

Investigations into the Potential for using Reciprocal Pedalling Exercise to Assess, Measure and Enhance Lower Limb Function after Stroke

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Abstract

Upright Pedalling (UP) exercise offers opportunities for stroke survivors to participate in functional, repetitive lower limb activity with similarities to walking. Such functional activity is required to enhance the brain changes underlying recovery of motor function after stroke. UP might also offer opportunities for assessment and measurement of lower limb impairment during functionally-relevant activity.

A systematic review using Cochrane methodology investigated effects of reciprocal pedalling (RP) on lower limb motor function after stroke. Despite some beneficial, though not definitive, effects, it was not possible to make clinical recommendations supporting or refuting RP after stroke, due to inter-study heterogeneity, wide confidence intervals around effect sizes and risks of potential biases.

A feasibility study investigated participation in Upright Pedalling (UP) by people in the first month after stroke, with substantial weakness and not able to walk, and explored characterisation of lower limb movement during UP. 84.6 % (n=11) of people tested were able to participate in UP. Smooth, reciprocal pedalling was evident in stroke survivors with substantial weakness, using heterogeneous patterns. Though 84.2% (n=16) of those approached consented to participate, attrition was high due to service reorganisation, with 2.2% (n=9 of 411) of those screened actually randomised.

A prospective measurement study explored the reliability and discriminative ability of impairment measures derived during instrumented UP (smoothness of pedalling, muscle activation timing, reciprocity of muscle activity). Results indicated that instrumented UP could be used to discriminate between stroke survivors and healthy age-matched volunteers for timing of onset and offset muscle activation (multi-variate ANOVA, difference in activity according to wheel position, $p=0.034$) and reciprocal activation (two-sample t-test, difference -0.249 (CI: -0.491, -0.010; $p=0.044$) for quadriceps. It was not possible to establish definitive test-retest repeatability with sufficient precision to make clinical recommendations.

UP is a new, promising technology for assessment, rehabilitation and measurement that is worthy of future investigation.

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Publications arising from this thesis

Papers

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Abstracts

Hancock, N.J., Shepstone, L., Winterbotham, W. & Pomeroy, V. Effects of reciprocal pedalling exercise on motor function after stroke: A systematic review. *Archives of Physical Medicine & Rehabilitation* 2010; 91: E27

Hancock, N.J., Shepstone, L., Winterbotham, W. & Pomeroy, V. What are the effects of reciprocal pedalling exercise on motor function after stroke? A systematic review. *Synapse; Journal of the Association of Chartered Physiotherapists Interested in Neurology* 2010; Spring.

Hancock, N.J., Shepstone, L., Rowe, P., Myint, P.K. & Pomeroy, V. Feasibility of Upright Pedalling as a rehabilitation intervention after stroke. *International Journal of Stroke* 2011; 6 (suppl.2): 54

Hancock, N.J., Shepstone, L., Rowe, P., Myint, P.K. & Pomeroy, V. Upright pedalling is a potential intervention for driving lower limb recovery in people who cannot walk early after stroke. *Cerebrovascular Diseases* 2013; 35 (suppl. 3): 550

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Chapter 1.0: Introduction and Background

1.1 Introduction to the thesis

Stroke is the single largest cause of adult disability worldwide. Each year, in England alone, 110,000 people suffer a stroke and approximate annual costs are: £2.8 billion in direct health and social care; £1.8 billion to the wider community in terms of lost productivity and disability; and £2.4 billion in costs to informal carers. The majority of these costs are the result of rehabilitation and life after stroke. Stroke rehabilitation is a research priority for the United Kingdom National Health Service (NHS).

Stroke survivors identify recovery of walking as a priority goal of rehabilitation. It is likely that the impact of improving recovery of walking after stroke is substantial and physiotherapy is key to enabling stroke survivors to achieve that goal. Physiotherapy can drive the brain recovery that is associated with better outcomes for stroke survivors, including those outcomes related to walking. For example, repetitive practice of goal-directed functional tasks has been shown to enhance the brain changes that underly recovery of motor function after stroke.

However, for people with substantial weakness after their stroke, repeatedly practising the reciprocal lower limb movements associated with walking, or indeed practising walking itself, presents a challenge. People are often too weak to adopt an upright posture and practise leg movements without substantial help. These difficulties are particularly evident early after stroke, in the vital period in which the brain is at its most active and responsive to extrinsic therapies.

A potential way forward is to provide static reciprocal pedalling exercise, as this is a repetitive, functional activity with similar reciprocal lower limb movement patterns to walking. There is some evidence that pedalling may facilitate phasic, co-

ordinated muscle activity even in patients with severe hemiparesis. Reciprocal pedalling is therefore a rehabilitation tool that might promote functional activity early after stroke.

In order to understand how pedalling might work, detailed assessment of how people move during the activity is required. This is important because stroke does not have uniform effects on neural networks; consequently, different people use different movement strategies to achieve the same functional goal. Although achieving a functional goal is good, abnormal movement patterns are less skilled and less energy efficient. In addition, practice of abnormal movement patterns may drive maladaptive brain recovery. Hence, a key aim of rehabilitation is to restore as normal a movement pattern as possible, as early as possible after stroke. Attention is therefore required to assess whether a new pedalling exercise intervention produces normal movement patterns in all stroke survivors. This cannot be achieved by just using established assessment tools that use clinical observation of movement. Characterisation of movement patterns is also required.

Furthermore, it is important that sensitive measures are used to assess whether rehabilitation interventions, such as pedalling exercise, are having an effect. It is essential to make rapid decisions about recovery potential and progress so that the important early period after stroke is not squandered. Additionally, therapists are under increasing pressure to make rapid decisions about progress, as resource-limited services seek to target therapy at those who might best benefit. Commonly used existing measures of impairment, e.g. the Motricity Index, are not sufficiently sensitive to the physiological changes that might indicate improvement. There is a need to develop a sensitive clinical measure of lower limb impairment after stroke.

Hence, this thesis presents three original studies that address the needs identified above, investigating reciprocal pedalling exercise after stroke. It begins with a systematic review exploring the effects of reciprocal pedalling on lower limb function after stroke. This is followed by two experimental studies that investigate

the potential of a new tool for the rehabilitation, assessment and measurement of lower limb function after stroke: Upright Pedalling.

1.2 Background: Principles of stroke rehabilitation and research

The purpose of this section is two-fold: to elucidate the importance of research into rehabilitation interventions after stroke; and to identify and explore the principles that should be prerequisite to the planning and execution of rehabilitation and research programmes after stroke. It begins with an overview of stroke research and rehabilitation principles and is followed by specific discussion of key principles underpinning the work in this thesis.

1.2.1 Overview: stroke rehabilitation and research

A stroke is caused by the interruption of the blood supply to part of the brain, usually due to blockage by a clot or a burst blood vessel (World Health Organisation, 2013). The supply of oxygen and nutrients to the brain is diminished or cut off; signs of cerebral dysfunction develop rapidly and last longer than 24 hours. It is known that 85% of strokes are due to cerebral infarction (the obstruction of blood supply to the brain and ensuing tissue death), 10% due to primary haemorrhage and 5% due to subarachnoid haemorrhage (Intercollegiate Stroke Working Party, Royal College of Physicians, 2012). Depending on the site of the stroke in the brain and how severely that area is affected, symptoms of stroke can include sudden weakness of the face arm and leg, most commonly on one side of the body (hemiparesis), difficulty in speaking and comprehending language, and problems with balance and coordination.

The impact of stroke is considerable: stroke is one of the top three causes of death and the largest cause of disability in the United Kingdom (Intercollegiate Stroke Working Party, Royal College of Physicians, 2012). There are 152,000 strokes in the UK each year, causing a greater range of disabilities than any other condition (Stroke Association: Stroke Statistics, 2013). Direct costs to the NHS are over £3

billion annually within a wider economic impact of up to £8 billion (Department of Health, National Audit Office, 2010).

Over 1.1 million people currently living in the UK have had a stroke and many live with persistent consequences. Of those that survive the initial stroke, 58% will have some form of disability, with 36% having disability categorised as moderate, severe, or very severe (Stroke Association: Stroke Statistics, 2013). In England alone, over 300,000 people are currently living with moderate to severe disabilities as a result of stroke (Department of Health, National Audit Office, 2010), including deficits of motor function. Indeed, restrictions in muscle activity and mobility are the most widely recognised deficits caused by stroke (Langhorne et al. 2009a). Hence, stroke survivors can have on-going health and social care needs across a spectrum of requirement, from daily intensive nursing and medical care and therapy, to home-based rehabilitation programmes and support with return to work and leisure activities. It is clear that this potentially life-altering condition can have devastating sequelae, for the individual, those involved in their care and for wider society.

This recognition of its far-reaching impact has driven extensive research into stroke recovery in the last thirty years. Whilst there is little doubt that research into the medical management of stroke is of importance, it is research into rehabilitation after stroke that has been at the forefront of recent developments, with recognition that interventions that do not rely on costly scanning and drugs are likely to be most beneficial (Langhorne et al. 2009b). Investment in rehabilitation research is justified: the majority of patients with stroke will survive the initial event and it is the ensuing consequences that have the greatest impact on stroke survivors, their families and society (Langhorne et al. 2011). After initial medical input, rehabilitation is the primary treatment option available for stroke survivors with on-going deficits. Stroke rehabilitation is the process by which people are enabled to reach their optimal level of function and independence, involving both restorative and adaptive strategies (Cramer, 2008; Cumberland Consensus Working Group, 2009). It is often regarded as cyclical, involving assessment, goal setting,

intervention and reassessment (Langhorne et al. 2011); with members of a skilled multi-disciplinary team working alongside patients and their families and carers.

Physiotherapists are an integral part of this stroke rehabilitation team (Intercollegiate Stroke Working Party, Royal College of Physicians, 2012). Physiotherapy is a health care profession concerned with human function and movement and maximising potential, key aspects of rehabilitation (Chartered Society of Physiotherapy, 2002). Hence, physiotherapists are healthcare providers with an important role in addressing the rehabilitation needs of stroke survivors; specifically, it is the re-education of motor function via movement experience that is central to the physiotherapist's role in stroke rehabilitation. Current evidence suggests that such behavioural experience is a driver for functional reorganisation of the brain after injury such as stroke (Nudo, 2006). Therapy after stroke aims to exploit such neural plasticity, by providing afferent stimulation with a variety of interventions (Pomeroy and Tallis, 2002). Indeed, beneficial cortical reorganisation has been demonstrated following just such therapeutic activity (e.g. Askim et al. 2009). Therefore, it is unsurprising that physical therapy approaches and interventions are on-going priorities in stroke research (Pollock et al. 2012).

The recent growth and advances in stroke rehabilitation research have enabled some key neuroscience principles about exogenous means of driving recovery to emerge. For example, it is known that the repetition of motor activity can produce changes in brain representation maps (Karni et al. 1995; Plautz et al. 2000) and opportunities therefore exist to drive functional reorganisation by including repetition in rehabilitation programmes. Furthermore, motor skill acquisition, or motor learning, has been demonstrated to play a central role (Buonomano and Merzenich, 1998; Perez et al. 2004), suggesting rehabilitation programmes should involve increasing levels of motor skill (Nudo, 2006). It has also been suggested that functional benefit may be gained from goal-directed activity, with the salience of a task considered an important element in rehabilitation programmes (Kleim and Jones, 2008). Finally, ensuring interventions are timely is important. The period early after stroke, from a few days to a few weeks since onset, provides an

important window for initiating restorative therapies (Cramer, 2008, 2011) and very early mobilisation has been shown to increase speed of recovery of functional activity (Cumming et al. 2011).

These principles underpin the understanding of how to drive recovery after stroke. Consequently, they should inform the planning and execution of rehabilitation research programmes, in order that current knowledge is best used to inform investigation of existing, and development of potential new, rehabilitation interventions. Other principles also underpin the development stage of potential new interventions. For example, as the feasibility of new interventions is investigated, it is essential to consider which population of stroke survivors might best be able to take part in any new therapy, and also, how progress might best be measured.

The research and rehabilitation principles identified in this overview have been central to the development of the studies presented in this thesis; hence each of these principles will be explored in detail in the next sections.

1.2.2 Principles informing stroke rehabilitation and research: rehabilitation early after stroke onset

This section will explore the existing evidence on rehabilitation early after stroke onset. For the purposes of this thesis, “early after onset” will refer to the period up to 31 days from the occurrence of stroke. Evidence from neurophysiology studies and then animal model research will be followed by a critique of clinical studies.

It is well-established that, after injury, the brain reorganises connectivity through neuroplastic changes and that there is potential for such changes to be influenced by sensorimotor therapies. It is known that mechanisms of plasticity are particularly active early after cortical damage (Kleim et al. 2003). It is also known that most spontaneous recovery tends to occur in the first three months after onset (Cramer, 2008; Carraugh and Summers, 2005), with significant spontaneous recovery of some motor functions within 30 days (Nudo, 1999).

However, whilst early rehabilitation intervention is currently encouraged after stroke (Intercollegiate Stroke Working Party, Royal College of Physicians, 2012), the optimal time window for provision of rehabilitation therapies to exploit the potential for behaviourally driven brain changes is still uncertain. Hence, research into the most appropriate time to initiate rehabilitation activity after stroke is gaining momentum. Indeed, Cramer (2008) describes a 'golden period' for initiating restorative therapies, starting in the first days after onset and continuing for several weeks, as repair-related events within the brain are at peak levels. Such molecular and cellular events include, for example, an increase in growth associated proteins and increased neuronal sprouting and dendritic branching; all of which are important biological targets for promoting repair after stroke (Nudo, 1999). The prominence of these events at this time might suggest that they could best be shaped to enhance recovery by the behavioural experiences offered by physical therapy, implemented in the first days to weeks after stroke.

Studies using animal models have sought to explore the impact of such early rehabilitation training on both brain changes and ensuing functional outcomes. Kozlowski et al. (1996) immobilised the impaired forelimb, the unimpaired forelimb (hence forcing use of the impaired limb) or neither forelimb of rats, from day one to day fifteen after an induced unilateral brain lesion. All groups were similarly housed, and a series of behavioural tests and limb-use observations made. Chronic, persistent behavioural deficits were found in rats that had their unimpaired forelimb immobilised, with an underlying dramatic exaggeration of lesion size. This suggested that excessive use of an impaired limb, during the early post lesion period, might damage compromised brain tissue surrounding injury and, on balance, the authors proposed a "use it but don't overuse it" strategy for early intervention. However, it should be noted that the experimental conditions meant that the impaired limb was used excessively considering the weakness- for example, the rats had to feed and move around throughout the long periods of immobilisation of the unimpaired limb.

There are inherent difficulties in translating animal model findings to humans. The level of use in Kozlowski et al.'s (1996) study is neither seen nor possible in human stroke rehabilitation- rats had the unimpaired forelimb constrained continually for 15 days, far exceeding the likely nature and intensity of clinical rehabilitation activity in people who have sustained a stroke. In fact, Schallert et al. (2003) suggested that the increased lesion size in the earlier study was a direct result of the intense forced use activity and that long durations of constraint should be avoided until later post-lesion periods. They proposed that including the non-impaired forelimb, hence encouraging inter-limb coordination early after injury, might optimise a therapeutic opportunity to shape synaptic plasticity for functional benefit.

Another interesting finding emanates from a randomised, controlled study of rats given enriched rehabilitation training, not involving limb constraint, at different time points after an induced lesion. Biernaskie et al. (2004) found that those beginning enriched training from day five demonstrated an increase in dendritic growth in a brain region previously established to be associated with recovery (Biernaskie and Corbett, 2001). This early enriched training group achieved a markedly enhanced functional outcome in comparison to those given similar training beginning at day 30, who improved no more than controls given social housing with no rehabilitation activity. The authors proposed that the post stroke brain is sensitive to rehabilitation activity early, in this case five weeks of ongoing rehabilitation initiated at day five after stroke, but that this sensitivity declines with time, and so delaying commencement of rehabilitation may reduce treatment efficacy and limit functional recovery. However, caution must again be observed in translating findings from animal models to humans. In particular, it could be questioned whether five days after stroke in an animal with a much shorter lifespan than a human should be considered "early" after a lesion. Indeed, one interpretation might be that initiating rehabilitation five days after the stroke was delayed treatment onset, not early rehabilitation experience.

Animal studies, therefore, suggest that whilst very intensive forced use of the impaired forelimb immediately after injury may have detrimental effects, enriched rehabilitation therapy without limb constraint, delivered within the first week, is associated with improved recovery. These animal studies justify further investigation of the possible benefits of early rehabilitation intervention after stroke in clinical populations.

One such study attempted to evaluate the effects of providing ten hours of additional upper limb therapy to stroke patients recruited one to five weeks after stroke (Lincoln et al. 1999). Participants were randomised to routine therapy, additional treatment by a qualified physiotherapist or additional treatment by a physiotherapy assistant and evaluated immediately after the intervention and at three and six months follow up, on a wide range of outcome measures. No additional benefits in motor function or activities of daily living were detected from the early, more intensive intervention. However, the authors noted the heterogeneity of the participants in this study with many severely impaired at study entry. Importantly, only around half in each intervention group were able to tolerate the additional treatment.

In contrast, Feys et al. (2004) found immediate and persisting improvements in upper limb function following intensive upper limb training early after stroke. A randomised controlled trial examined the effect of repetitive upper limb training, initiated between two and five weeks after stroke, in addition to conventional therapy. Outcomes were measured immediately after the intervention, at six and twelve months and at five years after stroke. Adding the specific upper limb training intervention in the early phase after stroke resulted in a clinically meaningful effect on motor function in the upper limb. The effects here were evident immediately after the intervention and at the six month follow up, and, notably, upper limb outcomes demonstrated significant differences between control and intervention groups at the five year follow-up. A clinically important long term effect was demonstrated from this intensive rehabilitation protocol initiated early after stroke.

Other studies have examined the effects of early versus late onset of general rehabilitation programmes. A large, multi-centre observational study of 1023 stroke patients found significant association between gains in functional independence, as measured by the Barthel Index, and rehabilitation onset, within 14 days of stroke (Massucci et al. 2006). Similarly, Paolucci et al. (2000) found earlier rehabilitation onset to be associated with favourable outcomes. This study recruited 145 patients consecutively admitted to a rehabilitation unit, who were then matched for age and Barthel score on admission to create homogenous sub groups. Participant data was then evaluated according to time from stroke onset to beginning rehabilitation. Early onset of rehabilitation was associated with significantly improved functional outcome according to the Barthel Index, and with a significantly higher probability of excellent therapeutic response. However, early rehabilitation in this case was considered to be within 20 days of stroke onset and no further stratified analysis was performed to examine effects of earlier rehabilitation onset.

Such an analysis was, however, carried out by Musicco et al. (2003), who examined the effect of time of initiation of rehabilitation activity as part of a large cohort study exploring the early and long-term outcomes of rehabilitation after stroke. Participants (n=1716) were recruited from consecutive admissions to 20 Italian rehabilitation hospitals, and time from stroke to initiation of rehabilitation was one of many sociodemographic, clinical and rehabilitation characteristics recorded. Risk analyses accounted for differences in age and disability scores at baseline for the comparisons. Patients who began rehabilitation within seven days had better long term outcomes in terms of residual disability and quality of life than those beginning at either 15 to 30 days or at greater than one month after onset. However, it is noteworthy that this study also found a borderline significant decrease in mortality in those with treatment initiated at 15 to 30 days compared to those treated within seven days (RR=0.61; 95%CI 0.37 to 1.00; p=0.06). The authors raise concern that, due to political and economic constraints, patients might have been transferred too early from acute services to the hospital rehabilitation unit. These findings, when considered alongside those of Kozlowski et al. (1996), suggest

that further clinical research into the effects of very early rehabilitation input is indicated.

Indeed, an international team is currently evaluating the effects of very early rehabilitation after stroke. The AVERT II study (Bernhardt et al. 2008) hypothesised that very early rehabilitation, emphasising mobilisation, may contribute to improved outcomes. An initial study explored the safety and feasibility of the intervention, recruiting 71 stroke patients less than 24 hours since stroke onset, randomised to standard care or very early mobilisation plus standard care. Primary and secondary safety outcomes, including number of deaths, were similar across groups with successful delivery of the intervention protocol (Bernhardt et al. 2008). Efficacy of the intervention is currently under evaluation. Interim findings of this multi-centre, randomised controlled trial, suggest that mobilisation within 24 hours of stroke and regularly thereafter, is associated with faster return to walking and good functional outcome at three and 12 months, in comparison to standard stroke care controls (Cumming et al. 2011).

In conclusion, therefore, both animal and clinical studies suggest that earlier rehabilitation intervention, which might exploit the time window in which neuroplastic mechanisms are at their most active, may be beneficial in terms of functional outcomes after stroke. This interpretation is supported by the narrative critical review papers by both Cifu and Stewart (1999) and Teasell et al. (2005). Concern has also been expressed that delaying rehabilitation onset might lead to established compensatory behaviours that could impair future recovery (Levin et al. 2009), and immobility might also prevent the brain from making the neurophysiological changes required to reacquire movement. Additionally, National Clinical Guidelines for Stroke (Intercollegiate Stroke Working Party, Royal College of Physicians, 2012) advise that people with acute stroke be mobilised as early as possible.

On balance, therefore, initiating therapies in the early period after stroke is logical. However, current clinical evidence is from either studies assessing specific upper limb rehabilitation programmes (e.g. Feys et al. 2004), large cohort studies

examining onset of general rehabilitation (e.g. Massucci et al. 2006), or recent work exploring general mobilisation very early after stroke (e.g. Cumming et al. 2011).

A gap exists, therefore, in research examining specific lower limb activity early after stroke. This is despite knowledge that training-induced cortical changes, similar to those observed in the upper limb, can occur with motor skill training of the lower limb (Perez et al. 2004). Additionally, there is considerable potential for improved lower limb activity to impact on important functional outcomes such as transferring and walking. Stroke survivors consider their principal goal to be regaining independence in walking (Dickstein, 2008), and evaluating interventions addressing mobility deficits has been identified as a stroke research priority (Pollock et al. 2012).

This section has therefore identified a need to explore specific therapeutic modalities targeting lower limb activity early after stroke.

1.2.3 Principles informing stroke rehabilitation and research: repetitive, task-specific activity after stroke

Scientific debate about the optimal intensity of therapy required to maximise neuroplastic change, and the consequences in terms of functional recovery, is ongoing (e.g. Kwakkel et al. 2006). However, it is beyond the scope of this thesis to engage specifically in these discussions. To clarify, repetition here simply refers to the repeating of a movement or movement pattern a number of times. Clinically, this repetitive practice of movement might occur many times in a single therapy session or over a number of therapy sessions.

It is known that the repetition of skilled motor activity can produce changes in brain representation maps. Animal studies have established a relationship between repeated behavioural experiences e.g. practice of a skilled upper limb task to retrieve food, and beneficial alterations in cortical representation maps (e.g. Kleim et al. 2002; Plautz et al. 2000; Nudo et al. 1996). Furthermore, animal model research found that up to 400 repetitions were required in a 30 minute session to induce changes in cortical representations (Kleim et al. 1998).

Such animal models have provided a basis for further research in human subjects. Karni et al. (1995) trained healthy young adults to perform a series of repetitive finger-tapping sequences with their non-dominant hand for 10 to 20 minutes a day over a five-week period. A control group performed the same movement only at baseline and outcome. At outcome, functional MRI was recorded whilst the tapping sequence was carried out. Unsurprisingly, daily, repetitive practice of the movement increased the speed and accuracy of the movement. These improvements were accompanied by specific changes in the primary motor cortex (M1), with an initial small area of activation on first performing the task, followed by a consistently larger area of activation after three weeks of daily practice. The authors suggested that the repetitive training led to a gradually evolving improved cortical representation of the skilled movement over time, supporting the concept of repetitive practice of a motor skill to enhance beneficial functional brain changes. However, in this observational study, conclusions were drawn from just six healthy volunteers performing simple hand and finger activity only. Small group studies exploring brain changes in healthy volunteers might provide a foundation for generating hypotheses; but the results cannot necessarily be generalised to stroke survivors with altered neural networks.

Work with stroke survivors has been carried out. Johansen-Berg et al. (2002) explored the effects of repetitive practice on brain activity in a small group of stroke survivors (n=7). Stroke patients with mild to moderate impairment six months or more after first stroke took part in a home-based, clearly defined graded exercise programme adopting the principles of constraint induced movement therapy. Functional MRI scanning was carried out before and after the therapy whilst performing a fast hand tapping task. Increased fMRI activity was detected in the premotor cortex and sensorimotor cortex contralateral to the affected hand and bilaterally in the cerebellum, after the therapy programme. This activity correlated with therapy-associated improvements in motor function, suggesting that the repetitive, graded therapeutic activity was having a beneficial effect on brain activity after stroke.

For pragmatic reasons, studies utilising brain scanning whilst participants carry out activity commonly use upper limb movement tasks, leading to difficulties in considering possible cortical effects of training lower limb activity. Perez et al. (2004) therefore attempted to evaluate cortical change following skilled movement training in the lower limb. The task of monitoring brain activity during lower limb movements is challenging using fMRI equipment. Hence, the authors used paired pulse transcranial magnetic stimulation techniques (TMS) to demonstrate cortical excitability following training of ankle muscles in healthy volunteers. The study recruited 25 young healthy volunteers who underwent 32 minutes of passive, non-skilled or skilled training of the lower leg. TMS was carried out before and after each training session to examine cortical excitability via short latency intra-cortical inhibition and facilitation of the motor evoked potential in the area controlling the primary muscle of dorsiflexion, tibialis anterior. Amplitudes of motor evoked potentials were significantly increased after skilled motor training but not after non-skilled nor passive training, suggesting that beneficial neuroplastic brain changes, more specifically in the primary motor area, M1, occurs when skilled activity is practised. These findings are similar to observations in the upper limb studies discussed and further support the contention that beneficial effects are noted following skilled, repetitive activity.

It has also been suggested that functional benefit may be gained from goal-directed activity; hence the salience of a task is considered an important element in rehabilitation programmes (Kleim and Jones, 2008). Indeed, findings from a systematic review of fourteen trials of specific, goal-directed, repetitive activity reported moderate improvements in lower limb function, particularly on walking outcomes (French et al. 2009). This review provides some support for developing task specific lower limb training programmes after stroke in addition to usual care; though it should be noted that there was no evidence of sustained training effects from any included programme.

