated the recovery of arm function during the period of time when the treatment was given but this did not persist once treatment stopped. The control group continued to improve during the follow up period although this was not statistically significant – the authors proposed that this was because the control group reached their plateau of recovery slower than the treatment group. The hiatus in improvement seen in the treatment group was reported to be because of a need for a period of consolidation of learning. | |
| Comments | Three participants died during the trial and a further two died during the follow up period. Treatment bias was reported to be minimised by having each therapist treat both intervention and control group. Effort was made to standardise motivation and enthusiasm although therapists could not be blind to treatment allocation therefore the potential for treatment bias was high. Both groups received standard physiotherapy delivered by a therapist | |

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| | outside of the treatment group – this was not standardised or recorded and therefore could have had an impact on the study outcomes. Treatment records were recorded daily but it is unclear whether the intervention was given over working days or everyday therefore the exact dose for this intervention is not possible to define and therefore replicate. The authors reported that the treatment group only received 18 sessions and that this might be the cause for the lack of improvement at follow up. Reasons for lack of treatment fidelity were not given. |

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| Study | Virtual reality based rehabilitation speeds up functional recovery of the upper extremities after stroke: A randomised controlled pilot study in the acute phase of stroke using the Rehabilitation gaming System<br>Da Silva Cameirao et al (2011) | | |
| Study Design | Randomised controlled trial with two control groups | | |
| Participant Characteristics | Experimental | Control (IOT) | Control (NSG) |
| Sample | Patients admitted to one rehabilitation unit | | |
| Inclusion criteria | Severe to moderate deficit of the affected upper limb | | |
| Sample size (analysed) | 10 | 5 | 4 |
| Male % | 50% | 60% | 25% |
| Age: Mean (SD) | 63.7(11.83) | 59.4(10.62) | 58.0(14.00) |
| Time since stroke onset: Months (SD) | 0.38(0.17) | 0.56(0.13) | 0.43(0.14) |
| Intervention | Virtual Reality and standard occupational and physical rehabilitation<br>3 weekly sessions of 20 mins over 12 weeks | Intensive occupational therapy (IOT) and standard occupational and physical rehabilitation<br>3 weekly sessions of 20 mins over 12 weeks | Non specific gaming (NSG) and standard occupational and physical rehabilitation<br>3 weekly sessions of 20 mins over 12 weeks |
| Primary Outcome | Barthel, Fugl-Meyer (FM), Motricity Index MI), Chedoke Arm and Hand Inventory (CAHI). Measurements were carried out at baseline, 5 weeks, 12 weeks (outcome and 24 weeks (follow up). | | |
| Findings<br>Barthel mean (SD)<br>Outcome<br>Follow up<br>MI mean(SD)<br>Outcome<br>Follow up<br>FM mean (SD)<br>Outcome<br>Follow up<br>CAHI mean(SD)<br>Outcome<br>Follow up | Experimental<br><br>94.9(8.9)<br>96.3(6.3)<br><br>73.6(16.1)<br>81.3(15.9)<br><br>84.6(18.4)<br>79.1(19.0)<br><br>90.2(17.0)<br>89.6(14.9) | Control (IOT group+NSG group)<br><br>88.0(17.8) p=0.2<br>92.9(7.1) p=0.2<br><br>60.2(20.0) p=0.052<br>66.3(20.9) p=0.065<br><br>66.9(22.9) p=0.065<br>72.0(18.8) P=0.252<br><br>70.6(18.2) p=0.025<br>81.9(12.3) p=0.08 | |
| Authors conclusion | Authors concluded that at outcome the experimental group proved better than the control groups on a number of the clinical scales although this only reached statistical significance for one of these.<br>Study used a Likert scale to assess various factors about acceptability of the intervention, analysis of these findings | | |

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| | suggested that the intervention was highly acceptable to the participants in this study. Authors acknowledged that scores at follow up did not show the same findings as at outcome and suggested that the intervention may not have been sufficiently intense or may have increased the speed of recovery to the point of plateau. |
| Comments | Twenty five patients were originally selected for the study but 5 people left before week 5 assessment, 4 moved to a different institution and 1 dropped all rehabilitation. The study tried to control for difference aspects of the gaming experience i.e. the motivation that a participant might experience by taking part in a 'game' and also the potential effects of the movement therapy experienced as part of the intervention. The sample size increases the risk of a type II error but it appears from this study that the intervention was feasible and acceptable and did have the potential to show some effect. Methods for random sequence generation and allocation concealment were unclear in the reporting of this study therefore it is at risk of selection bias. |

| Study | Dynamic thigh muscle strength after auditory feedback training of body weight distribution in stroke patients<br>Engardt and Knutsson (1994) | |
|---|---|---|
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Participants who had previously been part of an earlier study | |
| Inclusion criteria | Included in previous study | |
| Sample size (analysed) | 16 | 14 |
| Male % | 75% | 29% |
| Age: Mean (SD) | 67 (6.05) | 65 (8.46) |
| Time since stroke onset: Months (SD) | 33.2(6.6) | 34.3(5.8) |
| Intervention | Auditory feedback from a force platform during sit to stand. Training lasted 15 minutes a day, 3 times a day for 6 weeks. | Sit to stand training without the addition of the auditory feedback. Training lasted 15 minutes a day, 3 times a day for 6 weeks. |
| Primary Outcome | Body weight distribution (BWD) on the paretic leg in rising to stand and sitting down. This was a follow up study so measurements were taken after training (outcome) and then again approximately 33 months after training finished (follow up). | |
| Findings<br>BWD up (%) mean (SD)<br>Outcome | 47.8(6.7) | 44.2(6.6) |

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| Follow up<br><br>BWD down (%) mean(SD)<br>Outcome<br>Follow up | 37.7(7.1)<br>P<0.001<br><br>47.9(5.3)<br>40.9(4.8)<br>P<0.001 | 39.5(7.0)<br>P<0.05<br><br>43.5(7.6)<br>42.5(7.1)<br>Not statistically significant |
| Authors conclusion | The decrease in body weight distribution on the affected leg at follow up was due to decreased muscle strength in the hemiparetic limb which had led to dependence on the unaffected limb. They also postulated that the participants had become dependent on the auditory feedback in the original trial and therefore when it was removed had not built up any internal mechanisms to compensate for this. | |
| Comments | There was a very long time between the outcome and follow up measures; it is unlikely that without ongoing intervention that participants would have maintained the training effect. Ten of the original participants had not taken part in this follow up study, 6 people were too unwell, 2 had moved away and 2 could not be contacted. It is difficult to draw any conclusions from this study as the time period between the measurements was so long and therefore confounding effects of other interventions and activities in that time period cannot be controlled for. It could suggest however that this intervention would need to be repeated/have a longer intensity for any effects to be maintained or that a self-directed training post intervention may have been indicated. | |

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| Study | Action observation has a positive impact on rehabilitation of motor deficits after stroke. Ertelt et al (2007) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Inpatients at a local rehabilitation centre | |
| Inclusion criteria | Younger than 76 years with a moderate paresis | |
| Sample size (analyse) | 8 | 8 |
| Male % | 63% | 75% |
| Age: Mean (SD) | 57.1(8.7) | 55.4(10.8) |
| Time since stroke onset: Months (SD) | 48.42(41.39) | 23.83(11.87) |
| Intervention | Action observation of an upper limb task and physical practice of the same. | Watching a video with geometric symbols and letters and physical practice. |
| Primary Outcome | Frenchay Arm Test (FAT) and Wolf Motor Function Test (WMFT). Measurements were taken 14 days before the onset of the therapy, day before the therapy and at the end of the treatment (outcome). Follow up measures were only done for 7 of the participants. | |
| Findings<br>WMFT mean(SD) Outcome<br>FAT mean (SD) Outcome | <br><br>277.4(17.0)<br><br>7.041(6.856) | <br><br>252.5(25.33) p=0.0525<br><br>16.97(15.94) p=0.0005 |
| Authors conclusion | Action observation and intensive repetitive practice of the observed actions provides a significant improvement in motor functions in chronic patients diagnosed with a stroke who had an established motor impairment. | |
| Comments | This study demonstrates improvement in motor deficits in participants who were within the chronic phase of recovery – the experimental group were on average over two years more post stroke than the control group. There is no description of recruitment methods or fidelity to treatment protocol therefore little can be learned about these aspects from this trial. Despite claims of efficacy by the authors this was a small trial which would be better viewed as a pilot study. | |

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| Study | Mental practice with motor imagery in stroke recovery: randomized controlled trial of efficacy<br>Ietswaart et al (2011) | | |
| Study Design | Randomised controlled trial | | |
| Participant Characteristics | Experimental | Control | |
| Sample | All stroke admissions to several acute hospitals were recorded and screened for inclusion. Participant information was given to patients if they were interested whilst they were inpatients in the hospital. | | |
| Inclusion criteria | Action Research Arm test score of between 3 and 51/57 | | |
| Sample size (analyse) | 39 | Attention controlled: 31<br>Normal care: 39 | |
| Male % | 56% | Attention controlled: 71%<br>Normal care: 64% | |
| Age: Mean (SD) | 69.3(10.8) | Attention controlled: 68.6(16.3)<br>Normal care: 64.4(15.9) | |
| Time since stroke onset: Months (SD) | 2.73(1.83) | Attention controlled: 3.03(2.11)<br>Normal care: 2.68(2.09) | |
| Intervention | Motor imagery intervention including mental practice and action observation on a one to one basis during 45mins, 3 days a week and 2 x 30 mins working independently over 4 weeks. | Two control groups: Attention controlled placebo – visualisation programme matched for therapist time and self directed practice over the same time period.<br>Normal care with no additional training. | |
| Primary Outcome | Action Research Arm Test (ARAT) recorded before the intervention and at the end of the treatment phase (outcome). | | |
| Findings<br>ARAT mean (SD) Outcome | 31.51(20.68) | Attent. Ctrl.<br>32.87(20.76) | Normal<br>30.38(20.53)<br>p=0.77 |
| Authors conclusion | No evidence for the benefit of mental imagery intervention on movement recovery in the subacute period of recovery after stroke. | | |
| Comments | Analysis was based on an intention to treat, adherence to treatment protocol is not reported in terms of dose however there were a number of drop outs from the study. One person withdrew from the experimental intervention, and 10 withdrew from the control groups suggesting that the intervention may have been more acceptable to the participants than the control interventions. Reasons for withdrawing from the | | |