The need for salient lower limb rehabilitation interventions is further reinforced by knowledge that stroke survivors themselves cite recovery of walking as a primary goal (Dickstein, 2008). Hence, they wish to engage in therapeutic activity

contributing to this aim. However, practising relevant walking activities to improve walking after stroke can be challenging for patients and therapists- stroke survivors often have substantial weakness and require considerable support to take just a few steps. Whilst patients may be able to practise component parts of the activity, opportunities for repetitive practise of complete, reciprocal, antagonistic lower limb activity in walking-like postures can be limited, particularly early after onset.

Section 1.2.2 identified a need to explore specific therapeutic interventions targeting lower limb activity early after stroke; this section has identified that such rehabilitation interventions should incorporate opportunities for repetitive practice of functional activity.

1.2.4 Principles informing stroke rehabilitation and research: prognostic indicators for participation in interventions after stroke

When developing potential rehabilitation interventions, it is important to identify which stroke survivors might be able to participate in those interventions, particularly early after stroke. This is because, as already noted, the first few weeks after stroke are when the brain is most likely to show the greatest amount of beneficial reorganisation in response to therapy (Cramer, 2008). Consequently, providing the most appropriate therapy in this time window could be crucial. Additionally, as resource limited stroke services are increasingly asked to make rapid decisions about prognosis it is essential that specific therapies are targeted at those stroke survivors who will actually be able to participate.

However, whilst therapists have a wide range of clinical interventions in their repertoire, as identified in the development of a lower limb treatment schedule (Pomeroy et al. 2005), there is a paucity of research evidence to guide clinical decisions on which patients are likely to be able to take part in which therapies. Clinical observations suggest that the ability to take part in therapy can be influenced by pathophysiological factors such as the area of brain affected, as well as clinical features including degree of hemiparesis and ability to take part in active repetitive training in the early stages after onset. Identifying prognostic indicators for probable ability to take part in specific therapies could be a useful part of early

phase research trials in order that subsequent trials can target therapies at those participants most likely to be able to participate, and clinicians can be informed in refining their range of interventions according to clinical presentation.

This section has identified, therefore, that it is important to record possible prognostic indicators for the ability to take part in therapies, as part of early phase trials of new interventions.

1.2.5 Principles informing stroke rehabilitation and research: measuring outcomes of interventions after stroke

A further important principle in the development of rehabilitation interventions is the selection of a range of valid and reliable outcome measures in order to accurately assess change (Medical Research Council, MRC, 2008). Current healthcare priorities demand that therapists demonstrate the effectiveness or otherwise of interventions and make rapid decisions about treatment programmes, patients' progress and their potential for recovery. It is known that measures of impairment can provide useful markers of progress and have the greatest capacity to differentiate between treatment groups (Barack and Duncan, 2006).

However, the appropriate measurement of outcomes, in both clinical practice and research, can present a number of challenges to therapists. Whilst it is clear that properly constructed, valid, reliable, specific and user-friendly measures are required for evaluating the effects of interventions (Barack and Duncan, 2006; Lennon and Johnson, 2000), published measurement tools do not always meet these key criteria for routine use in clinical settings. This is despite knowledge that therapists are more likely to choose measures that have demonstrable validity and reliability (Jette et al. 2009). Furthermore, determinants of outcomes in stroke survivors, particularly in terms of impairments, remain poorly defined and their complexities have contributed to difficulties in translation of rehabilitation science into clinical rehabilitation practice (Cumberland Consensus Working Group, 2009).

Additionally, therapists have expressed difficulties in assessing and monitoring treatment effects: tools do not measure performance in functional activities relevant to therapeutic aims (Lennon and Johnson, 2000). For example, therapeutic

goals after stroke often relate to rehabilitation of walking, but measures of impairment frequently use specific static positions and postures for testing rather than measuring during more relevant functional movement. Laboratory-based motion analysis systems are available e.g. Vicon (Vicon Motion Systems Ltd, Oxford, UK), but this equipment is expensive, requires considerable expertise and technical support and is therefore inaccessible to the majority of clinical therapists (Pomeroy et al. 2006). Such equipment also requires stroke survivors to have achieved some independent mobility in order for the data to be recorded during the activity.

Consequently, there is a need to measure motor impairment reliably outside the laboratory, in functional activities that relate to walking. However, detailed analysis of physiological function in the clinical setting is currently unattainable and therapists commonly use simple “hands-on” measures, such as the Motricity Index, to assess and monitor impairment (Turner-Stokes and Turner-Stokes, 1997). Such measures do not enable therapists to accurately characterise the activity contributing to functional movement. For example, two individuals adopting two very different movement strategies might achieve the same score when assessing simple movement against gravity, as stroke does not have uniform effects on neural networks. Tools to accurately characterise movement patterns, particularly during development of potential new interventions, are therefore required. However, such tools should not be used in stroke research unless their psychometric properties have been assessed in a stroke population (Oremus et al. 2012).

This section has therefore identified a need to develop a valid and reliable movement-based measure of impairment that can accurately characterise movement, hence measuring the physiological change that might underpin future functional change.

1.2.6 Principles informing stroke rehabilitation and research: conclusions

This section of the background review firstly established the importance of rehabilitation research after stroke. It then identified that current evidence supports the use of early, task specific, repetitive activity to maximise potential for recovery of lower limb motor function after stroke. Additionally, it established that

it is important to understand which stroke survivors might be able to take part in such activity and how their progress might be sensitively measured.

However, whilst these essential underlying principles of rehabilitation have been accepted, it remains unclear a) which specific therapeutic modalities might be used to provide the repetitive, skilled activity necessary to facilitate functional brain changes early after stroke and b) how progress during participation such functional activity early after stroke might most sensitively be measured.

There is therefore an opportunity to explore a lower limb rehabilitation tool that enables repetitive, functional movement early after stroke and which can be instrumented to enable measures of impairment to be recorded during the activity.

1.3 Background: reciprocal pedalling exercise as a potential tool for assessment, measurement and rehabilitation after stroke

Reciprocal pedalling of the lower limbs is a repetitive, functional activity that, whilst familiar to many stroke survivors, is likely to require re-acquisition of motor skill following the onset of hemiparesis. Pedalling is characterised by an automated, rhythmic movement pattern of the lower limbs in a similar manner to walking. Indeed, there are a number of components of pedalling that are analogous to walking and have led to the suggestion that pedalling might provide both a walking-like rehabilitation intervention and a method of characterising and measuring motor impairment during a walking-like activity after stroke (Brown et al. 1997). Additionally, due to the constrained nature of the task, it is possible that pedalling could be used early after stroke for people with substantial weakness. As such, pedalling is a tool that incorporates the principles of rehabilitation identified in section 1.2

The purpose of this section, therefore, is to explore the potential of reciprocal pedalling exercise, both as a stroke rehabilitation tool as a possible measure of motor impairment after stroke. This part of the review will provide interpretation and synthesis of relevant published work in the form of a narrative literature review.

A systematic review addressing a specific research question, carried out in response to part of the findings of this background chapter, is presented in Chapter 3.0.

1.3.1 Reciprocal pedalling and walking: biomechanical and neurophysiological similarities

This section will explore the emerging body of research that has explored both biomechanical and neurophysiological evidence of similarities between pedalling activity and walking.

Both pedalling and walking require that agonist and antagonist lower limb muscles are contracted reciprocally i.e. in alternating pairs of muscle groups. Raasch and Zajac (1999) used a complex computer simulation of the musculoskeletal system to model such grouped muscle control during pedalling under different conditions, varying cadence, load and direction. Whilst it is important to recognise that this work was carried out using simulations, the detailed modelling and analysis provided key insights into pedalling activity. The authors suggested a number of ways in which pedalling might be likened to human locomotion from their findings: muscles were organised into functional groups and demonstrated both phase and amplitude control; afferent regulation of timed muscle activity was similar to ambulation, in that peripheral proprioceptive information was found to be crucial to execution of movement; and transitions between phases of muscle activity in response to changes in, for example, direction, were similar. Indications that sensorimotor control mechanisms for walking and pedalling are analogous might provide a basis for pedalling as a potential tool for the rehabilitation of walking.

Furthermore, in a study attempting to establish a link between hemiparetic severity and weaker leg contributions to walking, Bowden et al. (2006) used a pedalling protocol to examine anterior-posterior ground reaction forces (work production) in a small group (n=16) of chronic stroke survivors. Spatio-temporal gait characteristics were measured at self-selected walking speeds; then positive work, negative work and total work for each lower extremity were measured during pedalling. Measures of work production during pedalling were significantly positively correlated with propulsive impulses recorded during walking ($r=0.588$ $p=0.017$), suggesting

similarities between components of pedalling and walking, in this small group of stroke survivors.

Such work suggesting commonality of fundamental aspects of pedalling and walking has led to further research exploring the mechanisms involved in the production and control of pedalling movement. The underlying assumption here is that because of similarities in control mechanisms between pedalling and walking, pedalling could be a task-specific training tool for walking activity.

It is known that during simple human locomotor activity, descending corticospinal drive interplays with spinal mechanisms (e.g. Petersen et al. 2001). An emerging body of research has therefore begun to investigate whether similar mechanisms are used to generate and control the motor task of pedalling.

For example, Zehr et al. (2007), in a small study of ten healthy subjects, found that neural regulation of rhythmic lower limb movement was similar across locomotor tasks. Subjects performed three rhythmic tasks: treadmill walking, upper limb-assisted recumbent stepping and pedalling on a coupled leg and arm ergometer. Cutaneous reflexes were evoked during the activities, activity was recorded from five lower limb muscles using electromyography (EMG) and recordings were made of kinematic data using goniometry and force sensors located in the subjects' shoes. Using principal components analysis, reasonable correlations were demonstrated for background EMG and reflex amplitudes in the superficial peroneal nerve for walking and cycling ($r=0.57$ for background EMG; $r=0.43$ for reflex amplitude), and cycling and stepping ($r=0.48$ for background EMG; $r=0.49$ for reflex amplitude). It is proposed in this work that the correlations of reflex activity and muscle activity across tasks suggest commonality of control. However, it should be noted that the authors use a correlation of $r=0.40$ and above to draw a conclusion of good correlation and no correlation across any of the relevant components was above $r=0.57$. The sample size here was small, and neither p-values nor confidence intervals around the correlation statistics were expressed. It should also be noted that the stepping activity was in a non-functional recumbent posture. The comparisons between stepping and cycling might be considered less relevant than

those between walking and cycling when considering cycling activity as a possible rehabilitation tool for walking.

Direct cortical contributions to lower limb muscle activation during pedalling, in a similar manner to the cortical contributions previously observed during human locomotion, have recently been observed in small studies of healthy volunteers performing static ergometer pedalling (Sidhu et al. 2012; Jain et al. 2012). Jain et al. (2012) noted that cortical involvement could be involved in the more challenging phases of pedalling. This was demonstrated by particularly strong associations between cortical activity recorded using electroencephalography (EEG) and lower limb EMG activity during the transition phases between flexion and extension compared to other aspects of the pedalling cycle. It could be inferred that these associations during more challenging aspects of the movement suggest not only cortical involvement in the control of the activity, but that pedalling is a suitably challenging activity to beneficially influence cortical changes. Indeed, Yamaguchi et al. (2012) have recently explored the hypothesis that pedalling exercise might have a beneficial effect on the cortical leg area. This work had some similarities to that of Perez et al. (2004) (section 2.3.2): the study of ten healthy volunteers compared active and passive activity, in this case pedalling, and its effects on intracortical inhibition as measured by sub-threshold, paired pulse TMS. Whilst no changes were observed after the passive activity, intracortical inhibition of the cortical leg area was decreased after active pedalling, suggesting beneficial cortical reorganisation that might influence ambulation. Though the study only used a small group of healthy volunteers, it demonstrated the potential of active pedalling as a sufficiently skilled activity to induce beneficial cortical changes in the short term.

This section has therefore demonstrated an emerging evidence base in support of biomechanical and neural similarities between pedalling and walking, which have led to the suggestion that pedalling might be used as a tool for the rehabilitation of walking activity.

Nonetheless, it is prudent to recognise the differences between the activities when considering the possibilities of pedalling for rehabilitation of walking. Pedalling tasks

provide, via the crank-based system, inter-limb coupling that does not occur during walking; pedalling is a much more constrained, predictable task. During pedalling on an ergometer device, adjustments in muscle activity to account for challenges to balance are less likely than when walking. Pedalling is most frequently carried out on static bicycles and ergometers in seated and recumbent postures, unlike walking. Additionally, pedalling does not require use of the upper limbs to assist the rhythmic movement as during normal walking.

However, some of these differences might further support its possible use as a rehabilitation tool for walking rather than detract from them: stroke survivors often have substantial weakness, particularly early after onset but often persisting, that makes repetitive practise of walking tasks challenging, if not impossible. Hence, using a constrained ergometer pedalling device could provide important opportunities for practising repetitive, phasic lower limb movement similar to walking that might otherwise not be available.

1.3.2 Reciprocal Pedalling: a potential rehabilitation activity after stroke

The evidence of similarities to walking, potential for facilitating beneficial cortical changes, familiarity and accessibility of the task, and availability of equipment have all contributed to the investigation of pedalling as a potential stroke rehabilitation tool. This section will explore this evidence.

Over 25 years ago, Brown and DeBacher (1987) suggested that patients with spastic hemiparesis might benefit from independently practising repetitive movement on a bicycle ergometer. They began to define equipment requirements and suggested that feedback using electromyography might usefully be incorporated to re-educate lower limb muscle activity. An illustrative case of one young male stroke survivor was used to demonstrate positive changes in gait and lower limb muscle activity after ergometer training with EMG feedback. Though no detail was given of the specific pedalling protocol, the authors reported an observed increase in hamstring activity and reduction in abnormal gait parameters such as hip circumduction and trunk flexion, after training. This single case was the first report of an attempt to

quantify the possible beneficial effects of pedalling activity after stroke and work has continued to explore its possibilities for rehabilitation.

For pedalling exercise to be considered as a possible tool for the rehabilitation of walking, particularly for those stroke survivors who are too weak to walk, it is important that pedalling movement provides opportunities for practising phasic, coordinated muscle activity. Evidence from a small exploratory study of 17 non-ambulatory stroke survivors, who were later than three months since onset, suggested that pedalling could indeed facilitate such activity in patients with severe hemiparesis (Fujiwara et al. 2003). Lower limb muscle activity was recorded via surface EMG from four muscles during and after a one-off pedalling task, consisting of pedalling a seated ergometer for five minutes at the participant's comfortable speed. Visual inspection of EMG traces for quadriceps and hamstrings muscles suggested a phasic pattern of activity, though there was no statistical analysis of reciprocity. Whilst this small developmental study did not provide definitive evidence, there were indications that phasic activity occurred during seated pedalling activity even in people with severe hemiparesis.

In addition to the production of phasic lower limb movement, it has also been suggested that pedalling activity after stroke can have beneficial effects on lower limb muscle strength, balance and some walking outcomes.

For example, a small group study of eight chronic (median time since stroke onset= two years) male stroke survivors found significant effects on concentric knee extensor strength on the affected side, after 12 sessions of recumbent pedalling over four weeks (Perell et al. 2001). In the same participants after this pedalling intervention, additional observations, though not statistical comparisons, of improved ankle control (measured by direction of pedalling force) were made (Perell et al. 2000).

Additionally, a preliminary, small group (n=24) randomised controlled trial of early cycling training after stroke examined possible effects on balance, as measured by the Postural Assessment Scale for Stroke (PASS), and lower limb motor function, as measured by the Fugl-Meyer Assessment (FMA) (Katz-Leurer et al. 2006). In-patient

stroke survivors were randomised to a cycling exercise intervention daily for three weeks or to usual rehabilitation care control group, and were followed up for six weeks. Both groups improved on the PASS and FMA at the six week assessment. The exercise group demonstrated a significantly better performance on the PASS and FMA relative to controls at six weeks (PASS mean scores: exercise group 31.1, control group 26.4, $P=0.004$; FMA mean scores: exercise group 29.1, control group 22.1, $P<0.001$). It should be noted that this was assessed using a group-time interaction effect and not a between groups significance test and that no confidence intervals were given to enable interpretation of possible clinical significance of findings. Additionally, the pedalling programmes in this study were individualised to each participant and not standardised, and usual rehabilitation care details were not given. Furthermore, whilst the study recruited people within one month of admission to a rehabilitation unit, exact time since stroke onset was not specified. However, this pilot work indicated possible beneficial effects on balance and lower limb motor function after stroke.

Contrasting findings on the possible effects of pedalling exercise on walking outcomes have been found. A small randomised controlled study examined the effects of an eight week aerobic pedalling programme in comparison to a home based stretching programme (Quaney et al. 2009) in 38 chronic stroke survivors (mean time since stroke onset= 4.9 years). A significant decrease in time taken to rise from a chair, walk three metres, and return (the “Get Up and Go”, GUG, test), was found in the pedalling exercise group when compared to the stretching group immediately after the intervention (GUG mean scores: pedalling group 15.26, control group 29.11, $p=0.038$). The effect did not, however, persist to eight week outcomes.

Tang et al. (2009) also explored an aerobic pedalling programme, in this case early after stroke, in order to determine the feasibility of adding such a programme to conventional rehabilitation and to explore possible effects on aerobic capacity and walking outcomes. ‘Early after stroke’ here referred to a wide range of time since onset, from six to 62 days (mean 17.5 days), as inclusion criteria enabled recruitment of stroke survivors up to three months from stroke onset. This

developmental study used a matched control design, with an exercise group taking part in 30 minutes of graded pedalling activity in addition to usual therapy, three times per week. Eighteen pairs of exercise and control group participants, matched on the basis of age and sex, were compared on a range of outcomes. Findings here contrasted to those in the study of chronic stroke survivors (Quaney et al. 2009); whilst there were improvements in all scores in both groups, there were no significant between group differences on any walking outcomes, including preferred and fast-paced gait speeds. It should be noted that four individuals in each study group were non-ambulatory and therefore unable to take part in the tests of walking ability.

Whilst interpretation of developmental work must necessarily be cautious, this section has identified an emerging body of evidence that pedalling could be a potential rehabilitation intervention to enhance motor function, including walking recovery, after stroke. However, whilst there are some suggestions of benefit, the current evidence on pedalling exercise after stroke has not been synthesised systematically in order to inform clinical practice and future research.

1.3.3 An alternative potential tool for rehabilitation of walking after stroke

The background to the thesis thus far has used existing evidence to demonstrate that reciprocal pedalling is a possible tool for improving motor function, including walking, after stroke. It has also suggested that the “usual” methods of assisting people to repetitively practise walking, such as hands-on therapeutic approaches, are very challenging for therapists and people with stroke, particularly those with substantial weakness early after onset. Another method of potentially meeting these challenges has emerged in rehabilitation research in recent years: body weight-supported treadmill training, in which people with walking impairments can practise walking on a treadmill with their weight partially supported by a suspended harness. As a possible alternative to the new rehabilitation tool proposed in this thesis, it is important that this intervention is discussed; hence recent evidence on treadmill training after stroke will be critiqued in this subsection.

Body weight-supported treadmill training (BWSTT) is a tool that could meet some of the principles known to underpin successful rehabilitation after stroke: the concept here is that BWSTT offers opportunities for task-orientated, repetitive, progressive practise of walking and hence might facilitate activity-dependent neuroplasticity (Dobkin and Duncan, 2012). Due to the use of a patient harness, adjustable to enable graded body weight-support, it has been proposed that BWSTT might offer opportunities for rehabilitation of walking before over-ground walking can be achieved (Franceschini et al. 2009; McCain et al. 2008). Indeed, the feasibility of use of BWSTT in stroke survivors within six weeks of stroke onset, has been demonstrated (Franceschini et al. 2009). It is therefore unsurprising that BWSTT has become increasingly popular and the subject of a number of research studies and reviews in the past two decades (Moseley et al. 2005).

However, results of the effectiveness of BWSTT on walking outcomes after stroke have been disappointing, despite a number of well-designed randomised controlled trials (Dobkin and Duncan, 2012). A Cochrane systematic review and meta-analysis of 15 trials, including over 600 participants, found that there were no significant differences between treadmill training, either with or without body weight support and any other interventions for the continuous variable of walking speed or the dichotomous variable of walking dependence (Moseley et al. 2005). For those participants who could walk at the start of intervention, BWSTT did produce some trends to increased walking speed but this was a non-statistically significant effect (0.09 metres per second, [95% CI: -0.02 to 0.20]). For the only trial investigating people who were dependent walkers at the start of the intervention and that reported follow-up data (Nilsson et al. 2001), there was no evidence of an effect on walking speed when comparing BWSTT to usual over-ground walking training with a physiotherapist (-0.12 metres per second, [95% CI:-0.37 to 0.13]).

A more recent systematic review (Charalambous et al. 2013) further supported the contention that BWSTT interventions do not demonstrate superiority over control group therapies for walking speed outcomes after stroke. This review included 15 randomised controlled trials evaluating effects of treadmill training and/or BWSTT on final walking speed, change in walking speed and retention of any changes in

walking speed, published up to May 2012. A qualitative synthesis was reported, with calculation of within-group and between-group effect sizes. The synthesis found that, whilst treadmill training without body weight support did demonstrate some superiority over control interventions in both final walking speed and change in walking speed, no study examining BWSTT found a superior response over control group therapies on any walking speed outcome. However, limitations of this study, noted by the authors, included that both the tests used to determine walking speed and the training intensities varied across studies. Meta-analysis was not carried out and no justification was given for this decision. It is also of note that this review did not include the work of Franceschini et al. (2009), who conducted a moderately sized single-blind randomised controlled trial examining BWSTT versus over-ground walking training in early stroke survivors, including effects on walking speed. This study randomised 97 people, who were unable to walk at inclusion, to either BWSTT or conventional over-ground walking training within 45 days of stroke onset. Intervention group participants underwent 20 minutes of BWSTT followed by 40 minutes of conventional training, 5 days per week for an overall number of 20 sessions; control group participants underwent 20 sessions of conventional over-ground gait training for 60 minutes per session. Feasibility of use of BWSTT was demonstrated and participants in both groups demonstrated improvements in functional ambulation, muscle strength and walking speed, but no significant differences between groups were found. Hence, whilst Charalambous et al. (2013) did not include this paper, it would not have changed the conclusions of their review.

Moseley et al. (2005) and Franceschini et al. (2009) both concluded a need for well-designed further studies of treadmill based interventions. However, more recently, this suggestion of a need for further investigation of BWSTT has been challenged, with Dobkin and Duncan (2012) suggesting that it may be time to stop promoting and investigating the effectiveness of this intervention and encourage patients to participate in other activities that improve motor control, balance, strength and endurance. Dobkin and Duncan (2012) make this recommendation in the light of recent trials finding no evidence of benefit of BWSTT (e.g. Franceschini et al. 2009),

concurring with systematic review findings (Moseley et al. 2005). Additionally, treadmill training uses large-scale equipment that is unlikely to be transferable to a home setting and requires the expertise of physiotherapists to assist with positioning in the device and foot placement to ensure walking quality. Its possibilities as a task-orientated tool have also been challenged due to the nature of the walking activity involved, with the stroke survivor suspended by a harness, reacting to the ground moving beneath their feet, unable to self-adjust their speed or take visual cues from the passing environment (Dobkin and Duncan, 2012). Consequently, current clinical guidelines for stroke do not recommend BWSTT for retraining of gait after stroke (Intercollegiate Stroke Working Party, Royal College of Physicians, 2012) as there is insufficient evidence of it improving walking more than conventional physiotherapy for recommendations of clinical use to be made.

Hence, there remains an opportunity to develop another tool to promote motor function, including walking, early after stroke; reciprocal pedalling is an alternative to BWSTT. Reciprocal pedalling does not provide actual stepping movement in the manner of treadmill training, and some of the previously mentioned criticisms of treadmill training, including a lack of visual cues from the passing environment, might equally be levelled at static pedalling, but important similarities to walking have been established (section 1.3.1). Additionally, pedalling equipment is more accessible than large-scale treadmill devices and, once pedalling is underway, minimal intervention from the therapist is required. Existing evidence on BWSTT has not, therefore, precluded further investigation of reciprocal pedalling as a possible rehabilitation tool after stroke.

1.3.4 Reciprocal Pedalling: a potential tool for the measurement of motor impairment after stroke

The principles underlying the need to establish sensitive measures of motor impairment in stroke survivors were identified in section 1.2.5. This section will explore the possibility, emerging from current research that measures of muscle activity recorded during reciprocal pedalling might provide a sensitive method of quantifying lower limb motor impairment.

After stroke, many patients cannot ambulate effectively enough to perform a rhythmic test while walking, but they might be able to take part in reciprocal pedalling activity. Pedalling therefore has the potential to provide measurable walking like activity in both those with compromised walking ability and those able to ambulate after stroke.

It is well known that muscle activation during rhythmic human movement such as pedalling can be analysed in terms of muscle activity level and/ or muscle activation timing with portable EMG systems (Hug and Dorel, 2009). Surface EMG, using adhesive electrodes on the skin, provides relevant information from a larger mass of muscle tissue than with invasive wire electrodes and is usable in clinical settings (Hug and Dorel, 2009). Such tools are well-accepted by the biomechanics research community and their use is diversifying to include assessment in, for example, sports medicine centres (Dorel et al. 2008).

It is known that measures derived from EMG can be used to quantify muscle patterns during pedalling, not only in healthy volunteers, (e.g. Savelberg et al. 2003; Dorel et al. 2008) but also in stroke survivors. Indeed, a small body of studies has suggested that such pedalling measures can successfully characterise motor impairment after stroke. In particular, Brown et al. (1997) were able to characterise the lower limb motor performance of stroke survivors during pedalling in different positions, by successfully depicting changes in muscle activation timing via surface EMG, along with pedal reaction forces and pedal kinematics. Following this, the same team quantified the effects of increasing workload on muscle activity of stroke survivors during pedalling, using EMG. Again, measures recorded during pedalling were adopted to characterise patterns of movement, this time at different speed and workload contributions. Furthermore, Kautz et al. (2005), used EMG recording of lower limb muscle activity during pedalling to quantify motor coordination as an outcome measure in a trial investigating the effects of a combined exercise programme after stroke.

However, such detailed characterisation remains unexplored in early stroke survivors taking part in pedalling. It is particularly important that activity is recorded

in detail as this stage to establish the movement patterns being adopted to achieve the functional goal- abnormal movement patterns might be less skilled, use compensatory strategies and hence drive maladaptive brain recovery. Hence, it is important to establish whether measures that characterise movement during reciprocal pedalling can be derived early after stroke via the instrumentation of a pedalling device, and to explore whether those measures might be valid and reliable for clinical use and use in future studies.