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| | intervention other than through ill health are not reported. This study was at low risk of bias. |

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| Study | Effects of Motor Imagery Training on Gait Ability of Patients with Chronic Stroke.<br>Lee et al (2011) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Patients already participating in a rehabilitation programme in a community centre. | |
| Inclusion criteria | Able to walk 10m independently without an assistive device | |
| Sample size (analyse) | 13 | 11 |
| Male % | 46% | 36% |
| Age: Mean (SD) | 60.7(7.53) | 61.9(11.26) |
| Time since stroke onset: Months (SD) | Greater than 6 months | |
| Intervention | Motor imagery (MI) and treadmill training. 30 mins of MI training and 30 mins of treadmill 3 x week for 6 weeks. | Treadmill training only. 30 mins treadmill training 3 x week. |
| Primary Outcome | Walking speed taken before the intervention and after (outcome). | |
| Findings<br>Gait speed (cm/s) mean (SD)<br>Outcome | 55.68(17.72) $p<0.01$ | 51.50(19.73) $p<0.05$ |
| Authors conclusion | The change between pre and post test scores was greater for the experimental group and there were also statistically significant changes in other gait parameters which led the authors to conclude a positive effect of MI. | |
| Comments | This study was small and therefore should probably be interpreted as a pilot study. Participants were a convenience sample of individuals already attending a rehabilitation group and were arguably not left with a severe impairment, therefore may not be representative of all stroke survivors in the chronic stage of recovery from stroke. A total of 12 drop outs were reported but it is not clear from which group. This was a third of the original sample but without further details the impact of this for future studies cannot be extrapolated. Allocation concealment and blinding of outcome assessor were not reported so were at 'unclear' risk of bias therefore reliability of these findings needs to be made in light of this. | |

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| Study | Added Value of Mental Practice Combined with a Small Amount of Physical Practice on the Relearning of Rising and Sitting Post-Stroke: A Pilot Study Malouin et al (2009) | | |
| Study Design | Randomised controlled trial: pilot study | | |
| Participant Characteristics | Experimental | Control | |
| Sample | Convenience sample of inpatients in one rehabilitation unit | | |
| Inclusion criteria | Residual limb loading asymmetry but able to sit to stand without using their hands. | | |
| Sample size (analyse) | 3 | 3 | |
| Male % | 100% | Cognitive: 60%<br>No training: 100% | |
| Age: Mean (SD) | 57.1(8.7) | Cognitive:55.4(10.8)<br>No training: 61.8(9.5) | |
| Time since stroke onset: Months (SD) | 28.8(21.6) | Cognitive:42(34.8)<br>No training: 28.8(24.0) | |
| Intervention | Mental practice and physical training. Three times a week for four weeks. Each session took approximately 1 hour. | Two control groups:<br>No training – no training at all<br>Cognitive task and physical training. The same physical practice but with mental activities equivalent in time to the metal rehearsal in the experimental group for the same duration. | |
| Primary Outcome | Loading of the affected leg on rising and sitting, calculated as percent body weight. Measurements made at baseline, before training and after intervention (outcome). | | |
| Findings<br>% body weight on affected leg rising mean(SD) – outcome<br>% body weight on affected leg sitting mean (SD) - outcome | <br>43.3(8.9) p=0.04<br>44.27(3.83) p=0.04 | Cognitive task<br>43.4(4.02)<br>44.2(1.93) | No training<br>39.0(7.87)<br>39.21(7.92) |
| Authors conclusion | Only the experimental group had a statistically significant improvement in % body weight on the affected leg during both rising and sitting. | | |
| Comments | Allocation concealment was not reported therefore this was judged to be at ‘unclear’ risk of bias. This study may therefore be at risk of selection bias. Time spent in physical practice and either mental or cognitive practice was monitored during this study. Both groups received equivalent time on each of these activities therefore changes could not be attributed to dose. | | |

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| | Over the period of the intervention participants in the experimental group received a mean of 19.2 minutes physical practice and 157.6 minutes of mental practice. Adherence to treatment cannot be ascertained as it was unclear what the proportion of time in each activity was intended. The intended dose was reportedly approximately 60 minutes for both aspects of the intervention totalling an intended dose of 720 minutes. Only 24% of this was actually delivered however reasons for this were not suggested and therefore cannot inform the designs of future studies. |

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| Study | Effects of virtual reality training on gait biomechanics of individuals post-stroke. Mirelman(2010) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Sampling was not described but intervention took place in a gait analysis laboratory | |
| Inclusion criteria | Partial anti-gravity dorsiflexion but able to walk 50 feet without assistance. | |
| Sample size (analyse) | 9 | 9 |
| Male % | 83% | |
| Age: Mean (range) | 62 years (41-75) | |
| Time since stroke onset: Months (SD) | Greater than 2 years | |
| Intervention | Three times a week for 4 weeks for approximately 1 hour each time. Virtual reality to provide feedback on ankle movement. | Three times a week for 4 weeks for approximately 1 hour each time. The same exercises as the experimental group but with therapist feedback and pacing supplied by a metronome. |
| Primary Outcome | Self-selected walking speed (m/s). Measurements occurred 1 week before the intervention and after (outcome) and then three months after the end of the intervention (follow up). | |
| Findings<br>Walking speed m/s mean(SD) Outcome<br>Follow up | <br><br>0.80 p=0.003<br>0.76(0.18) p=0.013 | <br><br>0.70 p>0.05<br>0.67(0.29) p=0.97 |
| Authors conclusion | Task based virtual reality training was more effective than task based training alone. | |
| Comments | Risk of bias was ‘unclear’ for random sequence generation, allocation concealment and blinding of outcome assessment indicating that this study is possibly at risk of selection bias and detection bias. The recruitment process for participants was not described so cannot be used to inform future trials. All participants were reported to have taken part in all treatment sessions without adverse events – although these were not described so further information cannot be extrapolated. Feedback via virtual reality may be a useful adjunct to task specific training. | |

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|---|---|---|---|---|
| Study | Transcutaneous Electrical Nerve Stimulation (TENS) Combined With Task-Related Training Improves Lower Limb Functions in Subjects With Chronic Stroke. Ng and Hui-Chan (2007) | | | |
| Study Design | Randomised controlled trial | | | |
| Sample | Recruited from the community rehabilitation network | | | |
| Inclusion criteria | Able to walk 10m unassisted with or without walking aids | | | |
| | TENS | TENS+TRT | PLBO+TRT | CONTROL |
| Sample size (analyse) | 19 | 21 | 20 | 20 |
| Male % | 89.5% | 76% | 85% | 85% |
| Age: Mean (SD) | 56.4(9.1) | 58.4(7.1) | 57.1(7.8) | 57.3(8.6) |
| Time since stroke onset: Months (SD) | > 12 months | | | |
| Intervention | 60 mins of TENS | 60 mins of TENS followed by 60 mins of therapy based on Carr and Shepherd approach | Electrodes placed over acupuncture points (60 mins) and 60 mins of therapy based on Carr and Shepherd approach | No treatment |
| | Home programme 5 days a week for 4 weeks with 8 sessions in the laboratory to check competence and compliance. | | | |
| Primary Outcome | Gait velocity, measurements taken at baseline, after 2 weeks, after 4 weeks (outcome) and 4 weeks after the end of the intervention (follow up) | | | |
| Findings<br>Gait velocity (cm/s) mean(SD) outcome<br>follow up | <br><br>62.9(28.4)<br>58.8(26.5) | <br><br>68.2(34.5)<br>72.2(34.0)<br>p<0.01 compared to PLBO+TRT | <br><br>57.7(29.8)<br>58.3(28.8) | <br><br>63.9(24.1)<br>64.5(23.8) |
| Authors conclusion | Combining TENS with physical treatment was more superior to other interventions in improving motor functions in participants with chronic stroke. | | | |
| Comments | Although showing changes in gait speed, it is questionable whether these were clinically significant. The greatest gain in speed between the baseline and outcome was achieved by the intervention group but this was still only 17cm/s, therefore the impact of this intervention on the participant may not have been noticeable. Fidelity to treatment was measured by log | | | |

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| | books, the dose of each treatment session was not reported and therefore it is difficult to see if participants were compliant with the intervention and whether or not results were achieved because one group was more motivated and carried out more of the intervention than another. The recruitment strategy was not described therefore cannot be used to inform future interventions. |

| | | | | |
|---|---|---|---|---|
| Study | Does the use of TENS increase the effectiveness of exercise for improving walking after stroke? A randomised controlled trial.<br>Ng and Hui-Chan (2009) | | | |
| Study Design | Randomised controlled trial | | | |
| Sample | Recruited from the local rehabilitation network | | | |
| Inclusion criteria | At least $10^{o}$ of passive ankle dorsiflexion | | | |
| | TENS | TENS+TRT | PLBO+TRT | CONTROL |
| Sample size (analyse) | 25 | 26 | 23 | 27 |
| Male % | 81% | 78% | 80% | 69% |
| Age: Mean (SD) | 56.5(8.2) | 57.8(7.3) | 56.9(8.6) | 55.5(8.0) |
| Time since stroke onset: Months (SD) | > 12 months | | | |
| Intervention | 60 mins of TENS | 60 mins of TENS followed by 60 mins of task related activity | Electrodes placed over acupuncture points (60 mins) and 60 mins of task related activity | No treatment |
| | Home programme 20 sessions over 5 days a week for 4 weeks. Over this period of time participants attended the laboratory 8 times to check for competence and compliance. | | | |
| Primary Outcome | Gait velocity, measurements taken at baseline, after 2 weeks, after 4 weeks (outcome) and 4 weeks after the end of the intervention (follow up) | | | |
| Findings<br>Gait velocity (cm/s) mean(SD) outcome<br>follow up | 60.9(24.8)<br>61.2(27.3) | 66.6(32.5)<br>70.2(32.7)<br>p<0.01 compared to PLBO+TRT | 60.6(29.7)<br>61.3(28.6) | 60.9(24.8)<br>61.2(24.2) |
| Authors conclusion | Combining TENS with exercise produces greater benefit than either exercise or stimulation alone. | | | |
| Comments | Although showing changes in gait speed, it is questionable whether these were clinically significant. The greatest gain in speed between the baseline and outcome was achieved by the intervention group but this was still only 25.3cm/s, therefore the impact of this intervention on the participant may not have been noticeable. Fidelity to treatment was measured by log books, the dose of each treatment session was not reported and therefore it is difficult to see if participants were compliant with the intervention and whether or not results were achieved because one group was | | | |

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| | more motivated and carried out more of the intervention than another. The recruitment strategy was not described therefore cannot be used to inform future interventions. Authors reported ‘difficulties in recruiting’ but did not describe what these were making it difficult to learn from this for future studies. |

| | | |
|---|---|---|
| Study | Imagery Improves Upper Extremity Motor Function in Chronic Stroke Patients: A Pilot Study<br>Page (2000) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Local advertisements in doctors' offices, newspapers, newsletters and stroke support groups. | |
| Inclusion criteria | Exclusion criteria were listed only. | |
| Sample size (analyse) | 8 | 8 |
| Male % | 100% | 100% |
| Age: Mean (SD) | 63.2(4) | |
| Time since stroke onset: Months (SD) | 21.6 | |
| Intervention | Occupational therapy and imagery (OT+I). OT for 3 times/week for 4 weeks for 30 mins followed by a tape recorded imagery for 20 mins | Occupational therapy. OT for 3 times/week for 4 weeks for 30 mins followed by tape recorded instructions and information for 20 mins. |
| Primary Outcome | Upper extremity of the Fugl Meyer (FM). Tested before and after the intervention (outcome). | |
| Findings<br>FM mean(SD) outcome | 29.97(4.1) p=0.002 | 26.86(5.4) |
| Authors conclusion | Participants who received motor imagery showed statistically significant improvements compared to OT. | |
| Comments | The authors reported that no volunteers were excluded from participating in the study but the success of the recruitment strategy is still relatively unknown as the length of time for these advertisements was not given nor the scope of the advertising programme. Randomisation was used to match for characteristics; however the sample size is so small that any confounders were un likely to be controlled for within this process. Inclusion criteria were not described therefore generalising these findings is not possible. The study was at 'unclear' risk of random sequence generation, allocation concealment and blinding of the outcome assessment su7gesting risk of selection and detection bias. Adherence to the treatment protocol was not described. | |

| | | |
|---|---|---|
| Study | A randomised efficacy and feasibility study of imagery in acute stroke.<br>Page et al (2001) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Individuals who had responded to advertisements placed outside outpatient therapy department in four rehabilitation hospitals. | |
| Inclusion criteria | Upper limb hemiparesis in their dominant limb | |
| Sample size (analyse) | 8 | 5 |
| Male % | 75% | 80% |
| Age: Mean (SD) | 64.4(9.7) | 65.0(7.0) |
| Time since stroke onset: Months (SD) | 5.88(3.44) | 7.6(3.21) |
| Intervention | Therapy plus imagery. Three times per week for one hour for six weeks. After therapy participants listened to a tape recorded imagery intervention lasting approximately 10 mins. | Therapy only. Three times per week for one hour for six weeks. After therapy participants listened to a tape containing stroke information lasting approximately 10 mins. |
| Primary Outcome | Upper Extremity portion of the Fugl Meyer (FM) and the Action Research Arm Test (ARAT). Measures were administered twice before the intervention one week apart and then after the intervention (outcome). | |
| Findings<br>FM mean(SD) outcome<br>ARAT mean (SD) outcome | <br><br>43.0(10.1)<br><br>40.4(13.4) | <br><br>32.4(14.9)<br><br>25.0(11.7) |
| Authors conclusion | Imagery was a feasible intervention and the group that received imagery showed greater improvement between the baseline and outcome. | |
| Comments | The results describe a home practice schedule but this was not described in the methods in the reporting of this trial. Interview assessing acceptability of the intervention was also carried out but the results of these have not been reported. The presence or not of blinding of the outcome assessor was not reported and therefore is at ‘unclear’ risk of bias. This trial was reported as a pilot study assessing feasibility and therefore little information can be derived about efficacy, poor reporting also makes it difficult to extrapolate any findings on acceptability and adherence to the treatment protocol. | |

| | | |
|---|---|---|
| Study | Modified Constraint-Induced Therapy Combined with mental Practice. Thinking Through Better Outcomes Page et al (2009) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Volunteers recruited by advertisements placed in local therapy clinics | |
| Inclusion criteria | Ability to extend at least $10^0$ at the metacarpophalangeal joints of each digit and extend $20^0$ at the wrist. Score of <2.5 of the amount of use scale of the Motor Activity Log. | |
| Sample size (analyse) | 5 | 5 |
| Male % | 80% | 60% |
| Age: Mean (SD) | 58.4(9.8) | 6.4(9.0) |
| Time since stroke onset: Months (SD) | 26.4(13.6) | 30.6(11.4) |
| Intervention | Mental practice and modified constraint induced therapy (mCIMT). Mental practice was administered after the mCIMT.<br>30 minute therapy sessions 3times/week for 10 weeks with 30 minutes of mental practice. | Modified constraint induced therapy. |
| Primary Outcome | Fugl Meyer (FM) and Action research Arm Test (ARAT).<br>Administered twice before the start of the intervention, 5 weekdays apart and then after the end of the intervention (outcome) and then 3 months after the end of the intervention (follow up) | |
| Findings<br>FM mean(SD)<br>Outcome<br>Follow up<br>ARAT mean (SD)<br>Outcome<br>Follow up | <br><br>46.4(0.89) (change)<br>p=0.01<br>48.8(1.31)<br><br>42.6(1.20) (change)<br>p<0.001<br>43.5(1.50) | <br><br>43.8(1.09)<br>45.3<br><br>36.4(1.10)<br>38.0 |
| Authors conclusion | Both groups exhibited clinically relevant changes, the addition of MP facilitated more practice repetitions and therefore may explain the better outcomes seen in this group. | |
| Comments | Thirty people were screened for the study and 20 were excluded because they did not meet the recruitment criteria. There is no detail of the time period over which recruitment occurred. Compliance with the mental practice intervention was not | |

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| | measured and this aspect of the study was self-administered, however the improved outcomes seen in this group would suggests some engagement with this therapy. Allocation concealment was ‘unclear’ and therefore the study may be at risk of selection bias. |

| | | |
|---|---|---|
| Study | Single blind randomised controlled trial of visual feedback after stroke: effects on stance symmetry and function<br>Sackley and Lincoln (1997) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Inpatients in one city hospital in the UK | |
| Inclusion criteria | Able to stand for 1 minute and had an abnormal stance symmetry | |
| Sample size (analyse) | 12 | 13 |
| Male % | 83% | 77% |
| Age: Mean (SD) | 60.8(12.3) | 67.9(9.2) |
| Time since stroke onset: Months (SD) | 4.64(3.65) | 4.34(4.45) |
| Intervention | Symmetry training in standing using the Nottingham Balance Platform (NBP) enabling feedback.<br>60 minutes 3 times/week for 4 weeks | Symmetry training using the NRP but with no feedback<br>60 minutes 3 times/week for 4 weeks |
| Primary Outcome | Balance coefficient (BC)<br>Carried out before and after (outcome) the intervention | |
| Findings<br>BC mean(SD) outcome | 0.039(0.028) | 0.055(0.044) $p<0.05$ |
| Authors conclusion | Feedback delivered through the NBP led to a statistically significant improvement in stance symmetry compared to the group that received no feedback via the NBP. | |
| Comments | Consort or patient flow not described therefore difficult to ascertain how many patients were screened relative to those that were recruited. Two participants dropped out of the study, one from each group due to issues unrelated to the trial. Treatment fidelity was not recorded although treatment sessions were only reportedly dependent on the patient's tolerance and medical status; therefore it is unclear how much therapy each participant received. Allocation concealment was 'unclear' therefore the study may be at risk of selection bias. | |