Indeed, despite the adoption of EMG derived measures to characterise impairment after stroke (e.g. Brown et al. 1997; Kautz et al. 2005) the reliability and validity of such measures when used with stroke survivors, has not been investigated. Such assessment is important to reliably determine a) change over time in the same participant, which is highly relevant for monitoring responses to stroke physical therapy over a number of treatment sessions; b) whether there is any association with existing clinical measures; and, c) whether the measures are sufficiently discriminatory to be reliably used in clinical practice.

A small body of work has examined the reliability of such measures in healthy active adults. Dorel et al. (2008) examined the repeatability of ten lower limb muscle activation patterns in eleven tri-athletes during pedalling performed before and after a training session. Patterns were defined according to onset and offset of bursts of activity (timing parameters) and root mean squared muscle activity level. No significant differences were found between test and retest for any of the test muscles' activity levels. Vastus medialis (VM), soleus (SOL) and tibialis anterior (TA) demonstrated significant differences in timing parameters using the intra-class correlation coefficient, but on further analysis, these muscles demonstrated high repeatability of patterns using cross-correlation coefficients. Challenges to assessing repeatability of pattern using onset and offset might be apparent due to difficulties in deciding when a muscle is truly on and off and these are further reflected upon in Chapter 6.0.

More recently, Jobson et al. (2012) examined muscle activity levels and patterns in male cyclists and non-cyclists in eight muscles, on three separate occasions, using

surface EMG. Onset and offset for all muscles demonstrated no significant difference between visits in either cyclists or non-cyclists, though intra-session repeatability for tibialis anterior and rectus femoris onset was lower than for the other muscles in both groups. The results for rectus femoris were similar to that achieved by Dorel et al. (2008).

Whilst this work has begun to explore the components of EMG derived pedalling measures in unimpaired individuals, where movement patterns might be expected to be largely homogenous, no such work has been done elucidating the psychometric properties of these measures in stroke survivors. It is essential that testing is carried out in a group of stroke survivors with a broad range of clinical characteristics, as movement patterns here might demonstrate heterogeneity due to different effects of the condition on neural networks. In addition to the possibility of exploring the reliability of such measures in people after stroke, these physiological measures might present an opportunity to more generally quantify motor impairment. Testing their discriminatory ability between stroke survivors and healthy volunteers is therefore indicated.

Finally, the detailed characterisation of movement that might be offered by the EMG derived pedalling measures could provide physiological insights into the interpretation of findings of a reliability study.

This section has identified that instrumented reciprocal pedalling has the potential to be used as a measure of motor impairment after stroke in the clinical rehabilitation setting. The development phase of such a clinical measure necessitates investigation of its psychometric properties before recommendations to the rehabilitation community can be made.

It is currently unknown whether the measure of motor impairment by instrumented reciprocal pedalling is able to discriminate between muscle activity in stroke survivors and healthy comparison subjects; is repeatable (i.e. could be reliably repeated across therapy sessions) in stroke survivors; is congruent with existing clinical measures of impairments of motor function; and is representative of current ambulatory ability.

1.3.5 Conclusions: reciprocal pedalling as a potential tool for assessment, measurement and rehabilitation after stroke

This section of the background review has established that a) reciprocal pedalling exercise is a potential rehabilitation tool that incorporates the identified principles of rehabilitation identified in section 1.2; b) there are indications from current evidence that reciprocal pedalling has biomechanical and neurophysiological similarities to walking and that it might have beneficial effects on motor function after stroke and c) there are indications that measures recorded during reciprocal pedalling might be useful in sensitively characterising and measuring lower limb motor impairment after stroke.

However, to date there has been no systematic synthesis of the current research evidence on reciprocal pedalling after stroke. It also remains unclear if it is feasible for people to participate in reciprocal pedalling interventions early after stroke when the brain is at its most responsive to extrinsic therapies. Additionally, it remains unclear if measures recorded during reciprocal pedalling after stroke are valid and reliable.

There are, therefore, opportunities to systematically retrieve and synthesise current research on reciprocal pedalling after stroke, to explore the feasibility of reciprocal pedalling exercise early after stroke and to explore the reliability and validity of measures recorded during the activity.

Chapter 2.0: Statement of Aims

2.1 Introduction

The background chapters of the thesis have established that:

- current evidence supports the use of early, task specific, repetitive activity to maximise potential for recovery of lower limb motor function after stroke; reciprocal pedalling exercise is one such potential rehabilitation activity.
- there are indications from current evidence that reciprocal pedalling has biomechanical and neurophysiological similarities to walking and that it might have beneficial effects on motor function after stroke.
- it is important to understand which stroke survivors might be able to take part in such activity.
- it is important to understand how stroke survivors move during reciprocal pedalling and how their progress might be sensitively measured.
- there are indications that measures recorded during reciprocal pedalling might be useful in sensitively characterising and measuring lower limb motor impairment after stroke.

However, to date there has been no systematic synthesis of the current research evidence on reciprocal pedalling after stroke. It also remains unclear if it is feasible for people to participate in reciprocal pedalling interventions early after stroke when the brain is at its most responsive to extrinsic therapies. Additionally, it remains unclear if measures recorded during reciprocal pedalling after stroke are valid and reliable.

There are, therefore, opportunities to:

- systematically synthesise the current evidence on the effects of reciprocal pedalling exercise on motor function after stroke
- explore the validity and reliability of measures of lower limb motor impairment made during reciprocal pedalling
- explore the feasibility of participation in reciprocal pedalling early after stroke

Hence, the following research questions and ensuing aims for the investigations were developed:

2.2 The Research Questions:

Question One:

1. Does reciprocal pedalling exercise enhance motor function after stroke?

This question was informed by the need to systematically synthesise and understand the implications of the existing evidence on the effects of reciprocal pedalling on motor function after stroke. The driver for the question was the **hypothesis** that reciprocal pedalling exercise has beneficial effects on motor function after stroke.

The question gives rise to the following aims:

Aim 1a

To systematically retrieve and assess the robustness of the current research on the effects of lower limb reciprocal pedalling exercise on motor function after stroke.

Aim 1b

To consider the implications of current research findings on reciprocal pedalling exercise for future research and rehabilitation practice.

Aims 1a and 1b will be investigated using a systematic review (Chapter 5.0)

Question Two:

- 2. Are measures of lower limb motor impairment which are made during RP valid and reliable?**

This question was informed by the identified need to develop sensitive measures of impairment that might identify physiological changes underpinning clinical changes after stroke. Such measures have potential importance for use in both clinical practice and research.

The driver for this question was the **hypothesis** that reciprocal pedalling is a reliable and valid method of measuring lower limb motor impairment after stroke. This has not been tested to date.

This question gives rise to the following aims:

Aim 2a

To instrument the RP device to enable recording of measures of lower limb motor impairment during the reciprocal pedalling activity.

Aim 2b

To determine whether the measurement of motor impairment by UP, as expressed by a) changes in muscle activity timing and reciprocal activation measured by EMG and b) smoothness of pedalling activity, is repeatable across measurement sessions in stroke survivors with a variety of clinical characteristics.

Aim 2c

To determine whether the measurement of motor impairment by UP, as expressed by a) changes in muscle activity timing and reciprocal activation measured by electromyography (EMG) and b) smoothness of pedalling activity, has discriminative ability between stroke survivors and healthy volunteers and between different levels of function in stroke survivors.

Aim 2d

To determine whether the measurement of motor impairment by UP as expressed by a) changes in muscle activity timing and reciprocal activation measured by EMG and b) smoothness of pedalling activity, has any association with a commonly used existing clinical measure of impairment, Motricity Index; and of current ambulatory capacity as measured by the Functional Ambulatory Categories.

Aim 2a will be investigated as part of a feasibility study exploring reciprocal pedalling early after stroke (Chapter 5.0); Aims 2b, 2c and 2d will be investigated using a clinical measurement study (Chapter 6.0)

Question Three:

- 3. Is participation in reciprocal pedalling (RP) in the first 31 days after stroke feasible?**

Throughout this thesis, reciprocal pedalling is considered to be a complex rehabilitation intervention; that is, an intervention with a number of interacting components, as defined in the Medical Research Council Guidance for Developing Complex Intervention (Medical Research Council, 2008).

The final question was informed by the need to promote and achieve functional activity after stroke in a manner incorporating the identified underlying principles of rehabilitation.

The driver for the question was the **hypothesis** that reciprocal pedalling, used as an adjunct to conventional therapy, might enhance recovery of lower limb motor function in stroke survivors with substantial paresis early after stroke. This has not been tested to date in early stroke survivors.

However, before the hypothesis can be definitively tested in a Phase III clinical trial, and in accordance with Medical Research Council Guidance, it was essential that feasibility and pilot work be carefully planned and carried out (Craig et al. 2008). Whilst this development work might add to the time taken to develop an original rehabilitation intervention in this participant group, it is a crucial step to ensure that the eventual intervention is able to be accurately implemented, evaluated and replicated both in further research and practice (Craig et al. 2008). This stage in the development of a complex intervention can provide vital information on:

- feasibility of use of the intervention with the intended participants including recording of any adverse effects
- feasibility of implementation in the chosen setting including recruitment and retention to the study
- potential sample size required for a later phase study
- outcome measures required to accurately assess potential clinical efficacy- a range of measures is likely to be needed to make best use of the data at this stage including picking up any unintended consequences; and, finally,
- whether there is sufficient evidence of benefit to justify proceeding to subsequent larger trials

Hence, due consideration was given to these factors in development of an early phase study protocol and the following aims were established:

Aim 3a

To estimate the proportion of stroke survivors in an acute in-patient stroke unit who are able to participate in RP, within 31 days of stroke onset.

Aim 3b

To explore whether stroke survivors who are within 31 days of stroke onset can perform RP on a daily basis.

Aim 3c

To investigate whether there are any indications of which individuals may be able to take part in RP in the first 31 days after stroke, according to their clinical characteristics

Aim 3d

To explore the mechanisms that might be responsible for any future clinical change by the detailed characterisation of lower limb muscle activity patterns during RP in the first 31 days after stroke.

Aim 3e

To determine whether there is sufficient evidence of efficacy for RP to justify proceeding to subsequent clinical trials.

Aim 3f

To record and report any adverse effects occurring as a result of participating in RP in the first 31 days after stroke.

Aims 3a to 3f will be investigated using a feasibility study to explore reciprocal pedalling exercise early after stroke (Chapter 5.0).

Chapter 3.0: A Systematic Review of the Effects of Reciprocal Pedalling Exercise on Motor Function after Stroke

3.1 Introduction

It has been established that pedalling is an activity incorporating some of the underlying principles of rehabilitation that drive functional brain changes after stroke (Chapter 1.0). Hence there is a developing body of research exploring its potential as a rehabilitation tool (e.g. Katz-Leurer et al. 2006; Fujiwara et al. 2003; Perell et al. 2001, 2000). Chapter 1.0 demonstrated evidence from exploratory studies that pedalling activity may have a positive effect on strength, reciprocal activation of antagonistic muscle groups, balance and some walking outcomes in stroke survivors (Perell et al. 2001; Fujiwara et al. 2003; Katz-Leurer et al. 2006; Quaney et al. 2009).

This existing research evidence has not been synthesised nor its robustness evaluated. Hence, the purpose of this chapter is to investigate aims 1a and 1b using systematic review methodology.

3.2 Research question

This study addressed question one:

Does reciprocal pedalling exercise enhance motor function after stroke?

3.3 Aims

The aims of this study were to assess the quality of the current evidence on the effects of lower limb reciprocal pedalling exercise on motor function after stroke;

and then consider the implications for both future research and rehabilitation practice (aims 1a and 1b).

3.4 Methods

It is widely accepted that the most rigorous method for evaluating the possible effects of an intervention is to synthesise and assess the available literature via a systematic review. Systematic reviewing is a scientific technique that comprehensively integrates existing evidence, using a repeatable methodology that limits bias (Mulrow, 1994). Reliable assessments of available evidence are increasingly important in changing healthcare settings and rehabilitation professionals must be aware of the breadth and depth of research evidence available on the interventions they employ (Greener and Langhorne, 2002).

However, despite the emerging research into pedalling interventions identified in the background review, and clinical observations suggesting that many stroke unit therapy departments have exercise bikes available for stroke rehabilitation programmes, there has been no systematic review published on evidence on potential effects of pedalling exercise after stroke.

This research question was therefore addressed using systematic review methodology.

The design of the review followed recommendations of the Cochrane Collaboration, the established international body providing methodological recommendations for, and publication of, systematic reviews of health care.

The review was carried out by the lead author (NH) and an independent reviewer, Will Winterbotham (WW), Senior Physiotherapist, Addenbrooke's Hospital, Cambridge, UK.

3.4.1 Searching for studies

3.4.1i Electronic search strategy

The search was developed in liaison with a medical librarian and terms were adapted according to the specific requirements of each database. No funding was available for translation and hence the search was limited to English language papers only.

Search strategy used:

1.exp Cerebrovascular Disorders/

2.exp Stroke/

3.(cerebral or cerebellar or brainstem or vertebrobasilar or brain).mp.

4.(infarct* or isch?emia or thrombo* or embol*).mp.

5. 4 and 3

6. (cerebral or brain or subarachnoid or intracerebral or intracranial or cerebellar).mp.

7. (h?emorrhage or h?ematoma or bleed*).mp.

8. 6 and 7

9. (hemipleg* or hemipar*).m_titl.

10.8 or 1 or 9 or 2 or 5

11. limit 10 to (english language and humans and "all adult (19 plus years)")

12. (bicycl* or bike or pedal* or ergomet* or cycle or cycling or cyclical).mp.

13. (cycle* adjmenstrua*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

14. 12 not 13

15. limit 14 to (english language and humans and "all adult (19 plus years)")

16. 11 and 15

3.4.1ii Databases

The following databases were searched electronically:

- COCHRANE: Database of systematic reviews, database of abstracts of reviews of effects, Cochrane central register of controlled trials, Cochrane methodology register, Cochrane stroke group
- MEDLINE
- EMBASE
- CINAHL
- AMED
- PEDro
- PsycINFO

The initial search period was conducted to cover the period from the induction of the databases to March 2009 and this was updated in a subsequent search to March 2010, prior to submission for publication of the review (Hancock et al. 2012).

3.4.1iii Searching other resources

Reference lists of full text papers retrieved were hand searched by the lead author.

Personal contact was made with key authors in the field. These were identified as those publishing three or more papers in the area of study following the initial title scan. Three authors were contacted, Professor D. Brown, Professor T. Fujiwara and Dr K. Perell. Responses were received from Professor Brown and Professor Fujiwara.

3.4.2 Identification of Studies

3.4.2i Types of Studies

All study designs, including randomised studies (RS) and non-randomised studies (NRS). The initial scoping exercise revealed a limited number of randomised controlled trials of the intervention, a common finding in research into physiotherapy interventions. Restricting too stringently by design may have led to a number of studies of interest being excluded from the review.

3.4.2ii Types of Participants

- Adults (>18 years)
- Clinical diagnosis of stroke, in any brain area
- Stroke caused by ischaemia/infarct or haemorrhage
- Any time after stroke
- Paretic lower limb contralateral to stroke lesion
- With/without sensory loss
- With/without unilateral neglect

3.4.2iii Types of Interventions

No methodological restrictions on dose, frequency, intensity or duration of intervention were applied.

The following interventions were included:

- Reciprocal pedalling exercise designed to enhance motor recovery in the paretic lower limb.
- Reciprocal lower limb pedalling exercise as part of an aerobic exercise programme, where outcomes include evaluation of effect on motor function.

- Reciprocal lower limb pedalling exercise in any body position.
- Reciprocal lower limb pedalling exercise as a one-off intervention or series of interventions over time.

The following interventions were excluded:

- Pedalling exercise where used solely to achieve a maximal exercise stress test for the evaluation of aerobic capacity.
- Pedalling exercise where used as an adjunct to other therapeutic interventions e.g. with functional electrical stimulation; or as part of a combined therapeutic exercise programme.

3.4.2iv Types of Outcomes:

- All outcomes of motor function after stroke used in the included studies (excluding upper limb outcomes). “Motor function” here encompasses a spectrum- from the physiological functioning of body systems and structure, through to the execution of specific tasks by an individual. Outcomes included, for example, timing of onset and offset of muscle activity, reciprocity of muscle activity, muscle strength, balance and walking and stair climbing ability. Examples of measures by which such outcomes were obtained included EMG activity, the Motricity Index, the Functional Ambulatory Categories, timed walking and stepping tests and measures of functional independence. For this original systematic review of the intervention, and in accordance with recognised guidance (Higgins and Green, 2008) it was decided that using a wide range motor function outcomes would optimise information available for synthesis and interpretation.
- Measures of side effects and adverse effects were included if/where reported.

3.4.3 Data collection and analysis

3.4.3i Retrieving Studies

References retrieved from the electronic searches were collated using *EndNote X2.0.1* software and duplicates removed. References were also stored and given reference numbers in *Microsoft Excel 2007* for sharing with the independent reviewer.

3.4.3ii Selection of studies

In order to ensure consistency of understanding of the review's aims before the formal scan of titles for inclusion, 50 titles were initially randomly selected from the total pool, using a computerised random number system. These were sent to the second reviewer for his identification of potential studies. A preliminary meeting was then held, where compatibility of response was evaluated and any disagreements discussed.

The formal review then proceeded, with two reviewers working independently to identify eligible studies. The reviewers considered each reference independently via a title scan, followed by an abstract scan and full paper screen where necessary, deciding on inclusion according to the pre-defined criteria. Disagreements were resolved in one-one discussion. Any persistent disagreements were referred to a third party and were resolved by discussion and re-referral to the original paper.

A standardised proforma for identifying eligible papers according to the pre-set criteria was employed (*Appendix I*).

3.4.4 Data extraction and management

Data extraction was enabled by tabulation of key aspects of each study, including design, participants, type, dose and duration of intervention, equipment and setting. Data were extracted from included studies using a standardised proforma (*Appendix I*). The lead researcher carried out data extraction and consulted the independent reviewer for clarifying specific queries raised during the process.

3.4.4i Assessment of potential risk of bias

Criteria for assessing risk of bias in the randomised studies were derived from the Cochrane Collaboration tool (Higgins and Green 2008) (*Appendix I*). Each study was individually evaluated and tabulated according to the criteria by the lead author, in consultation with the review team. The same tool was used for the risk of bias assessment for the non-randomised studies. Whilst it was not developed with such studies in mind, the general structure is suggested as useful where studies are heterogeneous and no quantitative synthesis is planned. The use of this tool for the NRS allowed for heterogeneity to be clearly demonstrated. The assessment of risk of biases for all studies informed the interpretation of review findings and recommendations.

3.4.5 Measures of treatment effect

Where calculable, Cohen's effect sizes with 95% confidence intervals were calculated for continuous outcomes in the randomised controlled studies to demonstrate the magnitude of any effects and enhance the interpretation of review findings. Differences in the direction of measures were corrected for i.e multiplication by -1 for those scales where an increase in the measure indicates worsening motor function.

3.4.6 Data synthesis and interpretation

Though effect sizes have been stated where calculable, meta-analysis was not indicated due to heterogeneity across domains including design, participants, methods and outcomes. Combining such clinically diverse studies statistically would be meaningless and possibly misleading, thus it was decided that a narrative synthesis was most appropriate. Qualitative data synthesis was enabled by tabulation, with motor function outcomes classified according to the *International Classification of Functioning* (ICF; World Health Organisation, WHO, 2001). The use of the ICF is widely recognised to provide a conceptual basis and common language for understanding patients' health status. It was therefore anticipated that, by using this format, an interpretation relevant to health providers could be made, with information across the broad spectrum of motor function outcomes.

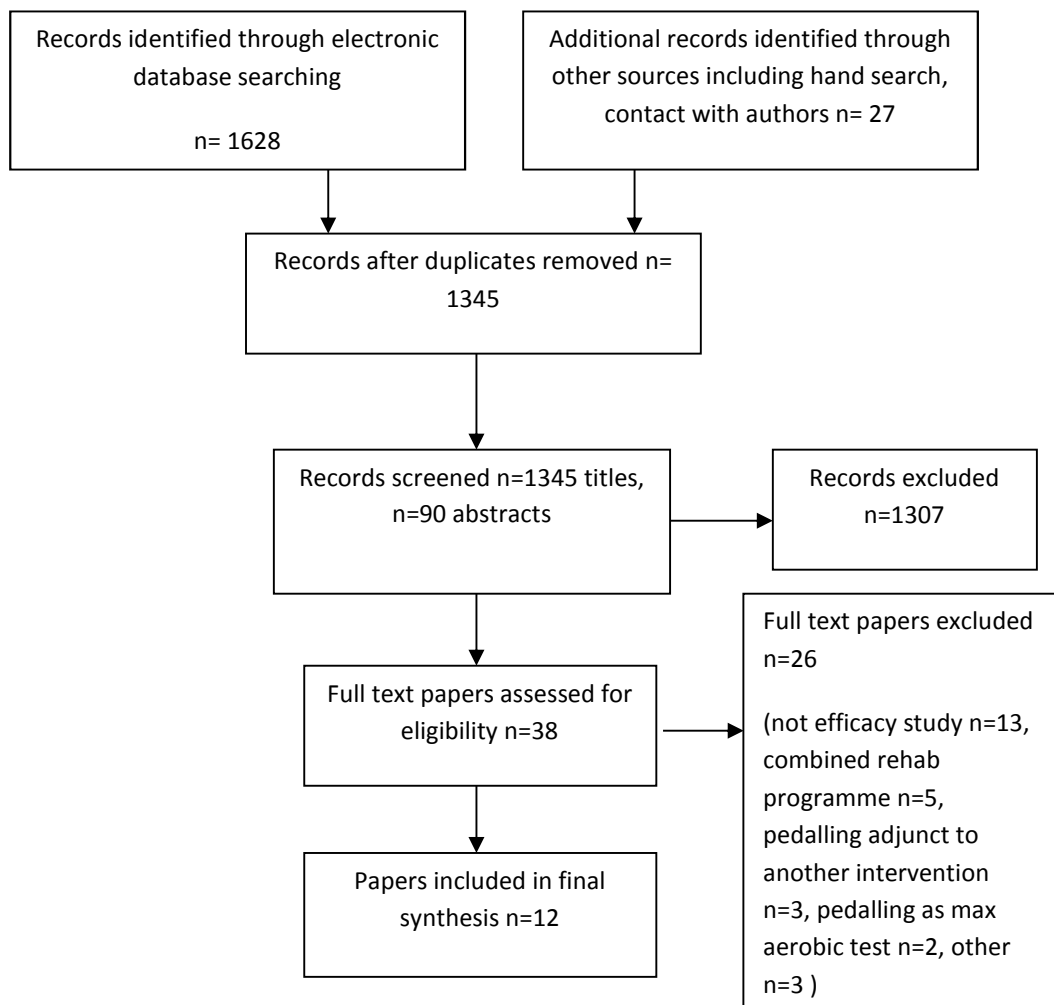
Interpretation was informed by the assessment of potential biases within the included studies.

3.5 Results

3.5.1 Summary of search results

The literature search identified 1628 bibliographic references from the electronic database searches. Contacts with lead authors produced 23 items and 4 were identified via the hand-search. After removal of duplicates, 1345 items progressed to filtering. Via title screening, 90 items were considered potentially relevant for abstract review, at which stage 52 were eliminated and 38 progressed to detailed filtering by full text review. Twelve papers (*Appendix I*) were finally selected for inclusion in this review (figure 1).

Figure 1: Flow diagram of results of search strategy



3.5.2 Included studies:

3.5.2i Design

The included studies demonstrated heterogeneity of design. Five of the 12 were described as randomised controlled, or randomised clinical, trials (Katz-Leurer et al. 2006; Katz-Leurer et al. 2003; Lee et al. 2008; Potempa et al. 1995; Quaney et al. 2009). Tang et al. (2009) used a prospective matched control design. Three studies used a 'before and after' design with a single group of participants (Fujiwara et al. 2003; Perell et al. 2000; Perell et al. 2001). Two of these used the same cohort of participants; the earlier paper reporting data on pedal forces (Perell et al. 2000), the second paper reporting functional outcomes after the pedalling intervention (Perell et al. 2001). Seki et al. (2009) was considered a 'before and after' study for the purposes of this review, as the only extractable data relevant to this review were from the single group of stroke survivors in their report.

Two case reports were presented in the paper by Brown et al. (2005). Holt et al. (2001) reported a single case study.

3.5.2ii Sample Size

Altogether there were 351 participants included in the 12 studies (range 1-92). Of these, data were extractable on 288 (1-90). No study used more than 92 participants, and four used less than ten (table 1).

3.5.2iii Setting

Of those papers reporting settings: six were based on in-patient rehabilitation units (Seki et al. 2009; Tang et al. 2009; Katz-Leurer et al. 2006; Brown et al. 2005; Fujiwara et al. 2003; Katz-Leurer et al. 2003); two were carried out in university exercise laboratories (Lee et al. 2008; Potempa et al. 1995); four papers did not make the setting explicit, but exercise protocols for three of these studies suggested use of out-patient rehabilitation facilities (Perell et al. 2000; Perell et al. 2001; Holt et al. 2001); and one paper suggested use of an exercise laboratory (Quaney et al. 2009).

Table 1: Participant Characteristics

Study	Study design	N	Side stroke lesion (n)		Type of stroke (n)		Time since stroke onset [mean(s.d where given) unless stated]	Age [mean years(s.d) unless stated]
			Left	Right	Ischaemia/ infarct	Haemorrhage		
Brown et al. (2005)	Case series	2	1	1	1, I not stated	-	10 days; 7.5 weeks	77 years, 68 years
Fujiwara et al. (2003)	Before-and-after	17	9	8	5	12	158.8(57.9)days	55.1(10.9)
Holt et al. (2001)	SCS	1	1	0	0	1	18 months	55
Katz-Leurer et al. (2003)	RCT	92	Not stated	Not stated	80	12	Not specifically stated but excluded those admitted to study rehabilitation unit >30 days since acute hospitalisation	63(11)
Katz-Leurer et al. (2006)	RCT	24	14	10	24	0	Not specifically stated but excluded those admitted to study rehabilitation unit >30 days since acute hospitalisation	63(9)
Lee et al. (2008)	RCT	52*	21	27	33	9	57(54) months	63.2(9)
Perell et al. (2000,2001)	Before-and-after	8	6	2	Not stated	Not stated	2 years (median)	64.5 (median)
Potempa et al. (1995)	RCT	42	19	23	Not stated	Not stated	>6 months	Range 21-77 years
Quaney et al. (2009)	RCT	38	Not stated	Not stated	Not stated	Not stated	4.9+/-3.3 years	Control group 58.96(14.7); Ex group 64.10(12.3)
Seki et al. (2009)	Before-and-after	10	5	5	6	4	68.7 days	69 (range 55-81)
Tang et al. (2009)	Matched controls	57†	11	12	17	5 (1 unknown)	17.8 days (range 6-62)	64.7 (range 19-90)

*4 participants discontinued after baseline, data stated in paper only for 48 participants; †complete participant characteristic data only stated for 23 participants originally allocated to the exercise group.
Abbreviations: RCT=randomised controlled trial; SCS= single case study

3.5.2iv Participants (table 1)

- Mean age:

In nine studies, participants' mean age was between 55 and 65 years (Fujiwara et al. 2003; Holt et al. 2001; Katz-Leurer et al. 2003; Katz-Leurer et al. 2006; Lee et al. 2008; Perell et al. 2000; Perell et al. 2001; Tang et al. 2009 and Quaney et al. 2009). One used participants with a mean age of 69 (Seki et al. 2009). In the case reports, participants were 77 and 68 years (Brown et al. 2005). One study gave an age range with no individual figures from which to extrapolate a mean (43 to 72 years, Potempa et al. 1995). Excluding Potempa et al. (1995), mean age across studies was 63 years.

- Time since stroke:

The majority of trials recruited participants who were more than three months since stroke onset (table 1). Katz-Leurer et al. (2003) and Katz-Leurer et al. (2006) allude to recruiting participants early after stroke but times since onset are not stated in the reports.

- Type and site of stroke:

Reporting of the exact site of stroke was sparse, only Brown et al. (2005) detailed the brain area affected, with one participant in the case series having a right parietal lobe stroke and the other a left frontal lobe stroke. Four studies did not give any information on type of stroke (Katz-Leurer et al. 2006; Perell et al. 2000, 2001; Potempa et al. 1995) and one did not report the side of stroke (Katz-Leurer et al. 2003). One study gave no information on side, site or type of stroke lesion (Quaney et al. 2009).

3.5.2v Comparison Groups

Of the five randomised trials, two had control groups undergoing routine therapy only (Katz-Leurer et al. 2003; Katz-Leurer et al. 2006). The control group in Potempa et al. (1995) underwent a passive exercise regime carried out for the same time per

session as the intervention. Lee et al. (2008) used a sham-exercise control to compare to aerobic cycling exercise. Control participants in the study by Quaney et al. (2009) underwent a home-based program of stretching exercise at the same weekly frequency as the pedalling intervention group, with telephone contact by a physical therapist once each week.

3.5.2vi Primary purpose, dose of intervention and type of exercise equipment used (table 2)

The primary purpose of the studies fell into two clear categories: those which aimed to investigate the effects of pedalling exercise on motor function after stroke and those investigating the effects of aerobic programmes, where pedalling exercise was used as the primary tool. These studies met the review criteria as they also included evaluation of motor function outcomes after the pedalling interventions.

There was heterogeneity of dose and duration of pedalling exercise and a variety of cycling equipment was used across the studies. Detailed information about equipment was limited across studies, except for Brown et al. (2005) and Seki et al. (2009) where descriptions were thorough. Despite differences in specific types of equipment, devices that allowed pedalling activity to occur in seated postures, such as leg cycle ergometers and static bicycles, predominated.

3.5.2vii Outcome measures and effect sizes: summary of findings

The 12 included papers evaluated effects using a wide range of outcome measures, time intervals for measurement points and types of analyses. Outcomes are classified and presented according to the *International Classification of Functioning* (WHO 2001) (tables 3 to 7). Due to the heterogeneity already demonstrated across study domains, meta-analysis was not indicated. However, where appropriate data were available, Cohen's effect sizes (defined as the difference in means divided by the pooled within group standard deviation) were calculated to enable presentation of the magnitude of any effects (table 3). An approximate 95% confidence interval for this effect size was calculated based on the method described by Reiser and Guttman (1986).

Table 2: Primary purpose of study, intervention, dose and equipment used

Study	Primary purpose of pedalling exercise (MF: motor function; AE: aerobic exercise)	Dose/duration of pedalling exercise	Type of exercise equipment used
Brown et al. (2005)	MF: Feasibility of limb-loaded cycling as exercise intervention for stroke	10 sets of 20 repetitions in each session. Patient 1- 13 sessions completed; Patient 2- 5 sessions of hybrid programme developed as unable to complete initial programme.	Recumbent seated limb-loaded cycling device
Fujiwara et al. (2003)	MF: Assessment of effects of pedalling exercise on lower limb muscle activity	Single session, pedalling for five minutes	Servo-dynamically controlled ergometer with trunk support
Holt et al. (2001)	AE: Effects of an aerobic programme on participant's functional mobility	8 weeks of 2 and 3 sessions per week on alternate weeks, 20 sessions total. 12 minutes pedalling incrementally increased by 2 minutes on alternate sessions to maximum of 30 minutes	Static bicycle
Katz-Leurer et al. (2003)	AE: Effects of early aerobic training on independence and activity at six months	Part 1: 10 sessions over 2 weeks, 2 minutes per session increasing within tolerance to 20 minutes per session Part 2: 9 sessions over 3 weeks, 30 minutes per session	Leg cycle ergometer
Katz-Leurer et al. (2006)	MF: Effects of early cycling training on balance	5 sessions per week for 3 weeks, individualised programme	Leg cycle ergometer
Lee et al. (2008)	AE: Effects of aerobic cycling programme on walking ability	30 sessions over 10 to 12 weeks, each session 30 minutes of cycling with resistance adjusted to achieve a target heart rate. After each session, underwent "sham" leg resistance training.	Semi-recumbent motorized isokinetic cycle ergometer
Perell et al. (2000, 2001)	MF: evaluation of pedal reaction forces following bicycle training	3 sessions per week for 4 weeks, each session consisted of 12 one-minute cycling trials with one-minute rests in between.	Recumbent bicycle with adapted pedals to allow for force measurements
Potempa et al. (1995)	AE: evaluation of response of stroke patients to aerobic training	3 sessions per week for 10 weeks, 30 minutes per session. For first 4 weeks, training load gradually increased, for final 6 weeks, highest training load maintained for each participant	Adapted cycle ergometer
Quaney et al. (2009)	AE: Effect of aerobic cycling programme on executive function and mobility	3 sessions per week for 8 weeks, progressing aerobic intensity from week 2	Stationary bicycle
Seki et al. (2009)	MF: Assessment of effects of pedalling exercise on lower limb muscle activity	Single session, pedalling for 8 wheel revolutions	Cycling wheelchair
Tang et al. (2009)	AE: feasibility of adding aerobic cycle ergometry to standard rehabilitation early after stroke	3 sessions per week, up to 30 minutes a session, individualise programme for each participant	Semi-recumbent cycle ergometer

3.5.2viii Risks of bias in included studies

Randomised and case-controlled studies were assessed for potential biases according to Cochrane methodology, considering six key features: sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias (table 8). Non-randomised studies (NRS) were included in the assessment according to the same criteria. Higgins and Green (2008) suggest the same domains are still relevant for NRS, particularly when quantitative synthesis is not proposed, in order to illustrate heterogeneity and inform the interpretation of review findings (table 8).

3.5.2ix Adverse events

None of the included studies reported any adverse events

3.5.3 Excluded studies

Of the 38 studies, 26 were excluded at the full text review stage (table 9). The main reasons for exclusion were:

- Pedalling used as a paradigm for analysing and evaluating movement after stroke, not designed to enhance motor recovery.
- Pedalling used as an adjunct to another intervention e.g. Functional Electrical Stimulation, FES.
- Pedalling used as part of a combined therapy programme where it was impossible to extract data from the pedalling intervention alone.
- Pedalling used solely as a maximal exercise stress test.

Table 3: Summary of Findings, Randomised Controlled Trials

Author & Date	N	Outcome Measurement Time Points	Outcome Measures	Means (s.d)		Outcomes categorised according to ICF			Cohen's Effect Size	95% CI's
				Control	Intervention	BS/F	A	P		
Katz-Leurer et al. 2003	92	Immediately post-intervention	FIM score	101.4(16.0)	105.8(12.5)		X		0.31	-0.10, 0.72
			Walking distance (m)	94.8(107.6)	122.8(143.0)		X		0.22	-0.19, 0.63
			Walking speed (m/s)	0.45(0.1)	0.51(0.1)		X		0.60	0.18, 1.02
			Stair climbing (no. stairs)	18.1(14.4)	25.4(14.1)		X		0.51	0.10, 0.93
Katz-Leurer et al. 2006	24	Immediately post-intervention	PASS total	23.0(4.3)	28.7(3.1)		X		1.50	0.61, 2.43
			PASS static	7.2(1.8)	9.3(1.5)		X		1.25	0.38, 2.15
			PASS dynamic	15.8(2.8)	19.4(1.7)		X		1.54	0.64, 2.47
			FMA score	19.3(7.1)	26.3(5.8)		X		1.07	0.22, 1.94
			FIM total	73.1(22.8)	77.5(21.8)		X	X	0.20	-0.61, 1.00
			FIM motor	9.2(3.0)	13.6(2.4)		X		1.60	0.69, 2.55
	23	6 weeks post-intervention	PASS total	26.4(3.8)	31.1(2.2)		X		1.50	0.60, 2.42
			PASS static	9.0(1.8)	10.7(1.7)		X		0.97	0.11, 1.83
			PASS dynamic	17.4(2.3)	20.3(0.7)		X		1.78	0.74, 2.67
			FMA score	22.1(6.8)	29.1(5.9)		X		1.09	0.23, 1.96
			FIM total	79.2(21.4)	87.8(23.5)		X	X	0.39	0.44, 1.20
			FIM motor	12.1(3.2)	16.1(2.0)		X		1.47	0.59, 2.41

Abbreviations: ICF=International Classification Functioning, BS/F=body structure/function, A=activity, P=participation; CES=Cohen's Effect Size; FIM=functional independence measure, PASS=postural assessment scale for stroke; FMA= Fugl Meyer assessment

Table 3 (contd.): Summary of Findings, Randomised Controlled Trials

Author & Date	N	Outcome Measurement Time Points	Outcome Measures	Means (s.d)		Outcomes categorised according to ICF			Cohen's Effect Size	95% CI's
				Control	Intervention	BS/F	A	P		
Lee et al. 2008	26	Within 1 week final intervention	6-minute walk (m)	278.1(162.1)	261.5(162.7)		X		-0.10	-0.87, 0.70
			Habitual gait velocity (m/s)	0.78(0.43)	0.74(0.41)		X		0.09	-0.68, 0.87
			Fast gait velocity (m/s)	0.93(0.54)	0.94(0.55)		X		-0.02	-0.79, 0.75
			Stair climb power (W)	116.5(67.8)	121.3(80.9)		X		0.06	-0.70, 0.83
			Max strength affected leg (N)	714.1(225.9)	768.0(352.7)	X			0.18	-0.57, 0.94
			Peak power affected leg (W)	269.8(140.2)	229.1(140.2)	X			-0.27	-1.07, 0.49
			Endurance affected leg (mean no. reps)	5.1(3.2)	5.7(4.0)	X			0.16	-0.60, 0.93
Potempa et al. 1995	42	Immediately post-intervention	FMI score	183 (7.9)	173 (10.4)		X		-1.11	-1.75, -0.42
Quaney et al. 2009	38	Immediately post-intervention	FMA score	81.42(36.80)	77.84(34.85)		X		-0.10	-0.73, 0.54
			Berg Balance score	39.05(14.27)	41.68(9.62)		X		0.22	-0.42, 0.85
			Get Up and Go fast speed (s)	29.11(45.26)	15.26(14.82)		X		0.46	-0.23, 1.06
		8 weeks post-intervention	FMA score	80.52(35.72)	76.39(33.93)		X		-0.19	-0.75, 0.51
			Berg Balance score	38.79(14.11)	42.06(9.87)		X		0.27	-0.37, 0.91
			Get Up and Go fast speed (s)	25.74(35.84)	16.78(18.32)		X		0.33	-0.33, 0.95

Abbreviations: ICF=International Classification Functioning, BS/F=body structure/function, A=activity, P=participation; CES=Cohen's Effect Size; FIM=functional independence measure, PASS=postural assessment scale for stroke; FMA= Fugl Meyer assessment

Table 4: Summary of Findings, Matched Control Study

Author & Date	N	Outcome Measurement Time Points	Outcome Measures	Means (S.E)		Outcomes according to ICF		
				Control	Intervention	BS/F	A	P
Tang et al. 2009	36 (18 matched pairs; Gait measures: 4 in each group unable to undertake as non-ambulatory and further 4 not assessed at discharge due to equipment failure)	Immediately prior to discharge, exact times not stated	Preferred pace gait speed (m/s)	0.82(0.08)	0.84(0.08)		X	
			Preferred pace gait symmetry (ratio, n=20 symmetrical at study entry)	1.15(0.02)	1.28(0.07)	X		
			Preferred pace gait symmetry(ratio, n=11 asymmetrical at study entry)	1.17(0.02)	1.29(0.04)	X		
			Fast paced gait speed (m/s)	1.19(0.1)	1.06(0.11)			X
			Fast pace gait symmetry (ratio, n=20 symmetrical at study entry)	1.11(0.01)	1.28(0.07)	X		
			Fast pace gait symmetry (ratio, n=11 asymmetrical at study entry)	1.14(0)	1.28(0.05)	X		
			Six-minute walking test distance (m)	288.4(38.9)	334.2(33.1)			X
		SIS QOL subscale	67.1 (4.6)	72.4(3.8)				X
Findings:			No significant between group differences (at p<0.05). Trends to improvement in gait speed and symmetry across both control and intervention groups.					

Table 5: Summary of Findings, Before and After Studies

Author & Date	N	Outcome Measurement Time Points	Outcome Measures	Findings	Outcomes according to ICF		
					BS	A	P
Fujiwara et al. 2003	17	Immediately after intervention, 30 minutes after intervention	Muscle activity during knee extension (integrated EMG quadriceps femoris, medial hamstrings, tibialis anterior, medial gastrocnemius)	Increased activity in quadriceps and tibialis anterior immediately after pedalling and continuing for 30 minutes. Medial hamstrings and medial gastrocnemius activities reduced after pedalling and reduction continued for 30 minutes	X		
Perell et al. 2000	4	2 days after intervention completed	Pedal reaction forces (N)	Tangential pedal reaction forces directed more posteriorly after pedalling training authors suggest this has implications for ankle control during pedalling	X		
Perell et al. 2001	8	2 days after intervention completed	Muscle strength (N): knee flexors and extensors	Eccentric muscle strength in knee extensors increased bilaterally; concentric muscle strength in knee extensors increased in involved limb (p<0.05)	X		
			50-foot walking speed (m/s)	Non-significant trend to improved pace of walking following intervention		X	
Seki et al. 2009	10	Immediately after intervention	Muscle activity during pedalling (EMG gluteus maximus, rectus femoris, hamstrings, tibialis anterior, soleus)	Significant increases in rectus femoris, tibialis anterior and soleus muscle activity of affected leg during pedalling in comparison with a baseline isometric contraction	X		

Table 6: Summary of Findings, Single Case Study

Author and Date	N	Outcome Measures	Measurement Time Points with Outcomes			Outcomes according to ICF		
			Baseline 1	Baseline 2 (within 19 days of baseline 1)	Post-training (20 sessions)	BS	A	P
Holt et al. 2001	1	10m timed walk (sec)	36.50	35.00	24.00		X	
		Speed gait during 10m(ms)	0.27	0.29	0.42		X	
		Steps during 10m walk	37.00	40.00	32.00		X	
		6-min walking distance	99.00	107.00	145.00		X	
		Speed gait during 6min walk (ms)	0.27	0.30	0.40		X	
		Motricity Leg Score	65.00	65.00	76.00	X		
		Ashworth Knee Score	2.00	2.00	1.00	X		
		Ashworth Ankle Score	4.00	4.00	2.00	X		
<p>Findings: Statistical analysis not carried out but progression demonstrated in walking speed, distance and muscle strength according to the Motricity index with no adverse effects on spasticity in the lower limb</p>								

Table 7: Summary of Findings, Case Series

Author and Date	N	Measurement Time Points	Outcome Measures	Outcomes according to ICF		
				BS	A	P
Brown et al. 2005	2	Varies across 2 participants as pedalling regimes varied according to ability	Dynamic Load Index (load x reps)	X		
		Three times during 10-13 pedalling sessions	Functional Independence Measure		X	
		Three times during 10-13 pedalling sessions	Ambulatory Statuses (description)		X	
<p>Findings: Statistical analysis not carried out. For each participant, measures used to demonstrate progression in ability. Progression in FIM score, walking status and Dynamic Load Index demonstrated for both over the intervention period.</p>						

Table 8: Potential Risk of Biases across Studies (*= non-randomised studies)

Study	Sequence Generation		Blinding			Incomplete Outcome data	Selective result reporting	Other potential biases
	Allocation concealment?	Adequate sequence generation?	Blinding participants?	Blinding providers?	Blinding Assessors?	Where relevant, incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Katz-Leurer et al. 2003	UNCLEAR	YES	UNABLE	UNABLE	UNCLEAR	YES	NO	YES
Katz-Leurer et al. 2006	UNCLEAR	YES	UNABLE	UNABLE	UNCLEAR	UNCLEAR	YES	YES
Lee et al. 2008	YES	YES	UNCLEAR	UNABLE	YES-primary NO-secondary	YES	YES	UNCLEAR
Potempa et al. 1995	UNCLEAR	UNCLEAR	UNABLE	UNABLE	UNCLEAR	YES	YES	UNCLEAR
Quaney et al. 2009	UNCLEAR	UNCLEAR	UNABLE	UNABLE	YES	YES	YES	YES
Tang et al. 2009*	UNCLEAR	UNCLEAR	UNABLE	UNABLE	NO	UNCLEAR	YES	UNCLEAR
Brown et al. 2005*	NO	NO	UNABLE	UNABLE	NO	N/A	YES	NO
Fujiwara et al. 2003*	NO	NO	UNABLE	UNABLE	NO	N/A	YES	NO
Holt et al. 2001*	N/A	N/A	UNABLE	UNABLE	UNCLEAR	N/A	YES	YES
Seki et al. 2009*	NO	NO	UNABLE	UNABLE	NO	N/A	UNCLEAR	NO
Perell et al. 2000*	NO	NO	UNABLE	UNABLE	UNCLEAR	N/A	YES	YES
Perell et al. 2001*	NO	NO	UNABLE	UNABLE	UNCLEAR	N/A	YES	YES

YES: LOW risk of bias; NO: HIGH risk of bias; UNCLEAR: unclear; UNABLE: not possible e.g participant blinding in trial where pedalling was the key intervention

Table 9: List of Excluded Studies

Author & Year	Reason for exclusion at full text review stage
Bowden et al. 2006	Not an efficacy study
Brown & DeBacher 1987	Not an efficacy study
Brown & Kautz 1998	Not an efficacy study
Brown & Kautz 1999	Not an efficacy study
Brown et al. 1997	Not an efficacy study
Chen et al. 2005	Not an efficacy study
Dawes et al. 2000	Not an efficacy study
Ferrante et al. 2008	Pedalling as an adjunct to another intervention (FES)
Janssen et al. 2008	Pedalling as an adjunct to another intervention (ES)
Katz-Leurer & Shochina 2005	Not an efficacy study, examined pedalling patterns as predictor of activity at six months: other
Kautz & Brown 1998	Not an efficacy study
Kautz et al. 2006	Unilateral pedalling: other
Kautz et al. 2005	Pedalling as part of a combined exercise programme
Kautz & Patten 2005	Not an efficacy study
Kelly et al. 2003	Not an efficacy study
Lennon et al. 2008	Pedalling as maximum aerobic test and upper limb pedalling involved
Makino et al. 2005	Physiological costs of pedalling activity & not a true efficacy study: other
Marklund & Klassbo 2006	Pedalling as part of combined programme
Perell et al. 1998	Not an efficacy study
Rosecrance & Guiliani 1991	Not an efficacy study
Rogers et al. 2004	Not an efficacy study
Sibley et al. 2008a	Pedalling as maximum aerobic test
Sibley et al. 2008b	Pedalling as an adjunct within a combined programme
Sullivan et al. 2006	Pedalling as part of a combined programme
Sullivan et al. 2007	Pedalling as part of a combined programme
Szecszi et al. 2008	Pedalling as an adjunct to another intervention (FES)

3.6 Interpretation

The effects of cycling exercise on motor function after stroke had not previously been comprehensively evaluated. This review was the first to adopt a systematic methodology to evaluate the current evidence on the effects of lower limb reciprocal pedalling exercise on motor function after stroke. Twelve studies were included and a narrative synthesis carried out.

Meta-analysis was not indicated due to heterogeneity across domains. However, some consistent themes emerged from the synthesis. These have contributed to the assessment of the robustness of the current evidence and hence the concluding recommendations. A discussion of key themes is presented first in this section, followed by an appraisal of specific studies according to design, potential risks of bias and outcomes within the ICF framework. Conclusions are drawn according to clinical implications and indications for future research, as per Cochrane recommendations (Higgins and Green, 2008). Further interpretation of this work is made in Chapter 7.0.

3.6.1 Key themes

The mean age of 63 (range 55-77) was non-representative of the UK stroke population, where 75% of first strokes occur in those aged 65 and over (British Heart Foundation, Coronary Heart Disease Statistics 2010). Generalisability to the majority of stroke survivors is therefore uncertain. This is important as older stroke survivors may present different rehabilitation challenges to younger survivors. For example, the likelihood of multiple pathologies alongside the stroke may be higher, leading to extraneous reasons why participation in rehabilitation activities might be limited. Further research into pedalling exercise in an older participant group is indicated.

As inclusion criteria for the present systematic review did not restrict by study design, sample size varied greatly, from n=1 to n=92 (median: n=24). Small, exploratory studies may be important in establishing feasibility and developing

protocols for larger studies, but caution must be used in interpreting results in relation to clinical practice as generalisability to the wider stroke population has not been tested.

Only three studies stated that they had recruited participants earlier than three months since stroke onset. The majority had sustained stroke more than three months before participation. It is possible that such patients are easier to recruit to exercise trials, as they tend to be more medically stable and with less fluctuation in their abilities. However, current evidence suggests that early therapeutic intervention might optimise potential for recovery. Clinical studies support the concept that early rehabilitation is important for improving outcomes (Cumming et al. 2011; Feys et al. 2004). Indeed, Cramer (2008) describes a 'golden period' for initiating restorative therapies, when the brain is galvanised to begin repair, starting in the first days after onset and continuing for several weeks. This review has identified that current research into pedalling as a potential therapeutic intervention has not utilised this important window and thus results cannot be generalised to early stroke survivors. Opportunities therefore exist for further exploration of the effects of pedalling exercise in stroke survivors early after onset.

Baseline characteristics of participants were predominantly well reported. However, studies demonstrated little information about the exact site of stroke lesion, though general information e.g. side of brain affected, type of stroke, was commonly reported. Stroke lesion location and size are probably important predictors of functional outcome (e.g. Pan et al. 2006; Chen et al. 2000) though there is little evidence about how these baseline characteristics might be linked to the ability to take part in specific rehabilitation interventions. Clearer reporting of potential prognostic factors in future is recommended in future trials to allow better informed decisions on which patients might be best suited to particular pedalling therapies.

Heterogeneity of type of equipment used was not unexpected due to the generally exploratory nature of the included studies. Whilst the inclusion criteria ensured that all studies involved reciprocal lower limb pedalling, there were 10 different

devices in operation across the 12 studies. Detailed descriptions of the equipment were largely inadequate, limiting replicability for future research and interpretation of potential use in clinical settings. However, it was clear that recumbent or semi-recumbent postures with standard leg cycle ergometers were favoured for the pedalling devices. Ease of use of such equipment is clear; patients may be seated or reclining in a chair or wheelchair and carry out cyclical lower limb activity. Seated pedalling negates the need for the substantial concentration and physical effort required to stay upright. However, this concentration and effort are components inherent in learning to walk early after a stroke; and upright pedalling postures are more likely to replicate walking-like activity necessary to ensure that a pedalling task offers opportunities for functional movement. Hence, an upright pedalling device might more appropriately replicate walking-like activity.

Dose of pedalling was also variable, from only 8 wheel revolutions in a single session (Seki et al. 2009) to 30 minutes of pedalling in each of 30 sessions over 12 weeks (Lee et al. 2008). Although the number of repetitions of an activity needed to facilitate brain reorganisation has not been established in human studies, animal model studies suggest that 300-400 repetitions in a 30 minute session might be needed. Pedalling exercise has the potential to provide high numbers of repetitions of lower limb flexion and extension but this review has revealed that further work is needed to explore optimal doses.

3.6.2 Study design, methodological quality and outcomes

Study design was varied as predicted in the scoping exercise for the review. Whilst the review included outcomes from five randomised controlled trials, only one of these was specifically designed to evaluate the effects of the intervention on motor function (MF) (Katz-Leurer et al. 2006). Whilst the potential risks of bias in this study were predominantly low, there was a lack of clarity of reporting on key elements, including blinding of assessors and concealment of allocation. Effect sizes were large for measures of balance (Postural Assessment Scale for Stroke) and the motor section of the Functional Independence Measure, immediately and six weeks after the intervention. However, the large effect sizes should be interpreted with

caution as sample size for this pilot study was small, with ten participants in the intervention arm and fourteen in the control. Definitive, generalisable conclusions cannot thus be drawn about effects on balance and motor ability before appropriately powered studies of the intervention are undertaken.

The other RCTs used pedalling exercise to evaluate the effects of aerobic exercise (AE) but included some motor function outcomes as secondary measures. Bias across these studies was again predominantly low, but a lack of clarity of reporting on allocation concealment was evident for Katz-Leurer et al. (2003), Potempa et al.(1995) and Quaney et al.(2009), and, additionally, on sequence generation for Potempa et al.(1995) and Quaney et al. (2009). Moderate positive, significant effect sizes for both walking speed and stair climbing were demonstrated by Katz-Leurer et al. (2003). Whilst Lee et al. (2008) had the least potential risk of bias of any of the RCTs, along with a moderate sample size, only small positive but non-significant effect sizes were demonstrated for outcomes including maximum strength and endurance in the affected leg. Potempa et al. (1995) demonstrated no effect on the Fugl-Meyer Index following an aerobic pedalling programme. Quaney et al. (2009) demonstrated some positive effects on balance, though effect sizes were small and non-significant. This study also demonstrated moderate, though non-significant effects on “get up and go” then ambulation, and though clarity of reporting was not ideal, the risk of bias for this study was low. These studies suggest that pedalling exercise might improve walking speed and stair climbing, with potential improvements in balance, muscle strength, and ability to transfer and ambulate in survivors greater than six months post-stroke, but none were sufficiently powered or sufficiently free of potential bias for clinical recommendations to be made.