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|---|---|---|---|
| Study | Musical Motor Feedback (MMF) in walking hemiparetic stroke patients: randomised trials of gait improvement<br>Schauer and Mauritz (2003) | | |
| Study Design | Randomised controlled trial | | |
| Participant Characteristics | Experimental | Control | |
| Sample | "All hemiparetic patients" | | |
| Inclusion criteria | Execute at least task 7 but failed at task 11 or higher of the Rivermead gross function score of the Rivermead Motor Assessment. Able to walk twenty minutes without any assistive device. | | |
| Sample size (analyse) | 11 | 12 | |
| Male % | No data given | | |
| Age: Mean (SD) | 50.0(12.0) | 61.0(12.0) | |
| Time since stroke onset: Months (SD) | 1.74 | 2.2 | |
| Intervention | Walking practice with musical motor feedback (MMF) providing feedback. 5 days/week 20 minutes each day for a total of 15 sessions. | Walking practice with a therapist for 20 minutes each day for a total of 15 sessions. | |
| Primary Outcome | Gait velocity m/s<br>Assessments taken before and after the intervention (outcome). | | |
| Findings<br>Gait velocity (m/s) mean(SD)<br>outcome | 0.81(0.29) | 0.80(0.35)<br>p=0.008 | |
| Authors conclusion | The authors reflected that whilst the results in favour of the intervention were statistically significant that this was due to very sensitive responders and those that failed to show an effect. | | |
| Comments | Sampling strategy was non specific and therefore not able to inform future trials. 37 people could have been recruited but only 23 gave consent, reasons for this were unknown. The sample size was small and therefore generalisation would not be possible - if the study authors wished to evaluate which responders would be most sensitive to this type of intervention then a different trial methodology might be useful. Fidelity to treatment intervention was not possible to extrapolate because information relating to acceptability and dose were not provided. The study was 'unclear' in respect of random sequence generation and allocation concealment, presenting a risk of selection bias. It was also 'unclear' in respect of blinding of outcome assessment making the study potentially at risk of detection bias. | | |

| | | |
|---|---|---|
| Study | Efficacy of an insole shoe wedge and augmented pressure sensor for gait training in individuals with stroke: a randomised controlled trial.<br>Sungkarat et al (2011) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Participants were recruited from one rehabilitation unit and the physical therapy clinic. | |
| Inclusion criteria | Able to walk at least 10m with or without assistance. | |
| Sample size (analyse) | 17 | 18 |
| Male % | 71% | 67% |
| Age: Mean (SD) | 52.1(7.2) | 53.8(11.2) |
| Time since stroke onset: Months (SD) | 3.94(4.79) | 4.7(5.8) |
| Intervention | Insole show wedge providing feedback<br>60 minute sessions 5 days a week for 3 weeks.<br>30 minutes of each session involved gait training with the insole and 30 mins conventional therapy | Conventional therapy and gait training.<br>60 minute session for 5 days a week for 3 weeks.<br>30 mins of each session involved gait training and the other 30 mins of conventional therapy. |
| Primary Outcome | Gait speed (cm/s)<br>Before and after the training (outcome) | |
| Findings<br>Gait speed cm/s mean(SD) outcome | 35.9(13.6) | 26.3(8.5) p=0.02 |
| Authors conclusion | The experimental group demonstrated 3x greater improvement in gait speed compared to the control group leading the authors to conclude that augmented feedback is beneficial. | |
| Comments | 5 people dropped out in total, 2 from the control group and 3 from the intervention group. None of these were for reasons related to the trial interventions. Authors did comment that although there was improvement the gait speed eventually achieved by the experimental group was still below that required for community ambulation. Treatment fidelity is not possible to extrapolate as this information has not been provided and this is a small sample size so the generalisability of these findings to other stroke survivors is limited. Inclusion criteria was not limited in respect of time since onset of stroke but the study design means that it is not possible to determine whether either of these populations responded in different ways to the experimental intervention. | |

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|---|---|---|
| Study | Effect of Thermal Stimulation on Upper Extremity Motor Recovery 3 Months After Stroke.<br>Wu et al (2010) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Little detail but appears to be outpatients in one rehabilitation unit. | |
| Inclusion criteria | Ability to sit on a chair for 30 minutes and move paretic hand away from thermal therapeutic pad independently, with and without the assistance of the nonparetic hand. | |
| Sample size (analyse) | 12 | 11 |
| Male % | 33% | 45% |
| Age: Mean (SD) | 59.9(11.4) | 54.3(10.3) |
| Time since stroke onset: Months (SD) | 10.0(7.3) | 7.2(5.4) |
| Intervention | 1 hour of physical therapy and 1 hour of occupational therapy. An additional upper extremity thermal stimulation protocol.<br>30 minutes, 3 times per week for 8 weeks. | 1 hour of physical therapy and 1 hour of occupational therapy. An additional lower extremity thermal stimulation protocol.<br>30 minutes, 3 times per week for 8 weeks. |
| Primary Outcome | UE subscale of the Stroke Rehabilitation Assessment of Movement and the Action Research Arm Test (STREAM)<br>Before treatment, after treatment (outcome) and week 12 of study (follow up) | |
| Findings<br>STREAM mean(SD)<br>Outcome<br>Follow up | <br><br>10.0(5.3)<br>10.0(5.3) p<0.001<br>Group x time analysis p=0.002 | <br><br>7.3(5.6)<br>8.0(5.6) p=0.005 |
| Authors conclusion | The thermal stimulation could lead to further improvement in upper extremity movement in stroke survivors who are more than 3 months after stroke. | |
| Comments | No information about treatment fidelity or recruitment methods was given. There were no drop outs from the study therefore it could be assumed that the intervention was acceptable to the participants. Both groups showed improvement after the interventions although this was less for the control group but does indicate capacity for further improvement in this population of stroke survivors. The study was at 'unclear' risk of bias for random sequence generation and allocation concealment indicating the potential for selection bias. | |

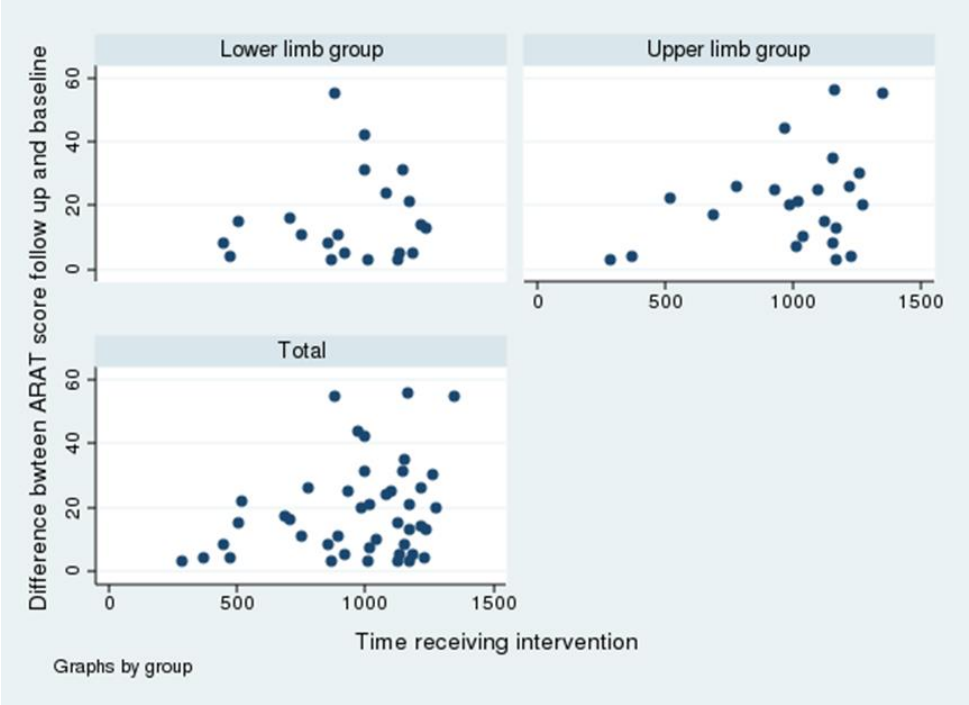
| | | |
|---|---|---|
| Study | Virtual reality-based training improves community ambulation in individuals with stroke: A randomised controlled trial<br>Yang et al (2008) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Subjects were recruited from community groups | |
| Inclusion criteria | Limited household walker, unlimited household walker, most-limited community walker by functional walking category. | |
| Sample size (analyse) | 11 | 9 |
| Male % | 45% | 56% |
| Age: Mean (SD) | 55.4(12.1) | 60.9(9.3) |
| Time since stroke onset: Months (SD) | 71.16(50.04) | 73.2(123.84) |
| Intervention | Walking on a treadmill in a virtual reality environment<br>20 minute session, three sessions a week for three weeks. | Walking on a treadmill and asked to carry out various tasks. 20 minute session, three sessions a week for three weeks. |
| Primary Outcome | Walking speed (m/s)<br>Before training, at the end of training (outcome) and 1 month after completion of the training (follow up) | |
| Findings<br>Walking speed m/s mean(SD)<br>Outcome<br>Follow up | <br><br>0.85(0.31) $p<0.05$<br>0.86(0.33) $p<0.05$ | <br><br>0.73(0.63)<br>0.77(0.71) |
| Authors conclusion | Virtual reality-based training improved walking speed compared to walking training alone. These results were maintained at follow up. | |
| Comments | Four participants dropped out of the study, three from the control group and 1 from the experimental group. Reasons for these drop outs have not been given. Treatment fidelity has not been described and recruitment methods have not been described. This study does suggest that stroke survivors in the chronic phase of recovery can still show capacity for improvement. This study was at low risk of bias for all aspects of the risk of bias assessment suggesting that the findings are generally trustworthy. | |

| | | |
|---|---|---|
| Study | Mirror Therapy Improves Hand Function in Subacute Stroke: A Randomized Controlled Trial<br>Yavuzer et al (2008) | |
| Study Design | Randomised controlled trial | |
| Participant Characteristics | Experimental | Control |
| Sample | Referred for inpatient rehabilitation from all over Turkey | |
| Inclusion criteria | Had a Brunnstrom score between stages I and IV for the upper extremity. | |
| Sample size (analyse) | 20 | 20 |
| Male % | 45% | 50% |
| Age: Mean (SD) | 63.2(9.2) | 63.3(9.5) |
| Time since stroke onset: Months (SD) | 5.4(2.9) | 5.5(2.5) |
| Intervention | Conventional stroke program and an additional 30 minutes of mirror therapy.<br>5 days a week, 2-5 hours a day for 4 weeks. | Conventional stroke program and an additional 30 minutes using non reflective side of mirror.<br>5 days a week, 2-5 hours a day for 4 weeks. |
| Primary Outcome | Motor recovery Brunnstrom stages for hand and upper extremity (UE)<br>Pre treatment , post treatment – after 4 weeks (outcome) and after 6 months (follow up). | |
| Findings<br>Brunnstrom hand mean(SD)<br>Outcome<br>Follow up<br>Brunnstrom UE mean(SD)<br>Outcome<br>Follow up | <br><br>3.5(1.3) p=0.001<br>4.0(1.4)<br><br>3.7(1.2) p=0.001<br>4.2(1.3) | <br><br>2.7(1.0)<br>3.1(1.2)<br><br>2.8(0.9)<br>3.0(1.1) |
| Authors conclusion | Mirror therapy in conjunction with conventional therapy was more effective than conventional therapy alone. | |
| Comments | Some follow up data was lost as participants were unable to travel to the rehabilitation centre for measurement (3 from the experimental group and 1 from the control group). Treatment varied in dose from between 2 and 5 hours and no information was given regarding length of treatment for either group. It is possible that the experimental group received more therapy and the improvements observed were as a result of this. Recruitment was via a convenience sample of inpatients and therefore little can be gained regarding recruitment to a community trial. The study was however at low risk of bias and therefore results can be considered trustworthy. | |