Potential risk of bias in the non-randomised studies was high, largely related to design, which ranged from “before and after” studies to case reports. Reporting according to the design adopted was generally clear. Again, sample sizes for these studies were low, from n=17 to n=1. They, do, however, give some indications of positive effects of pedalling exercise on: muscle activity during pedalling (Seki et al. 2009), reciprocal muscle activity immediately after pedalling (Fujiwara et al. 2003), knee extensor strength (Perell et al. 2001), and walking speed (Holt et al. 2001).

Due to the high risk of potential biases and small sample sizes, results should be interpreted with caution and clinical recommendations cannot be made in the light of these studies.

As might be expected from a rehabilitation intervention, outcome measures used were evenly spread across the body structure and function and activity levels of the ICF. Measures of muscle strength, balance and ambulation were most common. Two of the 'before and after' studies explored muscle activity via electromyography, providing physiological insights into activity during and after pedalling exercise.

Only Tang et al. (2009) included a participation level measure (Health-related Quality of Life) but demonstrated no significant effects. However, measurement was taken immediately after the exercise programme was completed, on discharge from hospital. It would be difficult to establish changes in quality of life directly related to pedalling exercise at this time point.

3.6.3 Limitations of the review

The main limitation of the review was, due to resource constraints, a lack of completely independent data extraction by a second reviewer. Extraction was carried out by the lead reviewer, leading to potential bias. However, the independent reviewer was consulted on any queries and monthly supervision of the review was undertaken by an experienced third party.

It is also possible that there was some influence by a publication bias as the search was limited to studies written only in English. However, studies included were carried out across a variety of international centres.

3.7 Conclusions

This systematic review is the first to synthesise currently available evidence on the effects of reciprocal pedalling exercise on motor function after stroke and consider the robustness of research findings.

Heterogeneity was found across multiple domains in the included studies, including design, participants, equipment, methods and outcomes.

Despite some beneficial, though not definitive, effects on balance, functional independence, muscle strength, sit-to-stand ability and gait speed, the review has found that is not possible to make clinical recommendations that support or refute the use of reciprocal pedalling exercise after stroke.

However, the findings provide proof-of-concept for pedalling interventions and provide a foundation for subsequent research, suggesting a need for further standardised, controlled clinical trials of clearly described pedalling interventions, across a broad range of stroke survivors and with subsequent transparent reporting of findings.

Chapter 4.0: Methods and Equipment Common to the Experimental Studies (Chapters 5.0 and 6.0)

4.1 Introduction

The purpose of this chapter is to present and justify the equipment and procedures that were common to both experimental studies, chapters 5.0 and 6.0. Methods and procedures that were unique to each of the studies are presented in the relevant sections of chapters 5.0 and 6.0.

4.2 Upright Pedalling: A potential tool for measurement and rehabilitation after stroke

This section will justify the choice of pedalling equipment used in the experimental studies. It will then present the structure and instrumentation of the equipment.

4.2.1 Upright Pedalling: background

It is reasonable to propose that the ideal method for improving walking is the practice of specific walking tasks. However, it has been established that repetitive walking practice early after stroke presents a number of challenges and is not always possible (section 1.2.3). There is therefore an opportunity to develop and test a tool to be used to practise walking like movements in the important window early after stroke and beyond.

Pedalling has been proposed as one possible intervention that might provide repetitive, skilled activity similar to normal walking (sections 1.3.2, 1.3.3). There are indications of similarities to gait in terms of both kinematics of lower limb activity and neural control. Despite this, existing work has not generally explored pedalling in walking like postures but has adopted recumbent seated pedalling as the intervention tool (e.g. Fujiwara et al. 2003; Katz-Leurer et al. 2003, 2006; Perell et al. 2001; in Chapter 3.0).

The complexities of producing movement in a variety of postures after stroke and the challenge of adapting already impaired motor function to altered task mechanics, have been noted (Brown et al. 1997). This study used a standing pedalling device on a tilting mechanism, enabling muscle activity to be measured via surface EMG recorded in various postures. The participants' trunks were strapped to an extended backboard throughout the measures, enabling only leg movement and no trunk movement to occur. Whilst this device enabled safe explorations of muscle activity in an upright posture, it should be noted that the sensorimotor experience here would be very different to normal walking. In this study, muscle activity patterns were characterised in terms of EMG activity present in four position phases of the wheel. Results from Brown et al. (1997) suggested that muscle activity can alter according to verticality- participants with motor hemiplegia showed an overall increase in muscle activity to achieve the cyclical movement in the most vertical posture and these participants were able to increase net positive work output as a response to the altered posture when upright. This increased excitability might be used therapeutically- the authors postulate that to minimise muscle tone, less vertical positions be used and to increase force generation, a more vertical posture is indicated. Hence, to increase muscle activity in stroke survivors, an upright posture might be considered beneficial.

Biomechanical explorations of cycling posture have been carried out, with emphasis on establishing the most efficient postures for normal cycling. In particular, Savelberg et al. (2003) carried out a small (n=8) study of young cyclists (mean age 22.3 years), in which the effect of three different trunk angles on muscle recruitment was examined. It should be noted here that the trunk angle differences were small- upright, 18.6 degrees backwards flexion and 22.3 degrees forward flexion relative to upright, with the leg angle kept constant according to the seat tube. Muscle activity in eight leg muscles was recorded via EMG during a pedalling task. Trunk angle was found to alter the kinematics of leg movement and muscle activity, not just at the hip but throughout the lower limb. This further knowledge that such adjustments in posture can facilitate changes in kinematics and muscle activity might reinforce the need for pedalling to be in upright positions where task-

specific re-education of walking is the goal. Additionally, Mazzocchio et al. (2008) suggested, in their review of the possibilities of cycling as a rehabilitation tool, that the range of movement in the hip is similar in upright pedalling and walking, being lower, and hence less normal, in recumbent pedalling. This adds further to the proposal that pedalling might best be provided in upright postures for the rehabilitation of walking.

Furthermore, physiological evidence exists that might further support rehabilitation in upright postures. It is known that regional cerebral blood flow, measured by Positron Emission Tomography (PET scanning), is different when standing compared to supine and sitting at a 75 degree incline; whilst arterial blood pressure, partial pressures of carbon dioxide (PaCO_2) and arterial pH does not change between postures (Ouchiet al. 1999, 2001). Brain activity is also different depending on what standing posture is adopted and whether eyes are open or closed in the absence of changes in systemic blood pressure or pulse rate (Ouchi et al. 1999). As changes in blood flow are used as an indicator of changes in brain activity, the inference here is that brain activity differs between quiet supine lying, sitting and standing postures (Ouchi et al. 2001). It could be further inferred that using an upright posture analogous to walking for rehabilitation activity is more likely to facilitate functional brain changes than more recumbent postures. Hence, re-educating the substrates for walking i.e. repetitive flexion and extension of the lower limb, in an upright posture, is indicated.

There is evidence, therefore, to suggest that an upright posture improves cerebral blood flow and, whilst this might be largely as a result of cerebral autoregulation, improved flow in comparison to more recumbent postures might facilitate beneficial brain changes. Potentially advantageous muscle activity changes have been demonstrated in stroke survivors in a modified vertical pedalling task and their capacity to modify and alter activity according to postural challenge has been observed. Upright postures provide opportunities for greater task-specificity in relation to retraining walking and allow stroke survivors to experience movement in more normal, functional postures than activities in lying and sitting. An opportunity therefore exists for investigations of an upright rehabilitation tool for those who

would otherwise not be able to achieve this posture, to help to more appropriately replicate walking-like activity. The use of a modified upright pedalling device in the early stages after stroke has never been explored. Hence, an upright pedalling device with adjustable trunk and lower limb support (U-PeD) was used for investigation in the experimental studies in this thesis. The details of the device are presented in the following section.

4.2.2 The Upright Pedalling Device (U-PeD): structure

The exercise bike used for the experimental studies was adapted so that postural support for the trunk was provided if needed (figure 2). The support was adjustable and enabled the back rest to be positioned to maintain the upright posture required.

Seat height was also adjustable to provide an upright pedalling posture. Upright here refers to the participant's trunk being aligned with the seat tube and the angle between the seat tube and horizontal approximately 90 degrees, as Chen et al. (2001).



Figure 2: The Upright Pedalling Device (U-PeD)

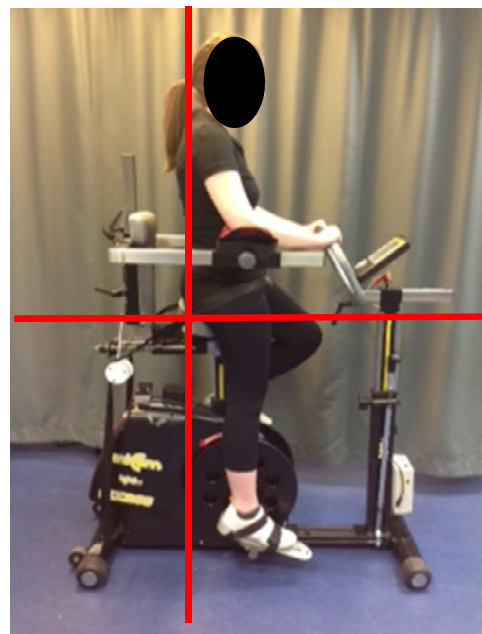


Figure 3: U-PeD, demonstrating Upright Pedalling posture

4.2.3 Upright Pedalling equipment: instrumentation

The bike wheel was demarcated into 45 degree segments using reflective tape, creating eight “wheel position bins” for analysis (figure 4). A “bin” simply refers to a clearly defined segment of the wheel. In this case, each segment was 45 degrees, enabling each turn of the wheel to be divided into eight equally spaced segments. Hence, muscle activity during UP could be accurately mapped to each 45 degree segment. Previous studies have generally used four position bins (e.g. Fujiwara et al. 2003; Brown and Kautz, 1998). During preparatory design work in the research laboratory, it was decided to extend this to eight position bins: muscle activation timing i.e. onset and offset of EMG activity was a measure chosen to assess characteristics of lower limb muscle activity during pedalling, and using an increased number of position bins enabled more accurate mapping of activity to crank angle. Hence, a more detailed assessment of timing and movement strategies used by people early after stroke could be made in this developmental work.

As the participant pedalled, an LED sensor placed at a fixed point on the bike frame was triggered as each of the eight markers passed (figures 4 & 5)

This trigger created a drop in voltage, causing a spike in the software. The spikes were recorded synchronously, via a digital channel on the EMG unit (4.3), with the EMG data. This system allowed for muscle activity to be related to the position of the pedal during the 360 degree turn. The crank angle was recorded between the right crank and the seat tube, where 0 degrees represents top dead centre (TDC) and 180 degrees represents bottom dead centre (BDC) of the wheel (figure 5).

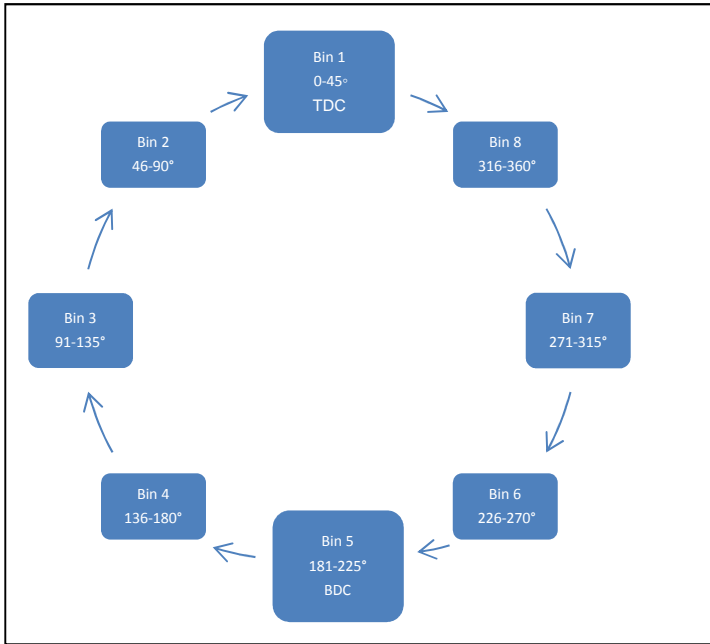


Figure 4: Schematic representation of wheel position bins;

TDC= top dead centre, BDC= bottom dead centre

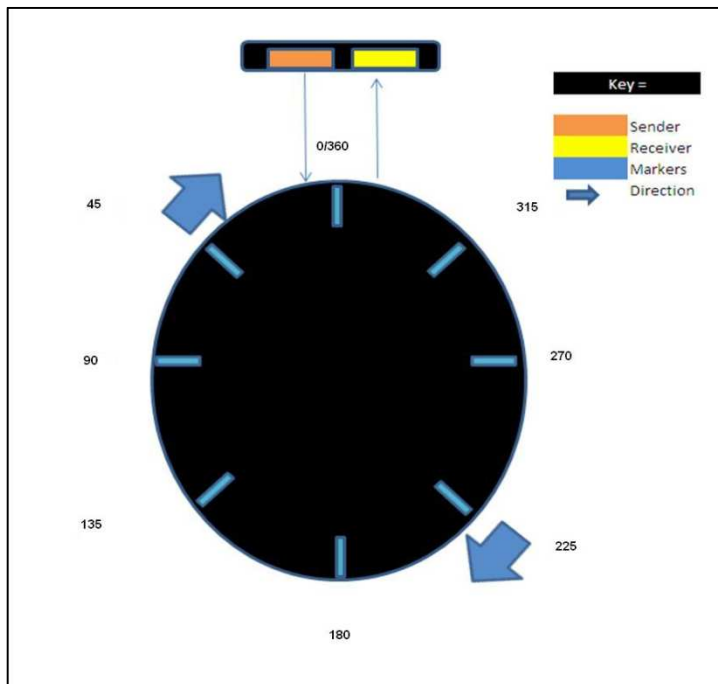


Figure 5: Schematic representation of crank angle sensor system

4.3 EMG collection and recording of muscle activity

Muscle activity data was collected using the *DatalinkEMG* system (Biometrics, UK).

Activity was recorded in quadriceps and hamstring muscles for each leg. When seated on the bike, and with feet supported on blocks with the knee in approximately 15 degrees of flexion, participants had a small (37mm x 18mm) pre-amplifier applied to the front and back of their thigh on both sides, following skin preparation with a recommended gel (*NuPrep*; Weaver & Co, Colorado) to minimise signal interference (*Appendix III*). According to manufacturer's advice, these sensors contained all necessary gain and filter circuits- high pass and low pass filters were included to minimise interference with a frequency range of interest of 15Hz to 450Hz, sufficient to represent the full energy spectrum of the muscles under investigation, as described by Cram et al. (1998). Further comment about interference to the EMG signal is made in section 4.4.

Electrode position is known to be a vital factor in achieving accurate EMG information (Merletti et al. 2001). Hence, it was important to follow published guidelines for electrode placement and, for the studies reported herein, a single researcher placed the electrodes for each participant and for every session. It was not possible, with the equipment available, to record from numerous muscles, so it was decided to use general quadriceps femoris and hamstrings anatomical groups with corresponding electrode placement (Cram et al. 1998). For quadriceps, this electrode placement concurred with that in the most current guidelines for sensor placement (SENIAM, 2013); for hamstrings there was a very slight variation (*Appendix III*).

A detailed description of the process for skin preparation, specific electrode placement and securing of electrodes is given in *Appendix III*, alongside the current European recommendations for surface electromyography (SENIAM, 2013).

Whilst the participants were positioned comfortably on the bike, the leads from the preamplifiers were connected to 4 analogue channels of the *Datalink* subject unit,

which was connected to the base unit. Information from the base unit was collected on a lap top computer running the *Datalink* software system. Continuous EMG data were thus recorded during pedalling.

Resting EMG activity was recorded as a voltage at 1,000Hz whilst the participant was sitting on the bike with their foot resting firmly on a box, with the leg still and supported with the knee in 5-15 degrees of flexion, for 30 seconds. This was undertaken for each leg in turn. EMG data (voltage) was collected continuously during pedalling for a minimum of 30 seconds.

4.4 Processing & analysis of the EMG signal for measuring lower limb muscle activity during pedalling

4.4.1 Introduction

The realisation that a muscle's function can be investigated via the electrical activity it generates has informed movement science since Galvani's pivotal work with frogs' legs in the 18th century (Basmajian and DeLuca, 1985). From this emergence of the science of neurophysiology to today, systems to detect, process, analyse and interpret muscles' electrical signal have been developed for both clinical and research applications.

Electromyography (EMG) has been used for the assessment of muscle performance for over half a century (Basmajian and DeLuca, 1985). Equipment to both collect data and refine signal quality has developed to enable simple application of surface EMG systems in laboratory and clinical settings (Hug and Dorel, 2009). However, the possibilities offered by EMG to characterise muscle activity must be tempered by an awareness of its limitations (Merletti et al. 2001). Over 20 years ago, Ryan and Gregor (1992) expressed concern that interpretation of muscle activity recorded via EMG during pedalling might be influenced by electrode placement and experimental design. Furthermore, the debate about approaches to signal processing and ensuing analysis is on-going.

It is widely accepted that accurate processing is essential to enable rigorous analysis and useful interpretation of findings (Cram et al. 1998). However, this section presents a critique of literature that exposes inconsistencies of approach across studies and, in some cases, a lack of transparently described methods. This section is not intended to present a formal, systematic review of the literature on this area. Rather, it is intended as a critique of relevant methodological aspects of the current literature, which then leads to the justification of a rigorous and repeatable method for processing and analysing EMG data since applied in the experimental studies presented in this thesis (Chapters 5.0 and 6.0).

4.4.2 Existing evidence

Throughout the literature searches for both the background and systematic reviews, and in developing research questions for this thesis, a number of studies examining cycling activity using EMG methods were critiqued. In developing methods for the original studies presented here and during the early stages of working with the data collected for the first experimental study (Chapter 5.0), varied information on key aspects of processing and analysis of the EMG signal was evident.

Table 10 summarises the key points of the critique of the existing evidence. A variety of papers from 1986 to 2012 were included, the consistent feature for selection being that all used EMG methodologies to characterise movement during pedalling activity and all used muscle activation timing parameters as an outcome. A synthesis of the observations made from the critique in table 10 follows.

4.4.2i Use of filters

The energy a muscle generates has a frequency spectrum and the prevalence of muscle energy at any given frequency can be plotted- as a power spectral density graph. Typically, a bandwidth of 20Hz to 300Hz represents nearly all the energy in the spectrum of a muscle (Cram et al. 1998). Filtering of the EMG signal is carried out in order to minimise the impact of external interference and noise, such as that experienced from a “power hum”. Such line interference, when examined as a power spectrum, can be typically seen as regular, pulsing elevations at 50 or 100Hz

intervals. Filtering is also useful to minimise the effects of factors such as movement artefacts or undue pressure on electrodes.

Modern EMG systems contain built in filters. For example, the system used in the current studies (*DataLink, Biometrics UK*) includes a bandwidth filter of 15Hz to 450Hz which should be sufficient to capture muscle energy in an appropriate range of frequencies (Cram et al. 1998). However, table 10 demonstrates that a variety of filters have been used in previous work, most commonly the expected band width filter, though with a number of differing ranges (e.g. 30Hz to 300Hz, Ryan and Gregor, 1992; 20Hz to 4000Hz, Brown et al. 1996, Brown et al. 1997).

Table 10: EMG analysis of pedalling activity: differences in characteristics of signal processing and analysis described across studies using muscle activation timing parameters. Studies presented chronologically from oldest to most recent

Paper (Author & Date)	Type of study and sample size	Information about use of filters	Information about smoothing & integration process	Information about establishing resting baseline signal	Information about establishing burst onset & offset	Other relevant information
Jorge & Hull (1986)	Observational study EMG eight lower limb muscles during pedalling N=6 experienced cyclists	None given	Rectified and integrated over 75ms window	Resting data not recorded but iEMG normalised according to each subject's maximum and averaged over the 6 subjects to allow comparative scaling of data between subjects	Simple visual inspection	Only 4 data collection channels available on equipment used so data collected from 4 muscles, then electrodes moved onto next four.
Ryan & Gregor (1992)	Observational study EMG ten lower limb muscles during pedalling N=18 experienced cyclists	Band width filter 30Hz to 300Hz. Further filtering with 30Hz moving average filter for records demonstrating movement artefact.	Rectified across 10 to 15 pedalling cycles	Resting data not recorded but data normalised to peak activity for each muscle and each subject, then averaged for each muscle across subjects	Average muscle activity patterns analysed for burst duration and timing. SD from each average used to examine consistency between pedalling revolutions	Not explicit how burst duration and timing were actually established, ?visual inspection
Brown et al. (1996)	Observational study EMG four lower limb muscles N= 11 healthy volunteers	Band width filter 20Hz to 4000Hz	15s section of data rectified and integrated	Exact procedure not described but clearly used resting data to establish bursts (see next column)	Considered "on" using threshold of at least 3SD above resting for more than 30ms but less than 1s.	Not explicit how process of rectification and integration was carried out. Some visual inspection to identify spurious bursts/noise

Table 10 (contd.)

Paper (Author & Date)	Type of study and sample size	Information about use of filters	Information about smoothing & integration process	Information about establishing resting baseline signal	Information about establishing burst onset & offset	Other relevant information
Brown et al. (1997)	Observational study EMG four lower limb muscles at different body orientations N= 12 healthy elderly subjects; N=17 stroke survivors	Band width filter 20Hz to 4000Hz	Rectified and integrated in each of 4 wheel phases	Not used, see next column	Burst onset and offset not used: activity expressed as iEMG in each of 4 wheel phases as percentage of total iEMG	Authors recognise burst onset and offset difficult to establish in subjects with hemiplegia. Not explicit how actual process of rectification and integration was carried out.
Neptune et al. (1997)	Observational study EMG eight lower limb muscles at different pedalling rates	High pass filter with cut-off at 12hz	RMS with 40ms moving average window	Subject supine, data collected for 10s and averaged	Considered "on" using threshold of 3SD above resting for more than 50ms. Results then examined cycle-by-cycle and the threshold increased if necessary to identify bursts	iEMG outside of the burst duration was not included in the analysis of muscle activity No explicit detail about the threshold increases given.
Raasch et al. (1997)	Observational study EMG five lower limb muscles N=9 healthy adult males	Low pass filter 25Hz	Rectified	Baseline established from "relaxed portion of the trial"	Considered "on" using threshold of at least 3SD above resting for more than 55ms. Manual checking and alteration of durations of up to 20ms carried out to best capture bursts	Not clear whether "relaxed portion of the trial" refers to the participant resting prior to the pedalling or an inactive portion of the EMG data

Table 10 (contd.)

Paper (Author & Date)	Type of study and sample size	Information about use of filters	Information about smoothing & integration process	Information about establishing resting baseline signal	Information about establishing burst onset & offset	Other relevant information
Kautz & Brown (1998)	Observational study EMG seven lower limb muscles N=15 stroke survivors; N=12 age-matched controls	Band width 20Hz to 4000Hz	Rectified and integrated.	Not used	Burst onset and offset not used: activity expressed as iEMG in each of 4 wheel phases as percentage of total iEMG	Detail of integration process e.g. time window not made explicit
Baum & Li (2003)	Observational study EMG seven lower limb muscles N=16 healthy volunteers	See next column. Environment free of noise with low motion artefact so band pass filter not deemed necessary	Rectified and smoothed using a low pass, fourth order, zero lag filter at 7Hz to create a linear envelope	Resting signal not used	Threshold value of 10% maximum value across all conditions chosen for onset. Where 10% considered inappropriate, 20% was used.	Explicit justification of lack of use of filter but less clear on how decisions were made regarding appropriateness of 10% threshold
Fujiwara et al. (2003)	Pre & Post test study EMG four lower limb muscles N=17	Wide band pass filter 30Hz to 2000Hz	Rectified and integrated.	Not used	Burst onset and offset not used: activity expressed as iEMG in each of 4 wheel phases as percentage of total iEMG	Detail of integration process e.g. time window not made explicit

Table 10 (contd.)

Paper (Author & Date)	Type of study and sample size	Information about use of filters	Information about smoothing & integration process	Information about establishing resting baseline signal	Information about establishing burst onset & offset	Other relevant information
Hakansson & Hull (2005)	Observational study EMG ten lower limb muscles pedalling in upright and recumbent positions N=15 cyclists	Zero phase digital filter with 12Hz cut-off	Rectified. Data “demeaned” and normalised to the highest value for each muscle; these data then analysed for activity and burst onset/offset	Resting data collected at end of experimental procedure in supine position. Mean of rectified resting data used to establish bursts.	Considered “on” using threshold of at least 3SD above resting for more than 50ms duration	Not clear why resting data was recorded after the activity session. Process of “demeaning” and normalising data not explicit.
Dorel et al. (2008)	Intra-session repeatability study 10 lower limb muscles during pedalling N=11 triathletes	Anti-aliasing filter with dynamically computed cut-off at half mean frequency of pulses delivered every 2 degrees of the crank	RMS with time average period of 25ms to produce linear envelope of activity. Values averaged per degree of rotation.	Resting data not used (see two ensuing columns)	Onset where signal was above threshold of 20% difference between peak and baseline EMG, offset when it was below this 20% threshold	Actual value of filter cut-off not clear. Not explicit exactly how baseline was judged when examining 20% of peak activity
Sidhu et al. (2012)	2 studies reported, observation of: 1) TMS effects on EMG in VL during pedalling; N=19 healthy volunteers; 2) how responses to TMS were modulated across the “locomotor cycle” (pedalling task); N=16 healthy volunteers	Band pass filter 30Hz to 1000Hz	Rectified and averaged over 25 pedalling cycles. Average trace with cortical stimulation overlaid with average trace without TMS	Not used (see previous column)	Rectified data set examined for burst onset and offset during period of no cortical stimulation	Not explicit exactly how bursts were defined in the part of the study examining activity during the pedalling cycle (study 2)

Abbreviations: RMS= root mean squared; ms= millisecond; iEMG= integrated EMG data; SD= standard deviation; VL= Vastuslateralis; Qds= Quadriceps muscles; TMS= transcranial magnetic stimulation

Other types of filter have been used, including high pass filters that remove energy generated at lower frequencies (Neptune et al. 1997) and low pass filters that remove muscle energy generated at higher frequencies (Raasch et al. 1997). Significantly, information justifying the use or not of filters, whether built in or additional filtering, was lacking. Only one of the papers, Baum and Li (2003) described explicitly how decisions were made about filtering- they established that the data collection site was free from high frequency noise and any movement artefact was less than 2Hz, and hence deemed the use of any band pass filtering unnecessary.

The concern here is that inappropriate filtering might culminate in actual muscle activity being removed from the signal before the next processing and analysis stage; and, conversely, energy that is unrelated to that generated by the muscle being recorded as muscle activity. Hence, decisions about the use of filters, particularly additional filtering to that built into the relevant EMG recording system, should be made clear.

4.4.2ii Smoothing and integrating the EMG signal

Whilst the raw EMG signal, representing the composite of a number of motor units firing in a random, staccotic manner, can provide a simple picture of the activity generated, it is widely accepted that the raw signal must be smoothed and integrated for it to be accurately quantified and for comparisons to be made across subjects.

All studies outlined in table 10 stated that rectification had been carried out. This is the process of artificially placing all data points above zero to ensure that they are positive values and hence enable further integration. Smoothing ensures that signal variability is reduced, visually taking out the jagged “bumps”. In the studies reviewed, details of exact smoothing methods were scant but the most commonly described method was a “moving average” over a set time window (Jorge & Hull, 1986; Neptune et al. 1997; Dorel et al. 2008; Sidhu et al. 2012). This is a frequently used, accepted processing method that simply averages the rectified signal over a

given period of time, “rolling” through the data set according to a pre-determined time window (Cram et al. 1998; Basmajian & DeLuca, 1985).

Clarity of description of integration method is important in reporting EMG data outcomes- changes in, for example, the time window used, can result in differences in the smoothness of the pattern. Hence, if different methods are used across different studies, useful quantitative comparisons of muscle activity patterns cannot be made.

4.4.2iii Establishing a resting baseline signal and quantifying activity bursts

Even following rectification and integration of the EMG signal, random activity and a less than smooth curve can make it challenging to decide the exact time point when a muscle is “on” beyond baseline levels. For example, figure 6 illustrates a screen capture of around two seconds from a rectified and integrated EMG recorded during pedalling activity- examining the integrated signal might lead here to an interpretation of the muscle being “off” at any of wheel bins two through to seven. However, making transparent and replicable decisions here is essential when quantifying the signal to determine “ons and offs” according to time and crank angle.

Previous work (table 10) has used a variety of methods, with some papers relying on visual inspection to determine bursts (e.g. Jorge and Hull, 1986; Brown et al. 1996). Brown et al. (1997) emphasise the challenge in making such decisions in subjects with impaired muscle function due to hemiplegia and, instead of defining definite bursts according to crank angle, chose to average activity in each of four wheel phases as a percentage of activity over the full cycle. This method was repeated by Fujiwara et al. (2003).

Dorel et al. (2008) established bursts by measuring peak to trough activity and considering the muscle on when activity was at 20% between trough and peak. However, their subjects were tri-athletes, likely to have repeatable regular muscle activity during the pedalling cycle; hence the trough to peak method might be more

reliably used than in subjects with impaired motor control and altered movement performance.

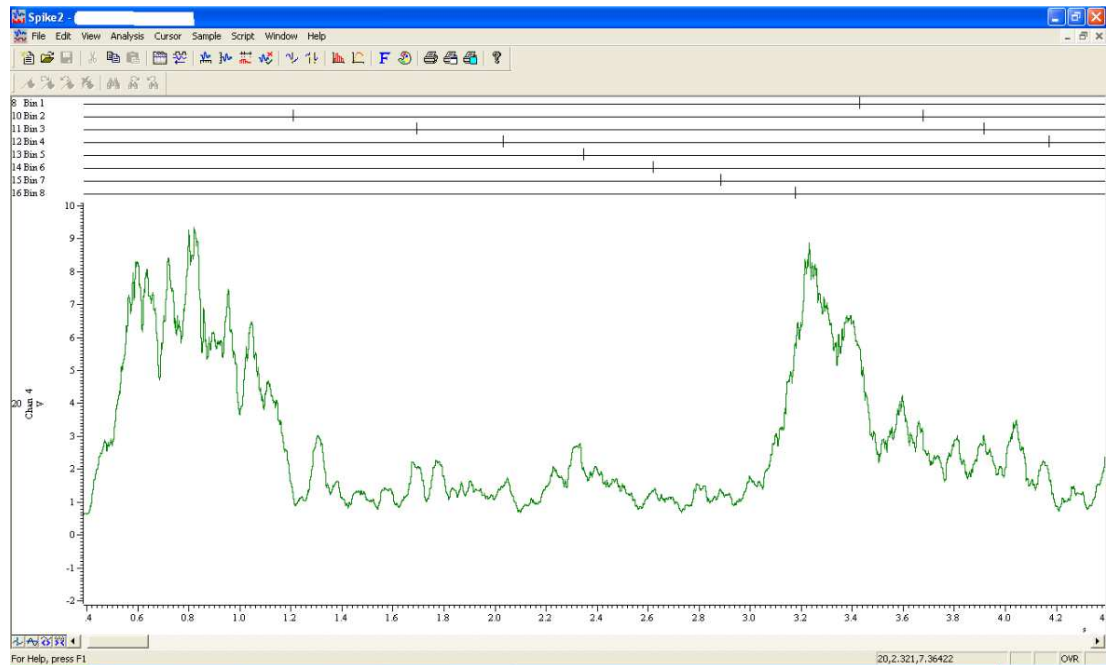


Figure 6: Screen capture illustrating challenges in deciding absolute time points for onset & offset of EMG activity above resting baseline. On simple visual inspection of this integrated EMG trace, the muscle might be considered off during any of wheel bins two to seven; such subjective judgement increases opportunities for misinterpretation of muscle activation timing during pedalling.

Table 10 illustrates that the most commonly used method for establishing bursts was to collect EMG data for a short period with the subject at rest and consider the muscle “on” if it was three standard deviations (SD) or more above this mean resting level for a pre-determined period of time (Brown et al. 1996; Neptune et al. 1997; Raasch et al. 1997; Hakansson & Hull, 2005). Two critical points emerge here: firstly, the period of time above the threshold required for the muscle to be considered “on” was seemingly decided without justification (Brown et al. 1996, 30ms; Neptune et al. 1997, 50ms; Raasch et al. 1997b, 55ms; Hakansson & Hull, 2005, 50ms). Raasch et al. (1997) went on to further alter burst durations by up to 20ms to best capture activity, though standardisation of this technique was not described.

Secondly, it was frequently unclear exactly how resting data was established, with Neptune et al. (1997) collecting with the subject supine and Raasch et al. (1997) describing a relaxed portion of the trial but without clarifying further detail. Hakansson & Hull (2005) established resting signal at the end of their experimental procedures with the subject supine; though, after pedalling activity in an experimental procedure, it might be questionable that this truly represented the muscle at rest. Indeed, the position alone used for collecting resting activity might impact on the amount of activity that is actually considered “resting.”

Therefore, the current literature does not clearly delineate a set procedure for the processing and analysis of the EMG signal that could be used in the studies in this thesis. Hence, it was necessary to develop well-defined, replicable procedures appropriate to the participants and task under investigation.

4.4.3 Developing methodologies for the current studies

It is clear that many different methods of processing and analysis have been used in the current literature exploring pedalling exercise using EMG. It was considered essential that, as the work presented in this thesis is at a developmental level, clearly defined methods that could be used in these and future studies, were developed. Hence, concurrent to the progress of each of the experimental studies, methods were developed for the processing and analysis of the EMG signal.

4.4.3i Use of filters: existing equipment and justification of additional filtering

In both settings used for data collection in the studies here presented- a hospital therapy room and a university laboratory- external interference to the signal was detected on a number of occasions. The interference was unpredictable and had no consistent pattern of occurrence, happening at random times of day and with various participants. It was clear that additional filtering was indicated to minimise the effects of this signal noise.

Furthermore, collecting EMG data from stroke survivors during pedalling activity is inevitably challenging (Brown et al. 1997), as motor control is impaired, leading to, for example, variations in muscle tone and altered patterns of activity. This might

include specific lower limb impairment and impairments in trunk control and balance, all of which might impact on activity. Hence, where the signal appeared “noisy” it was important to differentiate between altered activity and external noise from, for example, a power hum. This differentiation might then assist in making decisions about the use of additional filtering.

To ensure that decisions about additional filtering were made explicit for each individual data set, an algorithm was designed (Figure 7). Each data set was processed according to the algorithm, and where indicated, power spectral analyses carried out and additional filtering applied, using a band stop filter to specifically reduce external noise, parameters according to Cram et al. (1998). Sections 5.11.5 & 6.12 include reports of to which data sets filters were applied.

Figures 8 and 9 illustrate two different examples of the result of carrying out the power spectral analysis indicated in Figure 7. Figure 8 is a screen capture of the result of a spectral analysis on a data set clearly affected by external noise and hence additional filtering was indicated. Here, it can be seen that regular pulses of line noise at 100Hz are occurring. Such a regular, repeating pattern at this frequency could not have been caused by the random, staccotic firing of accumulating motor units and is due to an external source. Figure 9 is an example where there was no external signal interference and no additional filtering was required; the majority of the muscle activity is generated at lower frequencies and tails off within higher frequencies, with no additional regular bursts.

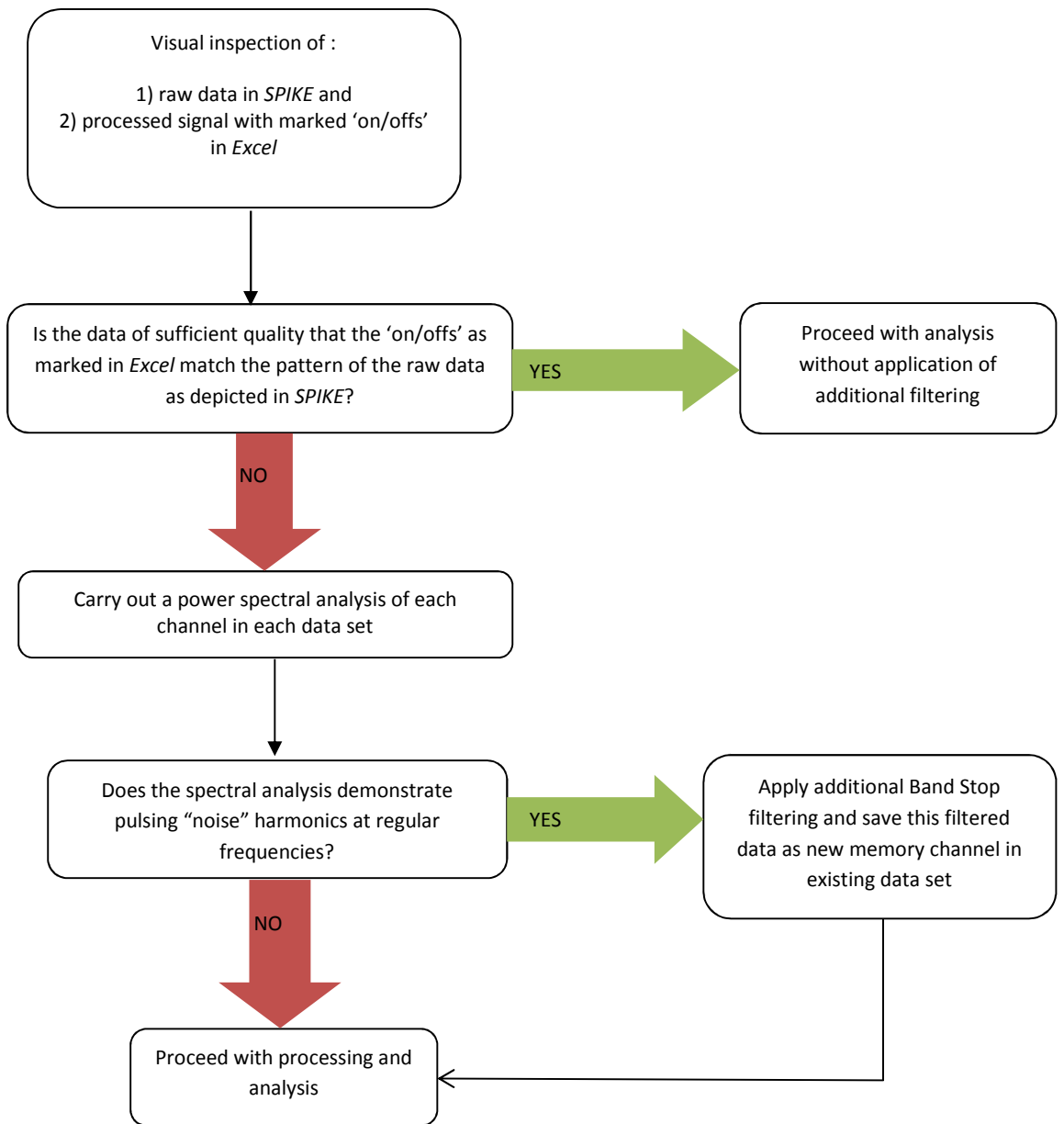


Figure 7: Algorithm used to inform decisions about the application of filters during EMG data processing for the experimental studies

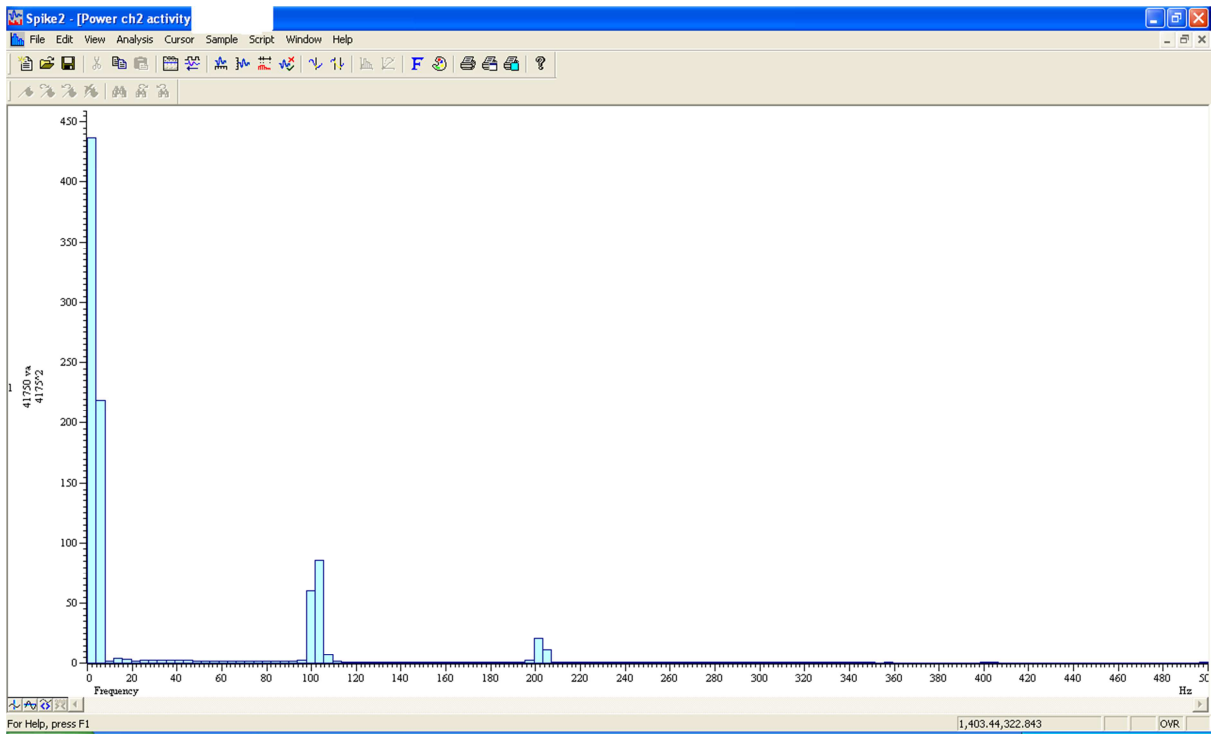


Figure 8: Screen capture of spectral analysis of data set where regular signal noise is demonstrated and additional filtering was indicated, according to the algorithm figure 7

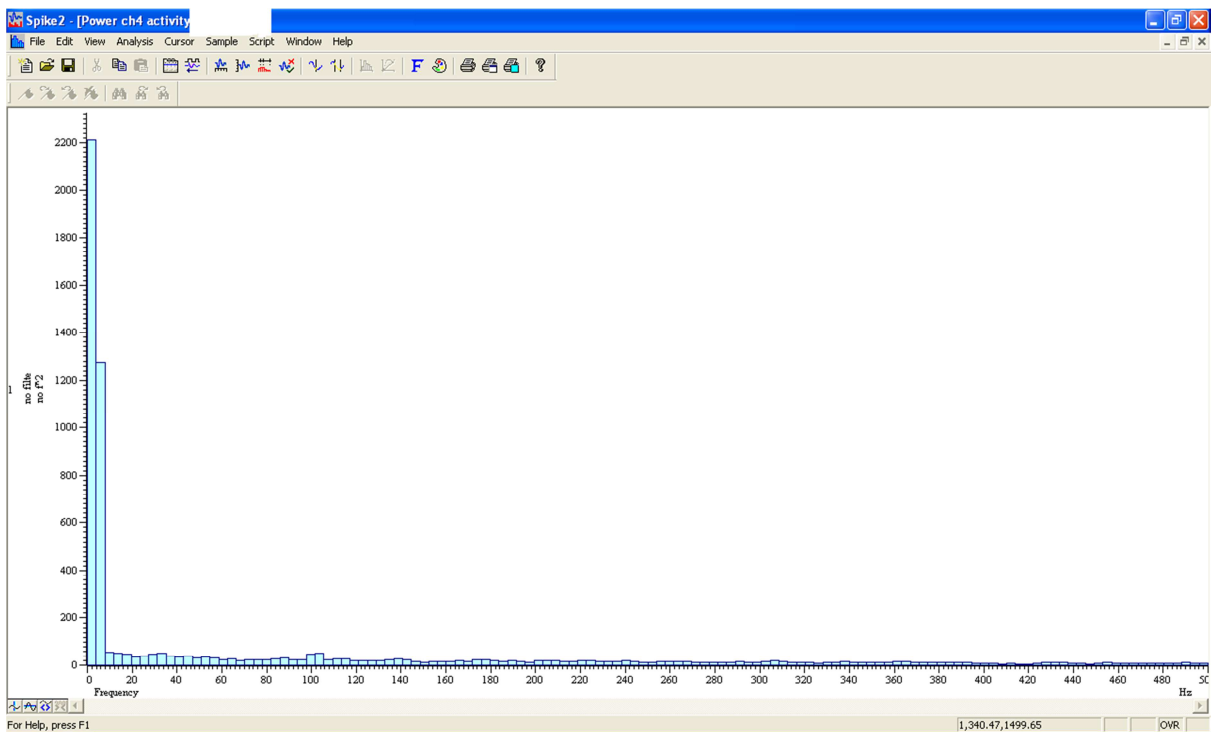


Figure 9: Screen capture of spectral analysis of data set where regular signal noise is not demonstrated and additional filtering was not indicated, according to the algorithm figure 7.

4.4.3ii Smoothing and Integration techniques

All data were initially processed using custom-written scripts in *Microsoft Excel 2007*. Raw signal was rectified, placing all negative points recorded above zero. To reduce signal variability and present an accurate mean trend of signal development, mathematical smoothing of the signal was carried out, with a moving average of 50ms, creating “linear envelopes” across each data set. These values thus represent the area under the curve for the selected epoch of 50ms. This method has been adopted in previous studies (table 10) and is an accepted method of smoothing (Hug and Dorel, 2009; Cram et al. 1998).

Furthermore, data were imported to and visualised in the *SPIKE 2 5.13* (Cambridge Instruments, Cambridge UK) package. This programme allows for very clear visual inspection of traces generated by the EMG signal and the addition of new channels alongside the original traces; this enabled the triggers defining wheel bins to be illustrated and mapped to the appropriate point of the signal.

4.4.3iii Identification of resting activity and activity bursts during pedalling

Following detailed examination of the literature in table 10, it was decided that the onset and offset of muscle activity would be determined using the commonly adopted method of establishing a threshold of three standard deviations (3SD) above a participant’s mean resting activity (Brown et al. 1996; Neptune et al. 1997; Raasch et al. 1997; Hakansson and Hull, 2005). Baseline (threshold) EMG values were then calculated from the integrated signal as the mean \pm 3 SD during the 30 seconds resting data collection period described in section 4.3. Where activity was above this threshold value, the muscle was considered “on” and where below this threshold value, the muscle was considered “off”.

However, guidance on how resting activity was established was less clear so a justified and repeatable method was needed for the current studies.

- **Determining resting activity**

The resting state of lower limb muscle following stroke is likely to be different to the resting state of a muscle in an individual without impairment, due to alterations in muscle tone, compensatory activity and challenges to balance. These differences might apply to both sides of the body. Hence, the “pre-peddalling” state of the muscle might mean it is not truly at rest, so defining activity recruited due to the pedalling activity itself presented a challenge. It was considered that measuring resting activity in a simple sitting or lying posture might not give an accurate picture of the muscle “pre-peddalling.” Hence, it was decided that quiet, background activity would be recorded from each muscle in upright sitting on the bike with the feet supported on blocks, knee resting at approximately 15 degrees of flexion. Any additional activity above this baseline should then reflect activity required to pedal the crank in the same upright posture.

- **Establishing muscle activity bursts**

The use of eight 45 degree wheel bins, defined with the use of an LED sensor mounted on the bike frame as described in section 4.2.3 enabled the bursts of activity to be mapped according to both the time of onset/offset and the crank angle. Within each bin, it was then possible to establish whether the muscle was “on” or “off”. Initially, an arbitrary figure of 20ms above the threshold was used to establish bursts.

During initial processing according to this method, two further challenges arose which required additional clarification:

Firstly, for some data sets, particularly where stroke survivors pedalled slowly, activity was above the threshold for only part of the position bin and not all, or there were periods of both “ons” and “offs” within a position bin. Hence, it was considered that simply making a binary decision of “on or off” did not accurately represent the complexities of the activity being performed. This was a particular concern as this was original work with no other example data sets of stroke survivors taking part in UP. Therefore, a more detailed picture of activity within

position bins, and hence across each turn of the wheel within each pedalling session, was indicated.

It was decided that the onset of activity would be described by the exact amount of time for which the activity was above the threshold, expressed as a percentage of total time for the relevant position bin. For example, if the muscle was continually above the threshold throughout a whole position bin, this would be 100% on, and if not above the threshold at all within a position bin, it would be 0% on, with any variations of percentage activity in between.

This method removes the need to arbitrarily select a timeframe above which the muscle is considered active. It quantifies the activity occurring during pedalling and enables objective comparisons between pedalling sessions and individuals. Examples of the phase diagrams created from the data, are given in section 5.11.6.

Secondly, there were occasional data sets where the mean resting signal was particularly low and the muscle presented as continually “on” according to the calculations of activity above threshold; though when the integrated trace was visualised, definite bursts were distinguishable. The type of presentation might have underpinned decisions in previous work to alter thresholds after visualising the trace (e.g. Raasch et al. 1997; Brown et al. 1996). Altering the threshold following simple visual inspection was not considered rigorous enough for the current studies, as rigour and reproducibility of the developed methods were considered essential. Accordingly, a second algorithm (figure 10) was developed and applied across all data sets. This describes a formal pathway by which the threshold was raised by further SD's if specific conditions were met. Reports of to which data sets the algorithm was applied are in 5.11.6 & 6.13.

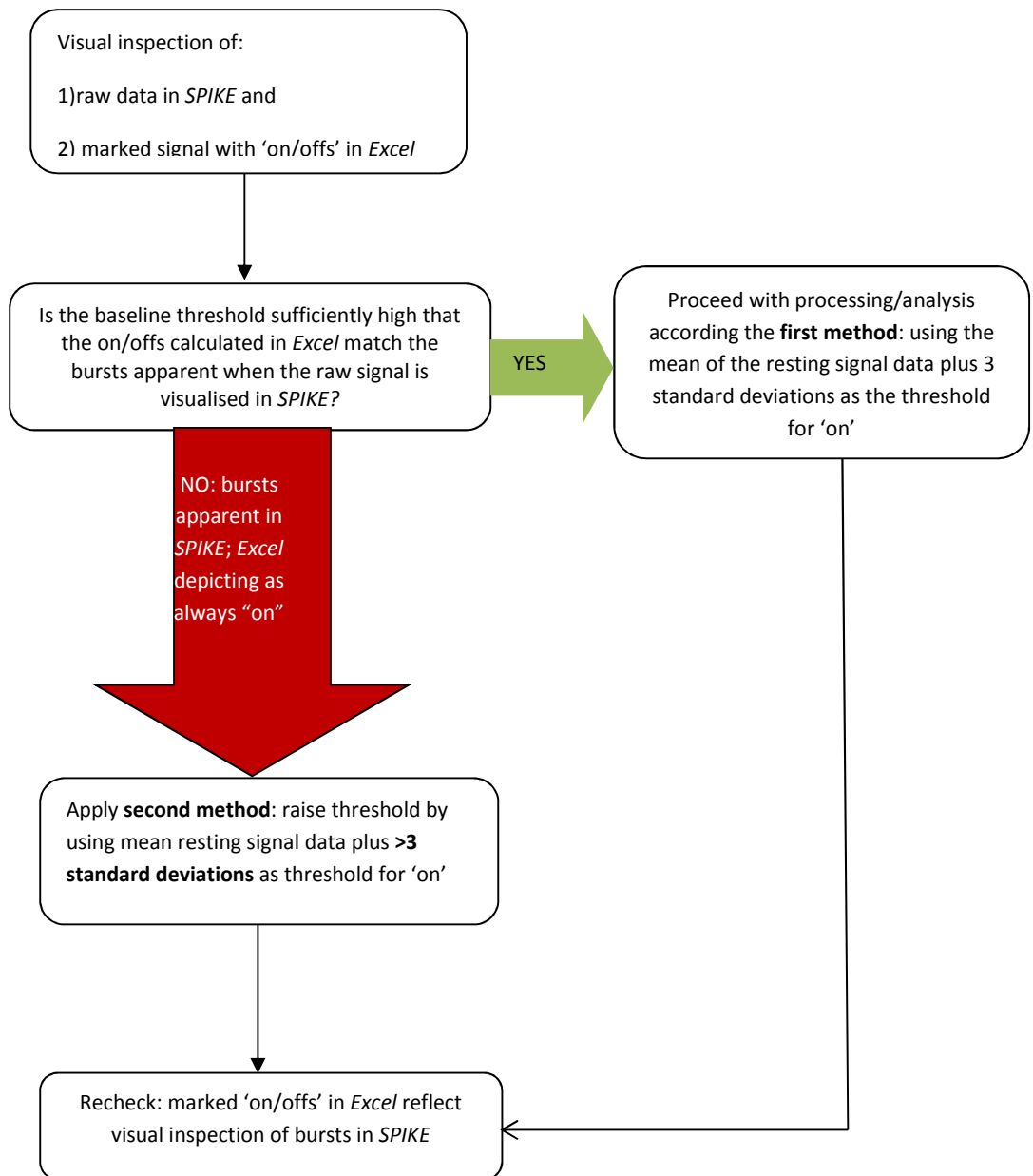


Figure 10: Algorithm used to inform decisions about altering the pre-determined resting threshold during EMG data processing, studies two and three

4.4.4 Conclusions: EMG data processing

It is clear that whilst there are general rules, there is not one simply described method for processing the EMG signal recorded during pedalling.