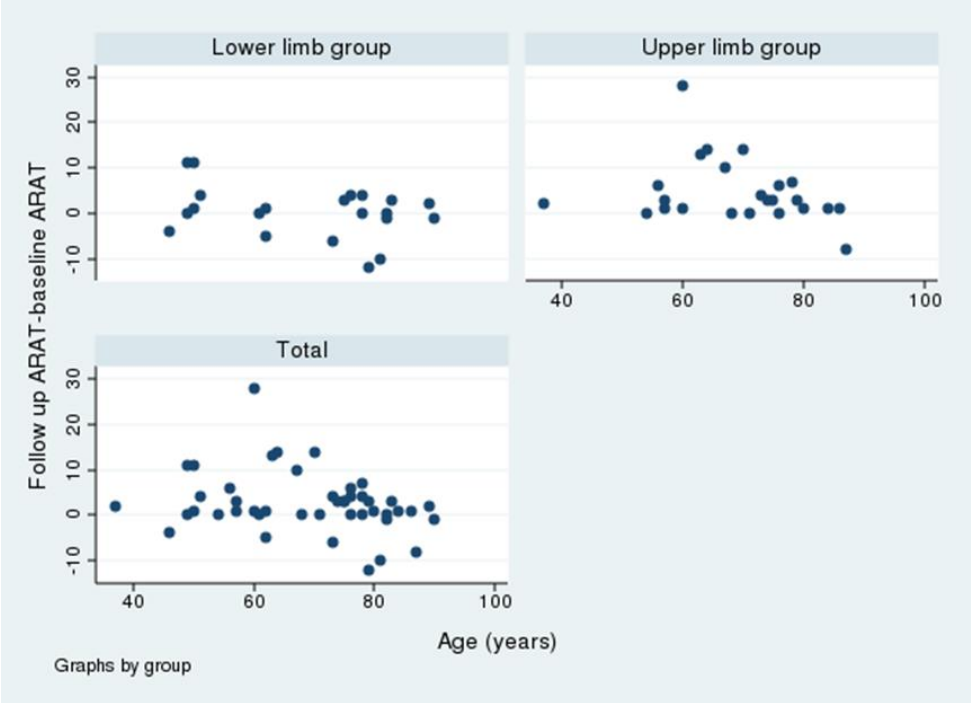
## Appendix XVII

Follow up results for ARAT

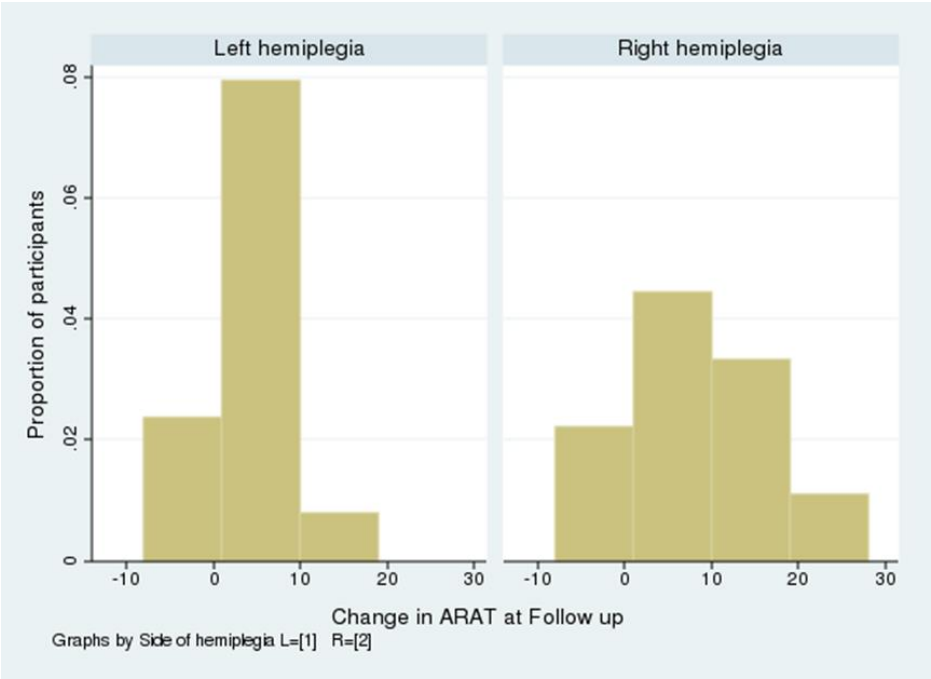
Secondary Analysis of Follow up Results for ARAT



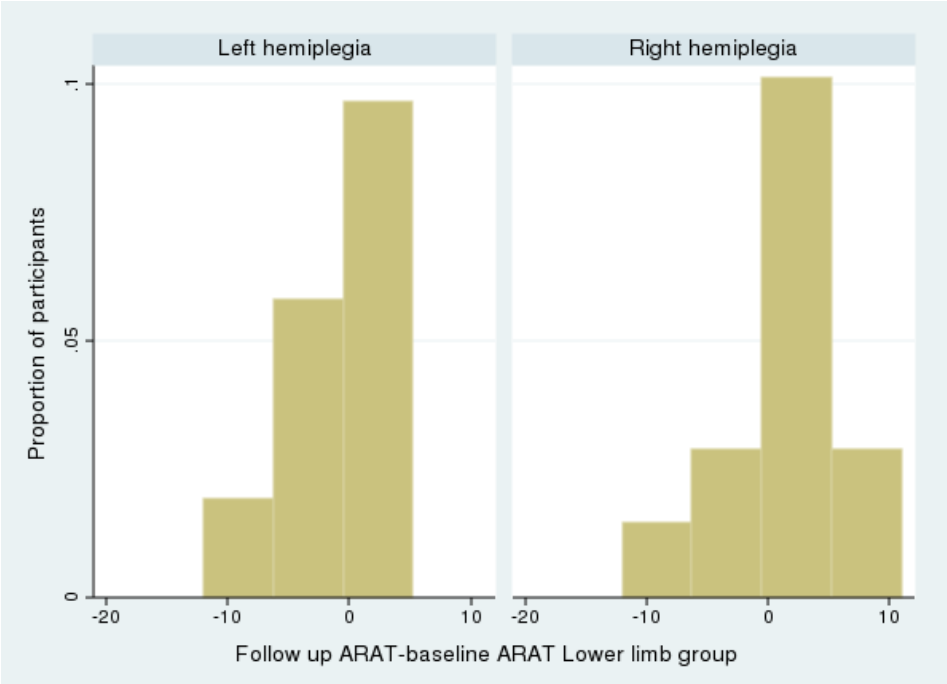

Scatterplot to show correlation between therapy time and change score of the ARAT at follow up



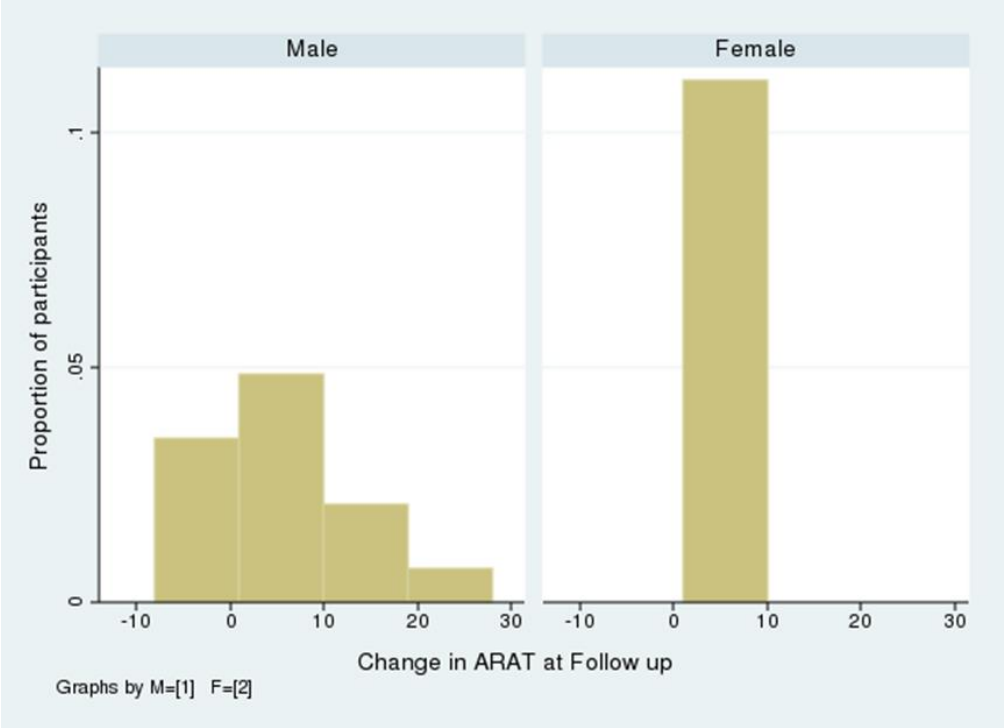

Scatterplot to show correlation between age in years and change score for the ARAT at follow up