This section has identified that there are some methodological inconsistencies in current published work, suggesting that no one existing method could be adopted for the studies in the thesis. Hence there was a need to establish a transparent, replicable methodology for use in the studies here presented and for future work investigating pedalling activity for stroke survivors. The processing methods adopted for the clinical studies in this thesis have therefore been described. Decisions about filtering, smoothing, establishing resting signal and determining activity bursts were all made following a comprehensive review of existing evidence.

4.5 Measures derived from EMG

This section presents the measures derived from the EMG data, processed as in section 4.4, common to both experimental studies.

In all cases where the measures described were used, data from the central 10 wheel turns of the completed data set were used to provide a representative sample of steady pedalling activity for each individual and each pedalling trial.

4.5.1 Onset and offset of activity of antagonistic muscle groups during pedalling

EMG recordings during pedalling activity have the potential to provide information about amount of muscle activity and muscle activation timing (Hug and Dorel, 2009). Incorporating a mechanical measure of crank position that can be used synchronously as EMG data is collected further allows for these patterns of muscle activity to be related to the position of the wheel. This “mapping” of lower limb muscle activity during a constrained kinematic task provides opportunity for assessment of impairment in people with abnormalities of function.

However, in stroke survivors who demonstrate variable muscle activity, particularly early after the onset of central nervous system damage, comparisons of actual amounts of activity might be less useful than patterns of activation timing according to the wheel position. Measuring amount of activity does not necessarily establish *type* of activity and the activity generated after stroke might be influenced by, for example, compensatory activity, raised tone or simply by being in the appropriate position to attempt the pedalling activity. Moreover, temporal components of muscle activity during pedalling, derived from EMG, have recently been demonstrated to be more reliable for measurement of adaptations in muscle activity over time than magnitude components (Jobson et al. 2012). Hence, for these studies, a decision was taken to determine the timing of activity via its onset and offset during pedalling as an important impairment level outcome.

4.5.2 Reciprocal activation of antagonistic muscle groups (muscle activity) during pedalling

Rectified, processed EMG data for each antagonistic muscle group were quantified using Jaccard's Coefficient (J). This statistic quantifies; of the time during which there is any activity above baseline in either muscle, how much of that time the muscles are active together i.e. not acting reciprocally.

The J-value was derived from the spread sheets used to determine whether a muscle was on or off according to a pre-determined threshold (section 4.4.3iii). Each data point, representative of one millisecond, was marked as on (1) or off (0) according to the threshold, in quadriceps and hamstrings for each data set. These values were then analysed using a cross tabulation in *SPSS (version 18)*:

$$J = \frac{a}{a + b + c}$$

where a= muscles active together, b=quadriceps active, hamstrings inactive and c= hamstrings active, quadriceps inactive

Hence, a J-value of 1.0 indicates perfect positive correlation, and therefore complete co-contraction, or no reciprocal activation, of an antagonistic muscle pair. A J-value of 0 indicates a perfect negative correlation, with no co-contraction

between the two muscles at all, and therefore complete reciprocal activation of antagonistic muscle groups. It should be noted that a J-value of 0 might also represent a situation where a muscle was not active at all about baseline; it has been made clear in the relevant results sections where this was the case.

4.5.3 Smoothness of pedalling movement (S-Ped)

Smoothness of pedalling movement (S-Ped) was quantified from the standard deviation of mean time spent in each of the eight position bins for each turn, over ten complete turns of the wheel. Hence, a high standard deviation represented less smooth pedalling than a low standard deviation.

4.6 Other measures common to both studies

In order to meet study aims, particularly 2d (exploring the association of UP measures and current clinical measures of lower limb impairment and walking ability), 3c, 3d and 3e (exploring participation in, and potential efficacy of, UP) it was important that commonly used measures of lower limb impairment and walking ability were included, in addition to the biological measures listed above.

Selection of these measures was guided by recommendations from the British Society of Rehabilitation “Basket of measures” of outcomes in rehabilitation (British Society of Rehabilitation, BSRM, 2005). In order to be included in the “basket”, measures have to be scientifically evaluated and in common use in the UK (by at least ten units). These guidelines were therefore considered appropriate for assisting with the selection of measures for the studies presented herein.

The recommended and most widely used measure of motor impairment is the Motricity Index (MI), with the Motor Assessment Scale proposed as the possible alternative option (BSRM, 2005). The Motricity Index is considered as a simple, short measure of motor loss for use after stroke (Wade, 1992), whereas the Motor Assessment Scale is a much longer, hierarchal score, including focus on disability (BSRM, 2005). Therefore, considering the requirements of the measure to assess

impairment specifically, and to be pragmatic for timely use with early stroke survivors in a clinical setting, the Motricity index was selected for use in the current studies (4.6.1; 5.8.2i)

The recommended and most widely used measure of mobility is the 10-metre timed walk, with the Functional Ambulatory Categories (FAC) proposed as a possible alternative option (BSRM, 2005). The 10-metre timed walk is considered to be very simple to use, valid, reliable and sensitive (Wade, 1992). However, in order to participate, stroke survivors need to have some ability to walk and therefore this was not a usable tool for the feasibility study here, which purposefully sampled those early stroke survivors with substantially impaired mobility. The FAC, conversely, enables categorisation of all levels of ambulatory ability, from complete dependence to independent walking function. It is also a scale which has been demonstrated to be simple to use and sensitive to change during the transition from immobility to walking (Merholz et al. 2007; Wade, 1992). Hence, this scale was considered the most useful for capturing the ambulatory ability of the stroke survivors included in these studies (4.6.2; 5.8.2iii).

4.6.1 Measurement of lower limb motor impairment: The Motricity Index (MI)

The Motricity Index (lower limb section) (Demeurisse et al. 1980) is a measure that can be used easily in the clinical setting to assess the severity of motor impairment. It is one of the most common measures of lower limb motor impairment used by physiotherapists after stroke.

It is an ordinal weighted scale with six measurement levels within each of three categories for the lower limb. The three categories are: ankle dorsiflexion, knee extension, and hip flexion. For each movement, a score of 0, 9, 14, 19, 25, or 33 is given, where 0 is no movement, 19 is full range movement against gravity not against resistance and 33 is normal power.

4.6.2 Measurement of walking function: The Functional Ambulatory Categories (FAC)

Measurement of walking ability was carried out using the Functional Ambulation Categories (FAC) (Holden et al. 1984). This scale is designed to give detail on physical

support needed by patients for walking, so has clinical relevance, and is simple to use. It has established validity and reliability for use after stroke (Merholz et al. 2007). It is an ordinal scale, patients scoring from 0-5, where 0 indicates a patient who is not able to walk or needs help of 2 therapists, and 5 indicates a patient who is independent in ambulation even on stairs. The Functional Ambulatory Categories (FAC) has demonstrated sensitivity in stroke survivors who cannot walk at the beginning of their rehabilitation period (Merholz et al. 2007); relevant to participants in this trial, who are not mobile at inclusion.

4.7 Procedures common to both studies

4.7.1 Overview of research procedures

At the beginning of each initial measurement session, participants were shown the research equipment and procedure explained again in full.

The researcher then measured the participant's heart rate and blood pressure to ensure that they were within the safe limits set for the study on the measurement day (see individual study criteria, 5.4.2, 6.3.1, 6.3.2)

Participant characteristics were recorded by the researcher.

Participants then changed, or were assisted in changing, into a pair of shorts and their skin prepared for EMG placement, using *Nuprep* (Weaver & Company, Colorado, USA) gentle skin abrasive and an alcohol wipe. They were then hoisted/transferred to the bike and positioned comfortably.

Surface EMG electrodes were then applied to the front and back of the thigh in the recommended position for recording from quadriceps and hamstrings. Electrodes were placed according to published guidelines (Cram et al. 1998; see also *Appendix III*) and secured to minimise movement artefacts and hence interference. Resting EMG data was collected from each leg with the participant's foot resting comfortably on a block in 5-15 degrees of knee flexion, whilst seated on the bike.

Participants were then asked to pedal at their comfortable speed, for one minute, to familiarise themselves with the equipment and testing procedure. They then stopped pedalling and the researcher ensured that the participant was in a comfortable position to begin the recorded pedalling session. They were then asked to pedal for a further minute in the same manner, during which EMG data was recorded. The central ten turns were later selected from the complete data set (section 4.5), to ensure that the steady pedalling phase, and not the acceleration and deceleration phases, were included in the analysis.

During pedalling, heart rate was monitored to ensure it did not exceed 85% age predicted maximum ($220 - \text{age} \times 0.85$) at any point.

The decision to hoist or transfer the participant onto the bike depended on ambulatory capacity. This decision was made by a researcher with considerable expertise in the handling of stroke survivors working in conjunction with the participant. Two staff were present throughout each measurement session and the research area was situated alongside an acute stroke unit for the hospital based experimental study (Chapter 5.0) and a Clinical Research Trials unit for the laboratory based study (Chapter 6.0); both with stringent procedures in place for action in the event of an emergency.

Chapter 5.0: Upright Pedalling (UP) Exercise Early after Stroke: A Feasibility Study

5.1 Introduction

The purpose of this chapter is to describe the methods and results of an experimental study exploring the feasibility of Upright Pedalling (UP) early after stroke. Methods common to both this study and the development of measures of lower limb motor impairment have been presented in Chapter 4.0.

The study presented here addresses aims 2a, 3a, 3b, 3c, 3d, 3e and 3f

Presentation of this chapter has been guided by the CONSORT guidelines for non-pharmacologic treatment interventions (Boutron et al. 2008).

Findings from the systematic review (Chapter 3.0) described a lack of transparency in reporting of studies investigating pedalling after stroke; hence, in accordance with CONSORT guidelines for transparent reporting of research trials (CONSORT, 2010) this study was registered on a clinical trials database (ISRCTN 45392701) and the protocol has been published in a peer-reviewed, open-access journal, *Trials* (Hancock et al. 2011; *Appendix IV*).

5.2 Design:

The study was a single centre, early phase randomised controlled trial (RCT) with observer blinding. This design is illustrated in figure 11.

The study design was used in order to enable data collected from a single cohort of early stroke survivors to be used to address all study aims. All participants recruited and undergoing baseline measures set one were given the opportunity to take part in a session of UP. Therefore, even those who were eventually randomised to the control group after baseline measures set two had active involvement in this study by participating in one trial pedalling session.

The challenge of carrying out in-patient neurological rehabilitation research has been documented (Cumberland Consensus Working Group, 2009), and it was intended that this pilot RCT also provide information on the feasibility of running such a trial in an acute stroke unit setting.

5.2.1 Randomisation

To examine the potential clinical efficacy of UP in this participant group, randomisation was considered essential- spontaneous behavioural recovery has been noted in the first weeks after stroke onset, though with considerable heterogeneity in natural recovery across stroke survivors (Cramer, 2008). Hence, a non-randomised, “before-and-after” type design risked erroneously ascribing benefit to the intervention when other mechanisms may have been responsible in this changeable phase of recovery. Therefore, to limit confounding influences and minimise allocation bias, a randomly allocated control group of participants, meeting the same study inclusion criteria as the experimental group, was required. Control group participants would not miss out on therapy at this crucial stage after stroke, as all trial participants would continue to receive usual therapy with the clinical team.

Randomisation order was generated before the trial began by a medical statistician, in blocks of four. Block randomisation was used to ensure equal numbers in each trial arm. Group allocation was concealed in sequentially numbered opaque sealed envelopes held by an independent administrator, who was not involved in the study and had no contact with study participants. The next highest number envelope was opened by the independent administrator in response to a telephone request from the research therapist. After opening, the envelopes were stored securely with the participants’ study data. Randomisation was concealed from the independent outcome assessor and participants were asked not to discuss group allocation with the outcome assessor.

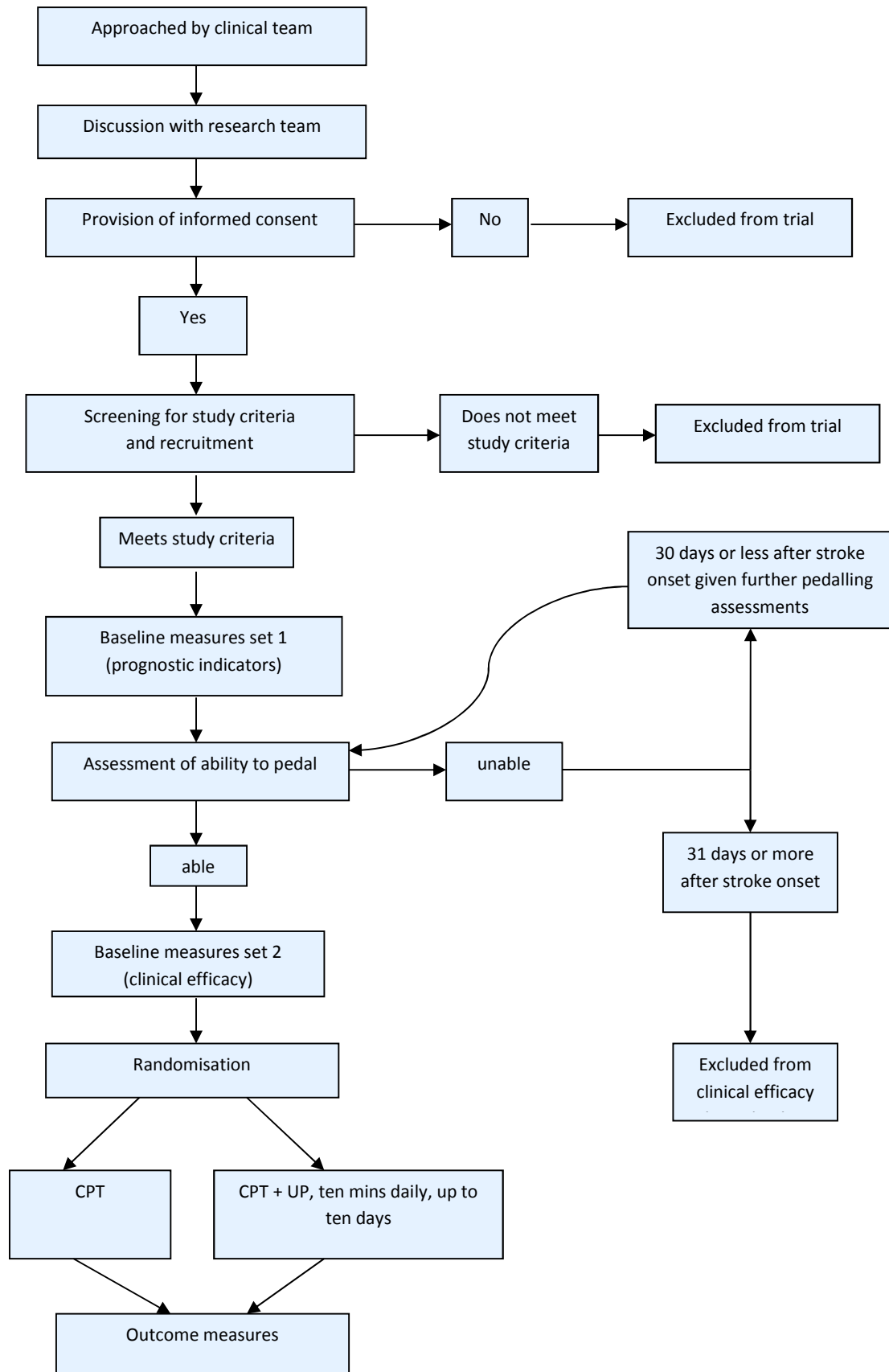


Figure 11: Flowchart illustrating study design

5.2.2 Blinding:

Blinding of research therapists in a therapy intervention study is not always feasible and patients are clearly aware that they are undergoing exercise-based interventions. Consequently, for this exploration of therapeutic pedalling exercise, blinding of therapists providing the intervention and of participants was not possible. The independent assessor of clinical outcome measures was a trained therapist blinded to group allocation.

5.2.3 Overview of Study Procedure

All participants underwent baseline measurement set one.

The common procedures described in section 4.7.1 for positioning participants on the bike were adopted.

Participants were then assessed for their ability to perform UP.

They were asked to pedal slowly for one minute to familiarise themselves with the equipment. They were then asked to pedal for one further minute and a visual observation of whether they could pedal or not was made and recorded.

Those who were unable to pedal and were 31 days or more after stroke onset were excluded from the randomised part of this trial. It was intended that those participants unable to pedal and who were 30 days or less after stroke onset be offered further pedalling assessments approximately every three days. The rationale for further pedalling assessments was that during the first 30 days after stroke people may have experienced fear of movement, lack of confidence in moving or emotional difficulties and therefore may have needed more than one experience of attempting pedalling within a therapeutic environment. Without repeated opportunities for pedalling assessment some participants may have been excluded unfairly from the opportunity to participate in UP. Additionally, more than one attempt at an activity more closely reflects the pragmatics of clinical practice.

Those participants able to pedal for one minute and who were 30 days or less after stroke onset, then undertook baseline measures set two. Participants were then

allocated randomly to either routine conventional physical therapy (CPT; control group) or to CPT plus UP (experimental group).

Participants were to receive their allocated intervention for up to ten minutes a day, for up to ten working days or until discharge from acute stroke care, whichever occurs first. On completion of the intervention phase participants undertook clinical efficacy outcome measures. Every attempt was made to undertake clinical efficacy outcome measures even if participants were discharged before the intervention phase was completed, in accordance with the “intention to treat” principle.

5.3 Setting

The study was carried out in the acute Stroke Unit at the Norfolk and Norwich University Hospital Trust (NNUH). The equipment was situated in the therapy room alongside the Stroke Unit. Prior to proceeding with screening for the study, and after ethical approval had been received, the lead researcher introduced the project as part of the clinical team training on the unit and spent some weeks familiarising all members of the clinical team with study criteria and all procedures. Consultant and therapy teams agreed to support this trial.

5.4 Participants

5.4.1 Recruitment process

Participants were recruited from the acute stroke unit, according to the following process:

Clinical team members, and in particular, physiotherapy staff, were familiarised with study criteria (5.4.2).

Stroke survivors were initially approached by a clinical team member responsible for their care, to briefly explain that the study was currently underway on the stroke unit and ask whether they would be happy to speak to the researcher. If they agreed, the researcher provided potential participants with verbal and written printed information (*Appendix II*) about the trial. A video of the procedure for getting on and off the upright bike was also available and potential participants invited to view it if they wished; though during recruitment to this study, no participants requested information in this way.

A minimum of twenty four hours later, written informed consent was sought. Those providing written informed consent were recruited as participants in this trial. All participants were then screened to check that they meet the study criteria (5.4.2)

5.4.2 Inclusion Criteria

Inclusion criteria were carefully considered in the development stages of the protocol. To meet study aims, it was essential to recruit participants with substantial weakness, early after stroke, but who were also considered fit enough to participate by the medical team. Hence, to be included in this study, all participants were:

- *adults aged 18+.*

The aetiology of paediatric stroke in the developing brain is a complex and entirely separate clinical field to adult stroke. The research aims here apply only to the adult stroke population and the research was based in a unit for adult stroke survivors only.

- *three to thirty days following a unilateral stroke resulting in unilateral muscle weakness with or without sensory deficit;*

The essential early period for instituting rehabilitation therapies after stroke has been discussed in Chapter 1.0. In recruiting stroke survivors within 30 days of onset, this research aimed to evaluate the possible efficacy of the intervention used during this important time window.

- *fit to participate as assessed by a consultant-led medical team with resting oxygen saturations 95% or above, resting heart rate 90 beats per minute or less and systolic blood pressure of 100-160 mmHg*

These criteria were set in close conjunction with the trial clinical collaborator, Dr Phyo. K. Myint and Principal Investigator, Professor Valerie Pomeroy

- *Not independently mobile, assessed by a score 0, 1 or 2 on the Functional Ambulation Categories (Holden et al. 1984).*

Clinically, this meant that participants were unable to walk; or needed the help of two or more people; or required firm continuous or intermittent support of one person assisting with weight and balance whilst they walked.

The need to develop rehabilitation interventions for stroke survivors with substantial weakness, who might otherwise have little opportunity to take part in the repetitive, skilled activity required to promote recovery of motor function, has been discussed in Chapter 2.0. The use of the FAC, to assess ambulatory capacity, ensured that a standardised tool was employed to ensure participants met this criterion.

- *able to sit unsupported for 30-seconds on the edge of a bed with feet on the floor.*
- *able to have sat out of bed in a chair or wheelchair at least once for a continual period of 15-minutes*

These safety criteria ensured that participants were able to a) sit forward for hoisting and transferring to the bike, and b) tolerate sitting out of bed for an appropriate time to take part in the cycling intervention.

- *able to follow a one-stage command*

This ensured that participants had sufficient communication and orientation to participate in this particular cycling intervention without excluding those with aphasia; it is important that participants with a wide range of communication strategies are included in research, to more accurately reflect clinical practice.

- *be independently mobile with or without an aid prior to the index stroke;*

5.4.3 Exclusion Criteria

People with the following were excluded from this study:

- *those having co-existing pathology contributing to observed impairment in the paretic lower limb e.g. osteoarthritis with associated knee deformity.*

This criterion excluded those with pre-existing mobility difficulties, unrelated to their current stroke, which might have a) affected their ability to be positioned on the bike and/or take part in the pedalling activity and b) adversely influenced the muscle activity data to be recorded.

5.5 Sample Size

This early phase trial was the first to explore Upright Pedalling with early stroke survivors. As the study was not designed to definitely demonstrate efficacy, it was not appropriate to base a sample size calculation on clinical efficacy. Sample size was therefore based on practical considerations, using estimates of the number of participants the researcher could expect to recruit within a 12 month time period; a pragmatic time period for PhD studies. Using data from previous trials of rehabilitation early after stroke led by the Principal Investigator for this study (Donaldson et al. 2009) and taking into account admission numbers to the acute stroke unit a recruitment rate of two participants per month was estimated. Therefore, the sample size was set at 24 participants. It was anticipated that data from this pilot work might inform sample size calculations for subsequent trials.

5.6 R&D Governance

The research study received the approval of the Essex 1 Research Ethics Committee, UK (09/H0301/52; *Appendix II*)

5.7 Intervention

It was proposed that all participants would receive routine conventional physical therapy (CPT) as deemed appropriate by the clinical team. A previously validated standardised schedule was used to record content and dose (minutes) of CPT (Pomeroy et al. 2005). Once a participant had been randomised, clinical physiotherapy team members were asked to complete a record for each CPT session and these were transferred to the research laboratory and stored with participant data. This could then provide information for replication of therapy dose in potential future studies.

5.7.1 Control intervention

Participants allocated to the control group received CPT only as described above.

5.7.2 Experimental Intervention

Participants allocated to the experimental group received UP in addition to CPT. All experimental participants were asked to pedal comfortably at up to 50 revolutions per minute (50 rpm).

Participants were monitored throughout to ensure that they maintained a heart rate of 85% or below their age-predicted maximum (i.e. less than $(220 - \text{age}) \times 0.85$ beats per minute).

If participants could not achieve 50 rpm, the research therapist was guided by their response in setting the maximum rpm. The approximate mean rpm achieved was recorded for each participant for each intervention session according to the visual display on the bike, and accurately verified at the data analysis stage using the

wheel sensor data. It was anticipated that few patients early after stroke would immediately manage ten minutes of pedalling, so the number of minutes pedalled, up to ten minutes, was recorded. Ten minutes was set as the upper limit, as, even at a slower pace of 30 rpm, this provides the 300 repetitions of lower limb cyclical activity in a single treatment session suggested as necessary by animal model studies (Kleim et al. 1998).

Each intervention session also involved recording the measures described in 4.5 & 4.6

5.8 Measurement battery

5.8.1 Participant characteristics

For all participants, characteristics recorded were:

- gender
- age (years)
- type and site of the stroke lesion (via liaison with medical team from scanning/clinical findings) and,
- time since stroke onset at entry to the trial and at each set of study measures (days).

5.8.2 Clinical efficacy measures

5.8.2i Primary outcome

- Ability to voluntarily contract paretic muscle, measured by the Motricity Index

A key aim of this pedalling intervention was to enhance the ability to voluntarily contract paretic muscle, hence the primary measure was intended to capture this change. The Motricity Index (MI) (lower limb section) (Demeurisse et al. 1980) is a measure that can be used easily in the clinical setting to assess the severity of motor impairment. The MI is described in section 4.6.1.

5.8.2ii Secondary outcomes

- Ability to walk independently

Regaining walking ability is a key goal for stroke survivors and independent mobility enables independence in other activities of daily living. Pedalling exercise after stroke might have a positive effect on ambulatory function. Hence walking ability was considered as a secondary outcome, as measured by the Functional Ambulation Categories (FAC) (Holden et al. 1984). The FAC is described in section 4.6.2.

Secondary measures derived from EMG

Therapists in the clinical setting frequently observe and record alterations in, for example, muscle strength and walking ability, but cannot accurately measure the specific underlying changes in muscle activity that might contribute to changes in movement and functional performance. In recording, processing and analysing EMG data, this research aimed to evaluate physiological change alongside frequently used clinical measures of paresis and detect changes in motor activity earlier than if using clinical measures of movement performance alone. Emphasis on such biological measures is considered important in the development phases of an intervention (Cumberland Consensus Working Group, 2009).