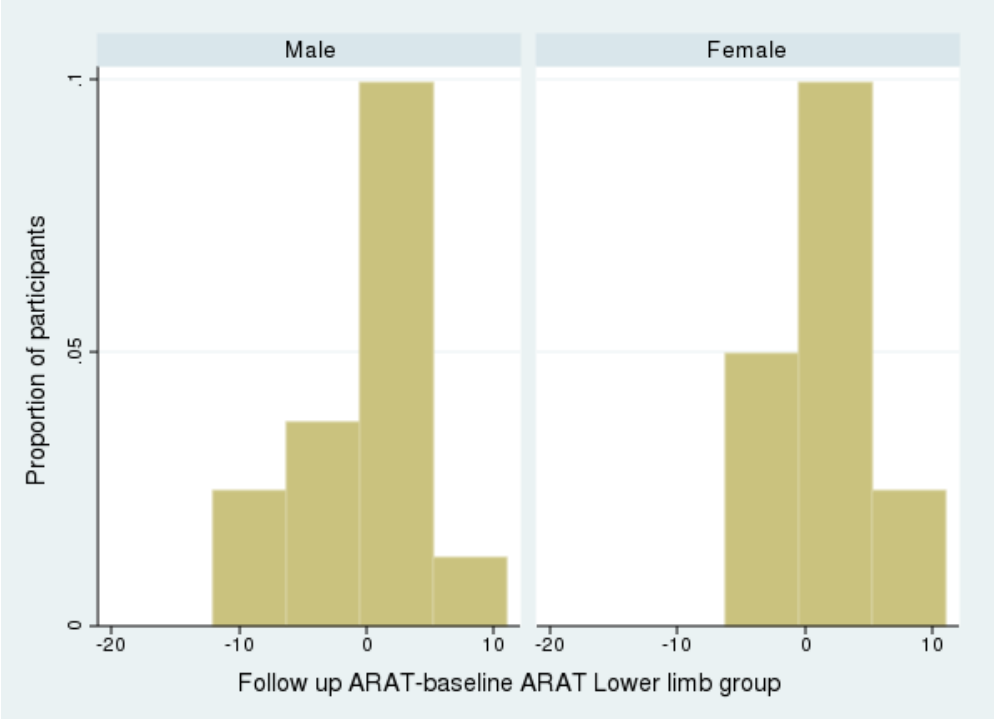

Histogram showing relationship between side of hemiplegia and change in the ARAT score at follow up for the upper limb group



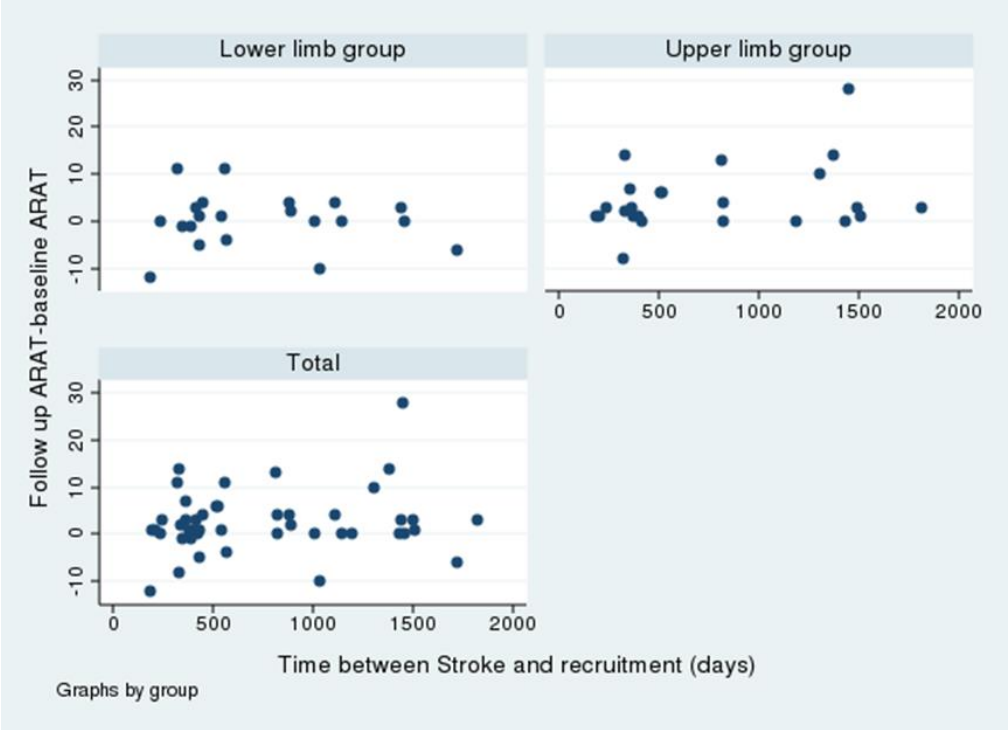

Histogram showing relationship between side of hemiplegia and change in the ARAT score at follow up for the lower limb group



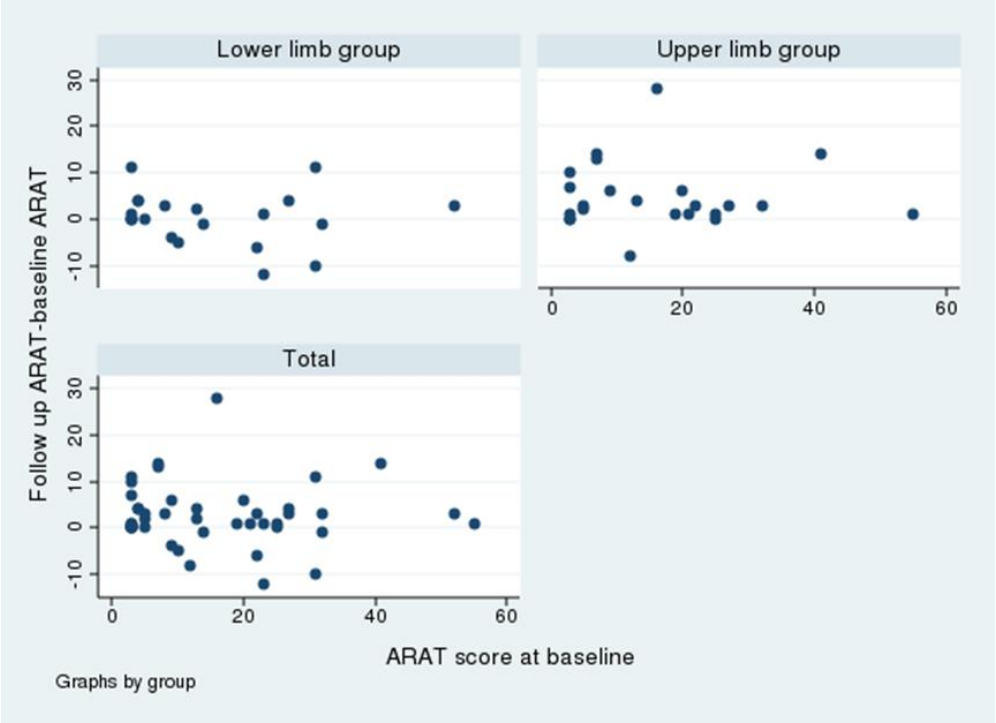

Histogram showing relationship between the gender of the participant and change in the ARAT score at follow up for the upper limb group



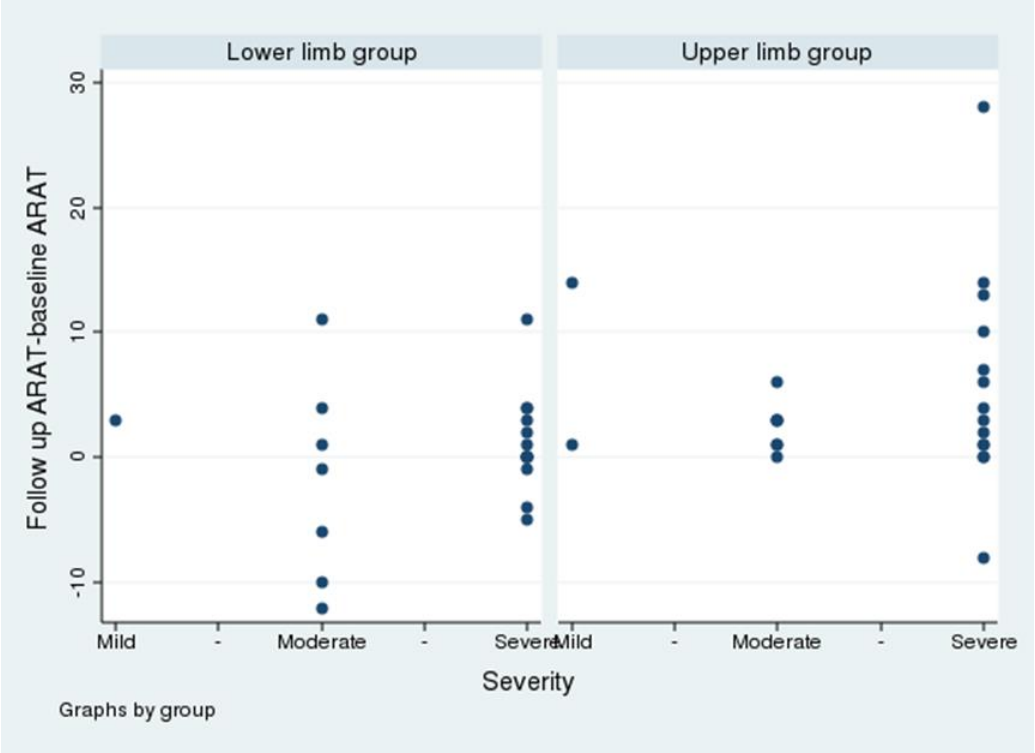

Histogram showing relationship between the gender of the participant and change in the ARAT score at follow up for the lower limb group




Scatterplot of the change in ARAT score at follow up and the time between stroke onset and recruitment to the study




Scatterplot to show the relationship between the change in ARAT at follow up and ARAT score at baseline

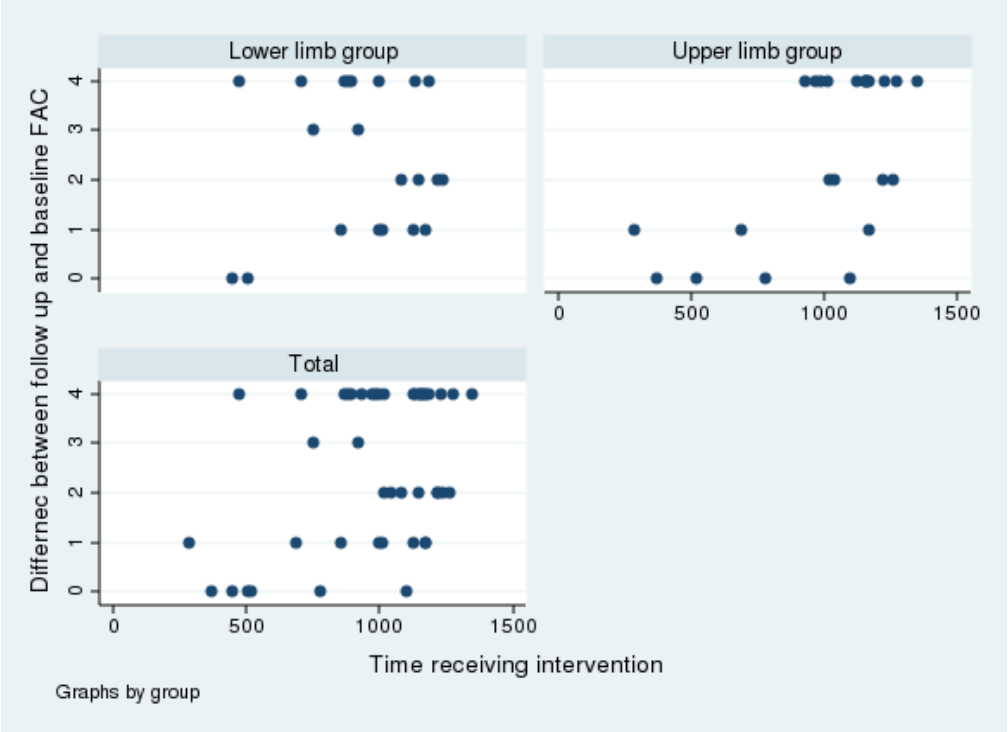



Scatterplot to show relationship between the change in ARAT at follow up and severity as categorised by the ARAT.

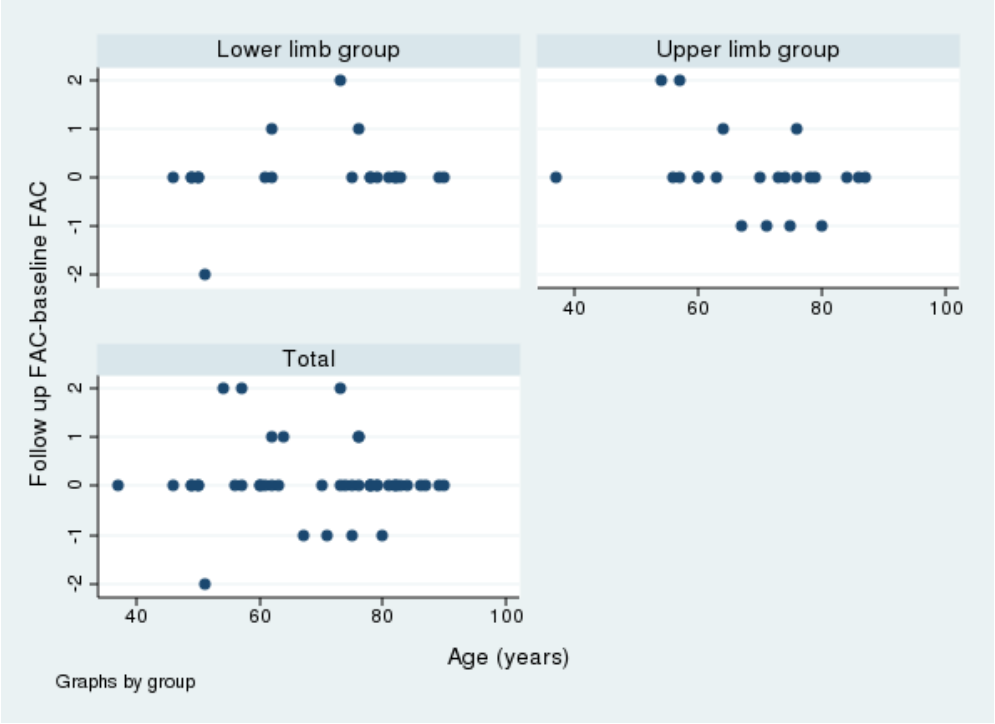
## Appendix XVIII

Follow up results for FAC

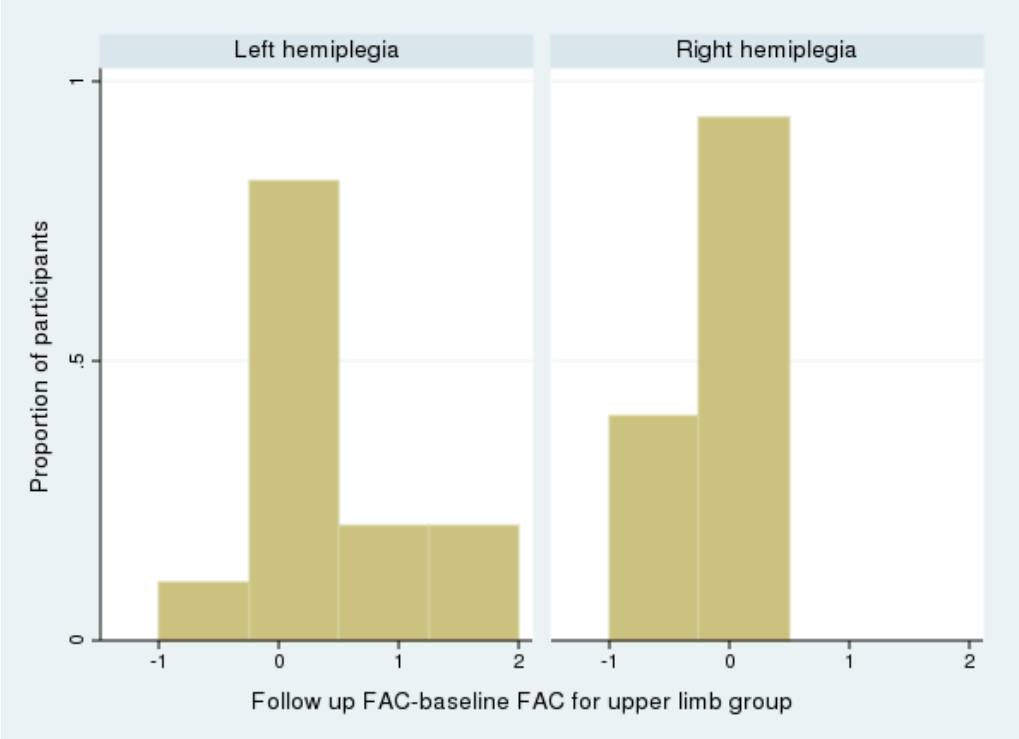
Secondary Analysis of Follow up Results for FAC



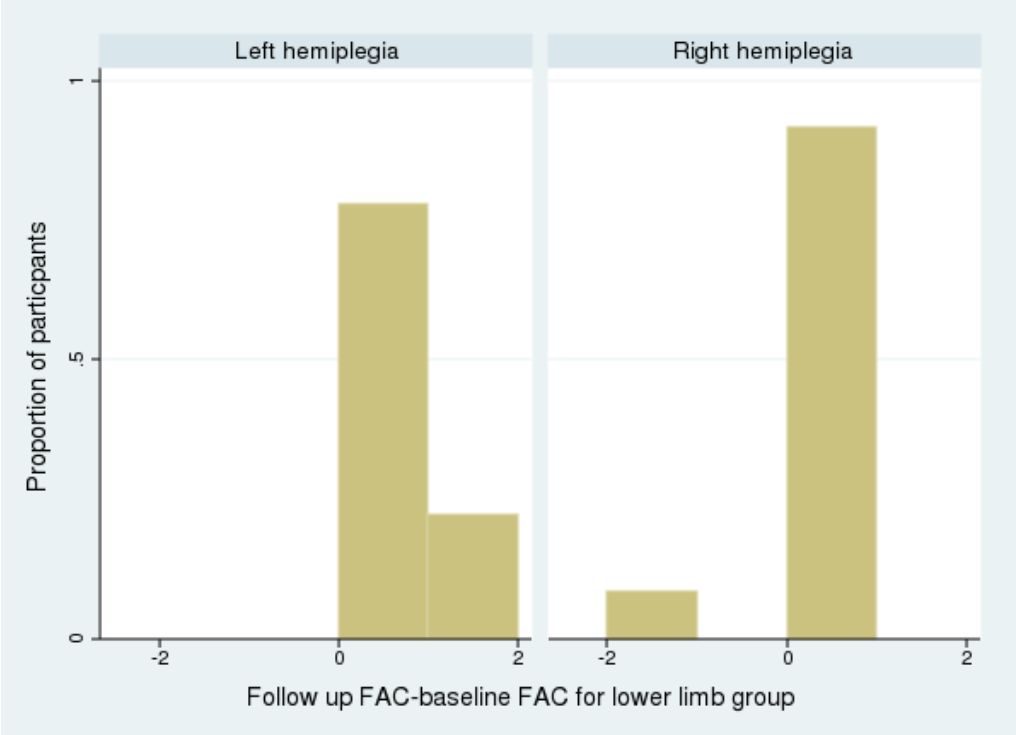

Scatterplot to show correlation between therapy time and change score of the FAC at follow up



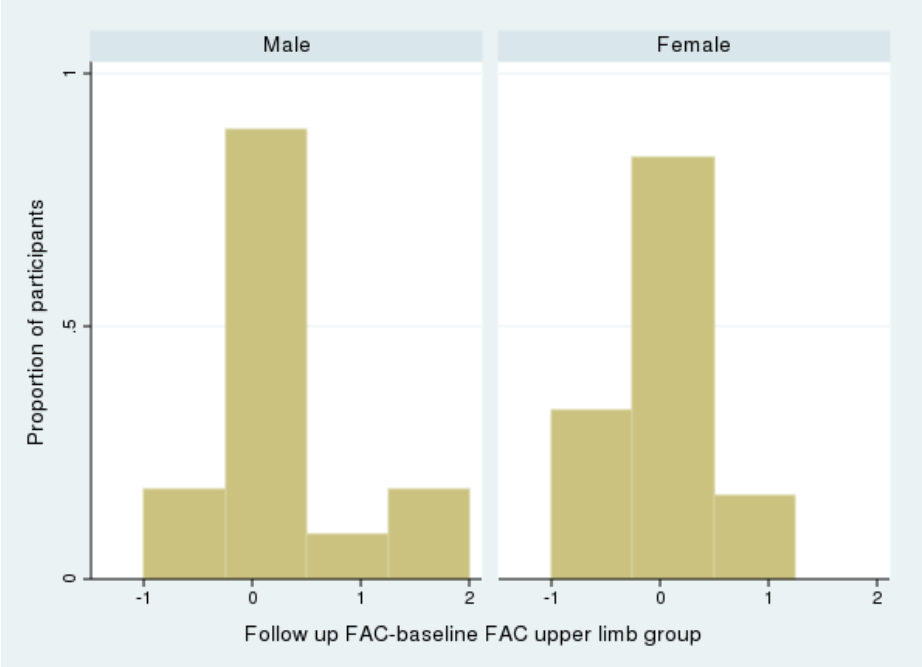

Scatterplot to show correlation between age in years and change score for the FAC at follow up



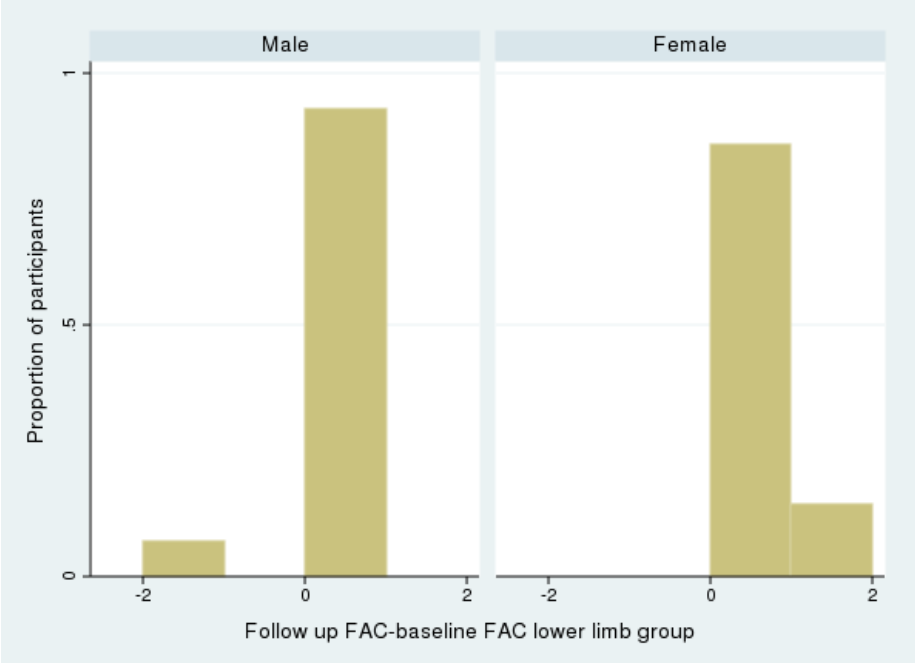

Histogram showing relationship between side of hemiplegia and change in the FAC score at follow up for the upper limb group




Histogram showing relationship between side of hemiplegia and change in the FAC score at follow up for the lower limb group

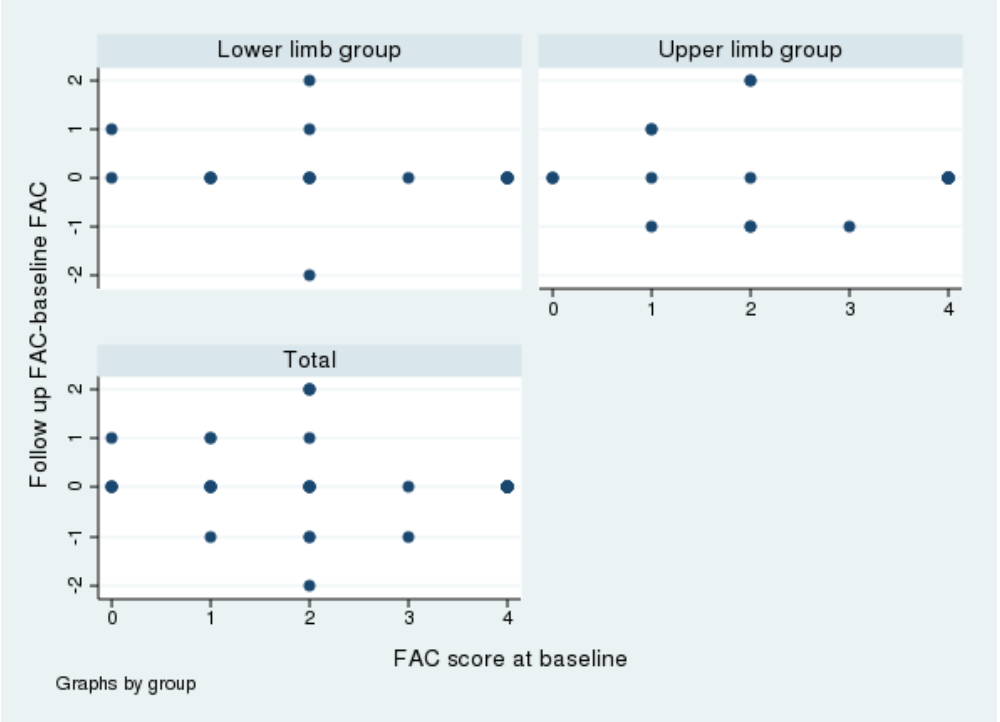



Histogram showing relationship between the gender of the participant and change in the FAC score at follow up for the upper limb group

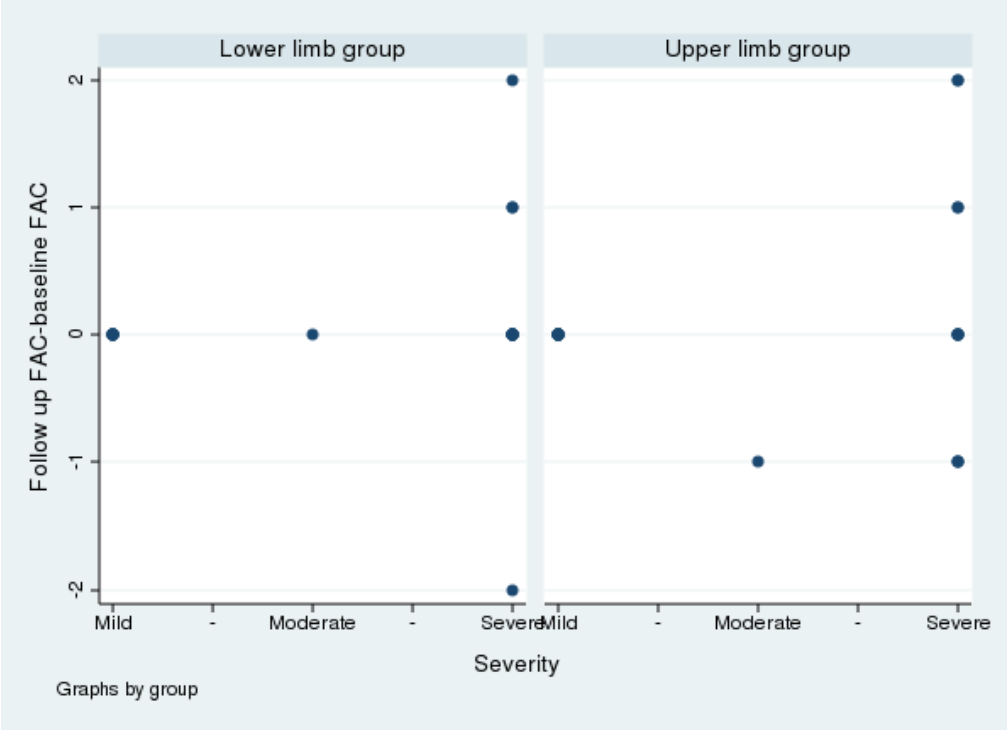



Histogram showing relationship between the gender of the participant and change in the FAC score at follow up for the lower limb group


Scatterplot of the change in FAC score at follow up and the time between stroke onset and recruitment to the study




Scatterplot to show the relationship between the change in FAC at follow up and FAC score at baseline




Scatterplot to show relationship between the change in FAC at follow up and severity as categorised by the FAC.