- Onset and offset of activity of antagonistic muscle groups during pedalling, derived from EMG recording

This measure enabled the timing of muscle activation throughout the pedalling cycle to be quantified, as described in section 4.5.1.

- Reciprocal activation of antagonistic muscle group activity during pedalling

Coordinated, phasic activity is a prerequisite for normal locomotor function. This measure, as described in section 4.5.2, was used to determine to what degree the quadriceps and hamstring muscles in both the affected and

unaffected lower limbs were working reciprocally in participants early after stroke.

- Smoothness of pedalling movement (S-Ped)

Motor hemiplegia following stroke inevitably leads to asymmetrical lower limb function and performing smooth, reciprocal movement such as pedalling can be challenging. Smoothness has previously been proposed as a kinematic measure of asymmetry during reciprocal pedalling (Chen et al. 2005). It is reasonable to assume, therefore, that increased smoothness of pedalling represents more symmetrical, efficient movement patterns, such as those required to perform walking. Smoothness of movement was quantified as described in section 4.5.3

5.8.2iii Prognostic indicator measures

- Site of stroke lesion

The location and size of stroke lesion have been demonstrated to be a prognostic factor for functional outcomes after stroke (Pan et al. 2006, Chen et al. 2000). It is possible, therefore, that this clinical factor might be linked to the ability to take part in and respond to rehabilitation interventions. Where possible, brain lesion location was therefore recorded from the clinical scan in liaison with the collaborating stroke physician.

- Severity of muscle weakness as measured by the Motricity Index

As described in section 5.8.2i

- Ambulatory Capacity as measured by the Functional Ambulatory Categories (see clinical efficacy measures section 5.8.2ii)

The FAC has been found to have good predictive validity for community ambulation after stroke (e.g. FAC \geq 4, sensitivity 100%, specificity 78%) (Merholz et al. 2007). It was proposed that pedalling exercise might have a positive effect on walking and thus postulated that the ability to walk might influence the ability to pedal and respond to pedalling intervention.

- Ability to control the trunk

As measured by the Trunk Control Test (Collin and Wade, 1990). This is a short, simple measure of motor loss developed for use after stroke. Patients are asked to do four movements- rolling to their weak side, rolling to their strong side, sitting up from lying down and balancing in a sitting position. Each movement is scored according to ability, either 0, 12 or 25, leading to a total score out of 100. Validity (comparison with Rivermead Motor Assessment at six, twelve and eighteen weeks post-stroke- Spearman's rho, $r = 0.70, 0.72$ and 0.79 respectively; inter-rater reliability, Spearman's rho, $r = 0.76, p < 0.001$) have been established (Collin and Wade, 1990).

Balance (trunk) control is highly specific to ambulatory control, and makes a crucial contribution to the ability to perform activities of daily living (Hsieh et al. 2002). The Trunk Control Test has been found to be a predictor of functional outcomes after stroke, including discharge Functional Independence Measure (Pearson's $r = 0.738$), gait velocity (Pearson's $r = 0.654$) (Duarte et al. 2002); and discharge walking ability (Spearman's rho $r = 0.71$) (Masiero et al. 2007). It is possible, therefore, that trunk control early after stroke might influence the ability to perform rehabilitation activities and thus it was assessed as a potential prognostic indicator for pedalling exercise after stroke.

5.9 Analysis

The aim of the analysis was not to definitively demonstrate efficacy in this early phase trial. However, assuming a normal distribution, it was anticipated that independent t- tests would be used to compare groups between trial arms for non-EMG derived follow-up measures, together with 95% confidence intervals to inform potential conclusions on clinical benefit. It was planned that within-group analysis be assessed using paired t-tests. A resultant non-normal distribution would indicate the use of analogous non-parametric methods.

It was planned that associations between potential prognostic indicators and the ability to pedal be tested using Fishers Exact test.

Analysis of the EMG signal is described in depth in Chapter 4.0

5.10 Adverse Reactions

There was a small risk that for some people, UP might lead to an “overuse” syndrome, as expressed through an increase in pain or fatigue. Participant reports of lower limb pain, either verbal or behavioural, were monitored during pedalling. Before the trial began, criteria for cessation of the intervention due to an adverse event were set as: intervention would cease and an adverse event recorded if a participant demonstrated a decrease of 2 or more minutes’ ability to pedal on 2 consecutive treatment days, or a 25% reduction in mean rpm on 2 consecutive treatment days.

5.11 Results

The purpose of this section is to present exactly what data were collected; to what extent analysis of those data enabled the aims of the study to be met; and the findings relevant to the study aims.

5.11.1 Screening, recruitment and attrition (aim 3a)

5.11.1i Screening and recruitment

Figure 12 describes screening and recruitment to, and participation in, the study, according to CONSORT guidelines (Boutron et al. 2008).

Liaison with the stroke unit’s inter-disciplinary team enabled screening of 411 potential participants during a twelve month period (Figure 12), of whom 392 did not meet study criteria. 142 (34.5%) were too unwell to participate and, in contrast,

111 (27.0%) were independently mobile. Other reasons are cited in figure 1 and included previous immobility, no unilateral weakness and other lower limb pathology. Hence, 4.6% of those initially screened were eligible.

Of the eligible participants given information about the study, 16 (84.2%) provided informed consent, with only 3 (15.8%) of those approached by the researcher declining consent.

Of the 16 participants recruited, one did not meet study criteria for blood pressure and/or heart rate following provision of informed consent; and one declined the pedalling attempt following the provision of informed consent due to feeling fatigued. One became unwell on the day of intended baseline measures and did not recover sufficiently to be included any further; hence 13 progressed to baseline measurement set one and the trial of UP.

5.11.1ii Attrition pre-randomisation

Immediately following a successful pedalling attempt, one participant was withdrawn due to technical reasons with the research space on the stroke unit and was transferred to an off-site rehabilitation unit before the research space issues were resolved.

Two (15.4%) participants were unable to complete the initial one-minute pedalling trial, with eleven (84.6%) successfully completing the task. According to the study protocol, those unable to pedal were to be approached at two to three day intervals to have a further attempt. Both participants concerned agreed to a further trial. However, both were transferred from the acute stroke unit before a second attempt at pedalling could be made.

Ten participants therefore reached baseline measures set two, with one transferred to another unit immediately following measures and prior to randomisation.

Hence, nine were randomised, five to the intervention group and four to the control group.

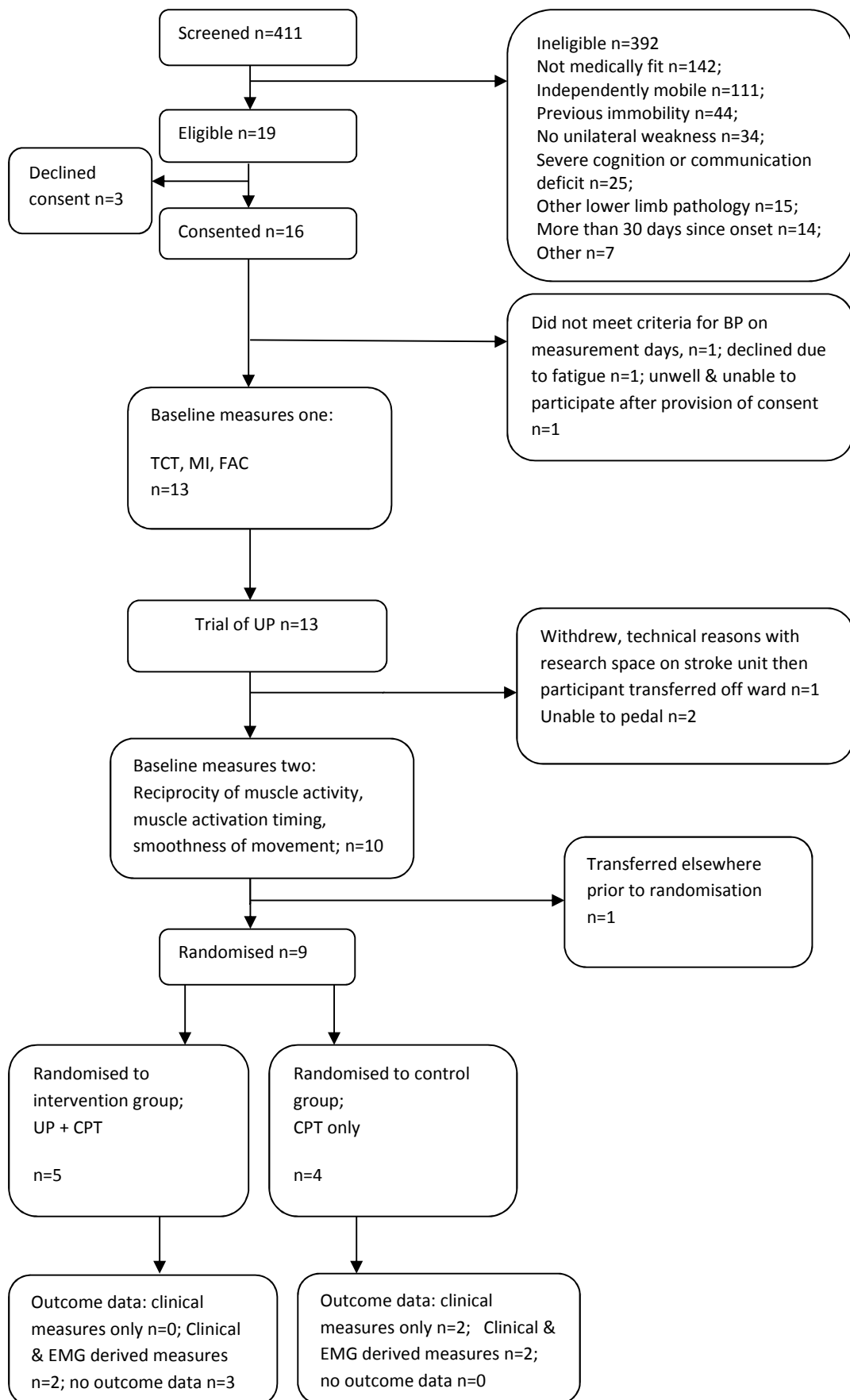


Figure 12: CONSORT diagram depicting screening, recruitment and attrition

5.11.1iii Attrition post-randomisation

Table 11 summarises the nature of the data collected during the trial.

No participants in the intervention arm of the trial underwent intervention on the maximum ten consecutive days proposed in the protocol. Two participants were moved from the acute unit after baseline measures two and randomisation, but before intervention began. Two participants had two days of intervention before transferring from the acute unit. One participant had four days of intervention but then became unwell with a serious unrelated event.

Clinical outcome measures (FAC, MI) were obtained for two participants in the intervention group and four in the control group. EMG data at outcome were recorded for only four participants, two in the intervention group and two in the control group. Two sets of these data were available for processing and analysis due to overwhelming electrical noise affecting two participants' data early in the study.

The research was carried out during a period of reorganisation of stroke services in Norfolk to ensure faster admission to, and transfer from, the stroke unit. The rehabilitation unit to which many patients were transferred was at another site across the city and was part of another NHS Trust. With only one prototype static upright bike, movement of equipment to and from the alternative site proved impossible. Movement of participants between units for intervention and outcomes was not considered appropriate in this early stage after stroke and, furthermore, funds were not available for transport. Intervention and collection of EMG outcome data according to the intention-to-treat principle was therefore impossible for participants who were moved off site.

Where possible, the blinded assessor undertook scoring of the FAC and MI lower limb for those participants transferred to the off-site rehabilitation unit, as she was part of a therapy research trial being undertaken on the unit.

Despite the challenges faced in relation to attrition during this clinical research, sufficient data were collected during the study to address aims 2a., 3a., 3b., and 3d; insufficient data were available to address aims 3c. and 3e.

5.11.2 Participant characteristics at baseline

Table 12 presents the baseline characteristics of all participants who reached baseline measures set one and the trial of UP.

Nine participants undergoing the trial of UP were male (69%). Mean age of participants was 70.8 years (range 48 to 87 years), with a mean number of days since stroke onset of 12.5 (range 4 to 26 days). Seven participants (54%) had right sided weakness. All had a Functional Ambulatory Category (FAC) score of zero. Mean Motricity Index (MI) score was 43.6 (range 10 to 78) and mean Trunk Control Test (TCT) score was 42.6 (12 to 100)

Table 13 separately presents the baseline characteristics for the two participants unable to pedal. Both participants were greater than two weeks from stroke onset (18 and 24 days), being too unwell to participate up to this point. Both had low scores on both the MI and TCT (Ped 10, MI 38 and TCT 24; Ped 11, MI 10 and TCT 12).

5.11.3 Establishing whether early stroke survivors are able to take part in Upright Pedalling in an acute hospital setting (aim 3b.)

Eleven (84.6%) participants successfully completed the initial one-minute pedalling trial; two (15.4%) participants were unable to do so.

Whilst the protocol planned for those unable to pedal to be approached at two to three day intervals to have a further attempt, both participants were transferred from the acute stroke unit before a second attempt at pedalling could be made. Both participants had expressed a wish to try again after the initial attempt.

Table 11: Data Collected

Participant	Able to complete initial pedalling trial (Yes/No)	Data collected										Notes
		Motricity Index		Functional Ambulatory Categories		EMG data			Sensor data			
		Baseline	Outcome	Baseline	Outcome	Baseline	Intervention days	Outcome	Baseline	Intervention days	Outcome	
PED 01	Yes	√	X	√	X	x	n/a: not randomised	X	X	n/a: not randomised	x	Withdrew after trial pedal
PED 02	Yes	√	X	√	X	X	n/a: not randomised	X	X	n/a: not randomised	X	Transferred after trial pedal
PED 03	Yes	√	√	√	√	√	n/a: control	√	√	n/a: control	√	Electrical noise EMG
PED 04	Yes	√	√	√	√	√	√	√	√	Baseline & day 2 only	√	Electrical noise EMG
PED 05	Yes	√	√	√	√	√	n/a: control	X	√	n/a: control	x	Transferred
PED 06	Yes	√	X	√	X	√	√ days 1,2,3,4	X	√	√ days 1,2,3,4	x	Withdrew unrelated event
PED 07	Yes	√	X	√	X	√	X	X	√	X	x	Randomised to intervention then transferred
PED 08	Yes	√	√	√	√	X	n/a control	√	√	n/a control	√	EMG tech fault at baseline
PED 09	Yes	√	√	√	√	√	√ days 1,2	√	√	√ days 1,2	√	
PED 10	No	X	X	X	X	X	X	X	X	X	x	One attempt then transferred
PED 11	No	X	X	X	X	X	X	X	X	X	x	One attempt then transferred
PED 12	No attempt											Unwell after consenting
PED 13	Yes	√	√	√	√	√	n/a control	X	√	n/a control	x	Transferred
PED 14	Yes	√	X	√	X	√	x	X	√	X	X	Randomised to intervention. BP raised, then transferred

Table 12: Baseline Characteristics, all participants undergoing the trial of UP

Participant	Gender	Age (years)	Days since stroke	Side of weakness	Description Stroke lesion From scan/liaison with medical team	FAC (0-5)	MI lower limb (/100)	TCT (/100)
PED 01	F	87	23	R	Left infarct; no further detail available	0	33	24
PED 02	M	66	26	L	Left pons infarct, right ischaemia anterior horn right lateral ventricle	0	48	24
PED 03	M	45	7	R	Left internal capsule infarct	0	29	74
PED 04	M	80	8	L	Right posterior lentiform infarct	0	59	37
PED 05	F	74	9	L	Right Posterior cerebral artery infarct	0	38	24
PED 06	M	81	6	R	Bilateral periventricular and pons ischaemia	0	78	50
PED 07	M	48	9	R	Ischaemia lentiform nucleus & internal capsule	0	33	74
PED 08	M	60	9	R	Left middle cerebral artery infarct	0	38	37
PED 09	M	67	4	L	Right frontal ischaemia	0	70	100
PED 10	M	62	24	L	Right middle cerebral artery infarct	0	38	24
PED 11	F	85	18	R	White matter ischameia, clinically left PACS	0	10	12
PED 13	F	79	11	L	Old Right lacunar infarct, clinically right PACS	0	29	37
PED 14	M	86	8	R	Small left corona radiata haemorrhage	0	64	37
Summary	69% male	Mean (range) 70.8 (48 to 87)	Mean (range) 12.5 (4 to 26)	54% right		Mean (range) 0 (0 to 0)	Mean (range) 43.6 (10 to 78)	Mean (range) 42.6 (12to100)

Note: Ped 12 and Ped 15 did not reach baseline, Ped 12 became unwell, Ped 15 declined due to fatigue. One further recruited not allocated study number as did not ever meet criteria for blood pressure before transfer from the acute unit

Abbreviations: M=male, F=female, R=right, L=left, FAC=Functional Ambulatory Categories, MI=Motricity Index, TCT= Trunk Control Test

Table 13: Baseline Characteristics, participants unable to pedal

Participant	Gender	Age (years)	Days since stroke onset	Side of weakness	Description stroke lesion	FAC (0-5)	MI lower limb (/100)	TCT (/100)
PED 10	M	62	24	L	Right MCA infarct	0	38	24
PED 11	F	85	18	R	White matter ischaemia, clinically left PACS	0	10	12

Abbreviations: M=male, F=female, R=right, L=left, FAC=Functional Ambulatory Categories, MI=Motricity Index, TCT= Trunk Control Test

All participants who were able to perform UP for the one minute trial were able to do so despite severe mobility limitations (FAC 0) and were, on average, within only 11 days of stroke onset (mean 10.9; range 4 days to 26 days). Most had substantial weakness of the lower limb (Mean MI 47/100; range 29/100 to 78/100).

Two participants were unable to pedal; one male and one female. Both were longer after stroke onset than the mean (24 days and 18 days respectively). Neither had been well enough to participate earlier after stroke.

5.11.4 Establishing whether it is possible to provide UP daily, on 10 consecutive days in an acute stroke unit setting (aim 3b.)

No participants in this trial took part in UP on ten consecutive days in the acute stroke unit setting.

Of the five participants randomised to receive daily UP in addition to conventional physiotherapy, one participant was transferred from the unit before intervention could begin, two had the intervention for two consecutive days and one had four days of intervention.

Both participants who pedalled for two consecutive days were then transferred to home or another rehabilitation unit and therefore unable to continue.

The participant having four days of intervention had a serious unrelated event hence it was impossible to proceed with the intervention.

Hence, outcome data that included both clinical and EMG derived measures were only available for two intervention group participants (section 5.11.1iii).

Of the four participants randomised to the control group, one remained in the study for seven days, two for six days and one for three days. Outcome data that included both clinical and EMG derived measures were only available for two control group participants (section 5.11.1iii).

As a consequence of these results, the collection of information via the standardised conventional physiotherapy (CPT) schedules was limited. Table 14 presents the amount of CPT for each of the randomised participants.

Table 14: Number of days in study with minutes of conventional physiotherapy recorded

Participant	Randomised	Days in studyinc baseline	Sessions/minutes of CPT recorded
PED 03	Control	7	1 session/15 minutes;& 1 session/20 minutes
PED 04	Intervention	4	None
PED 05	Control	6	1 session/40 minutes
PED 06	Intervention	5	1 session/20 minutes
PED 07	Intervention	1	None
PED 08	Control	6	1 session/45 minutes
PED 09	Intervention	5	1 session/25 minutes
PED 13	Control	3	None
PED 14	Intervention	1	None

Only one participant had more than one session of CPT and the maximum length of conventional therapeutic intervention in any session was 45 minutes.

5.11.5 Instrumentation of the U-PeD equipment and deriving possible measures for use in subsequent research (aim 2a.)

This aim investigated the possibilities of the instrumentation of U-PeD using EMG recording of major muscle groups alongside measurement of wheel crank angle to derive measures of lower limb impairment in early stroke survivors taking part in UP.

This data might then inform choice of measures for subsequent research. Measures were derived by quantifying muscle activity in each of eight wheel bins, determining reciprocity of activity between antagonistic muscle groups and determining smoothness of pedalling.

Though some challenges were met both in terms of quality of EMG data collected at the site and study attrition detailed, it was possible to instrument the device and hence derive and record measures of lower limb motor impairment during UP.

All available results of the measures are presented in tables 15& 16 and described in section 5.11.7, examining the potential evidence for UP to inform future trials.

Additionally, the measures were used to provide detailed characterisation of movement during UP (section 5.11.6)

5.11.6 Using measures identified to characterising lower limb muscle activity in early stroke survivors (aim3d.)

EMG data was processed and analysed according to section 6.4.3. Additional filters were applied to four data sets and the resting threshold was raised for two data sets; as per the algorithms presented in 4.4.3i & 4.4.3iii.

Using these methods, and where these data were available, it was possible to depict the muscle activation timing during the pedalling cycle and hence characterise the activity for individual participants.

A variety of patterns of muscle activity during pedalling were observed. Three illustrative cases of phase diagrams characterising muscle activity in the affected and unaffected legs are given in figures 13 to 15. These are followed by composite graphs of the activity in both quadriceps and hamstrings at baseline, across the 8 wheel bins for all participants for which this data was available (figures 16 & 17). Original data for figures 13 to 17 can be found in *Appendix III*.

Figures 13a and 13b depict movement patterns from a participant with an MI score of 64 and a FAC score of 0. Despite impaired lower limb control and an inability to walk, it can be seen that during UP, phasic activity is being generated in quadriceps and hamstrings in the affected limb.

In the affected limb, quadriceps activity is generated towards the top of the wheel and hamstrings activity is generated later in the cycle in a moderately reciprocal pattern ($J=0.053$). In the unaffected limb, however, hamstrings are active throughout the cycle, with quadriceps here contributing to the upstroke and the reciprocity of the unaffected limb is compromised as it assists pedalling ($J=0.245$). Whilst reasonable reciprocity was achieved in the affected limb, pedalling was only moderately smooth ($S\text{-Ped}=0.065$).

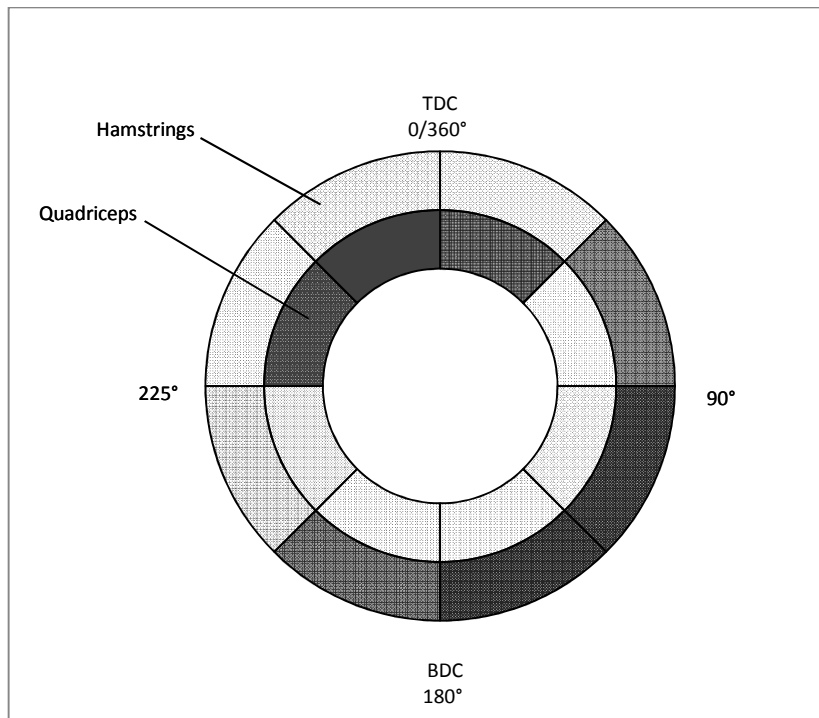


Figure 13a: Phase diagram: PED14, baseline affected leg (right), demonstrating onset/offset of quadriceps and hamstrings muscle activity according to angle. Participant scores: Days=8, FAC=0/5, MI=64/100, S-Ped=0.065, J (aff leg)=0.053, J (unaff leg)=0.245

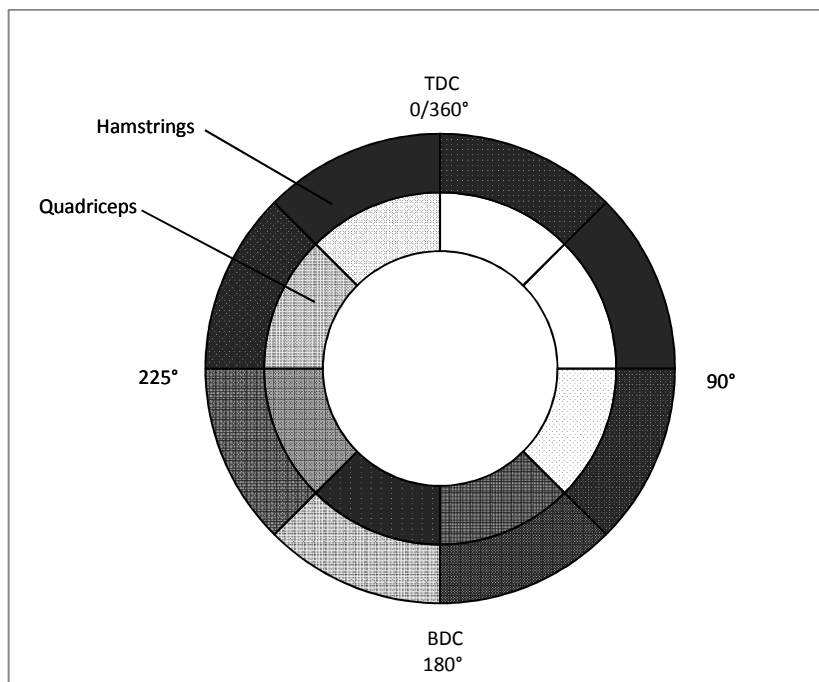


Figure 13b: Phase diagram; PED14, baseline unaffected leg (left), demonstrating onset/offset of quadriceps and hamstrings muscle activity according to angle.

Key: Outer circle= hamstrings, Inner circle= Quadriceps; Dark= Muscle "on", Pale= Muscle "off", Mixed shade= partially on/off graded shading; TDC= top dead centre, BDC= bottom dead centre. Abbreviations: Days=days since stroke onset, FAC=Functional Ambulatory Categories MI=Motricity Index lower limb, S-Ped=smoothness J aff=reciprocity affected leg, J unaff=reciprocity unaffected leg

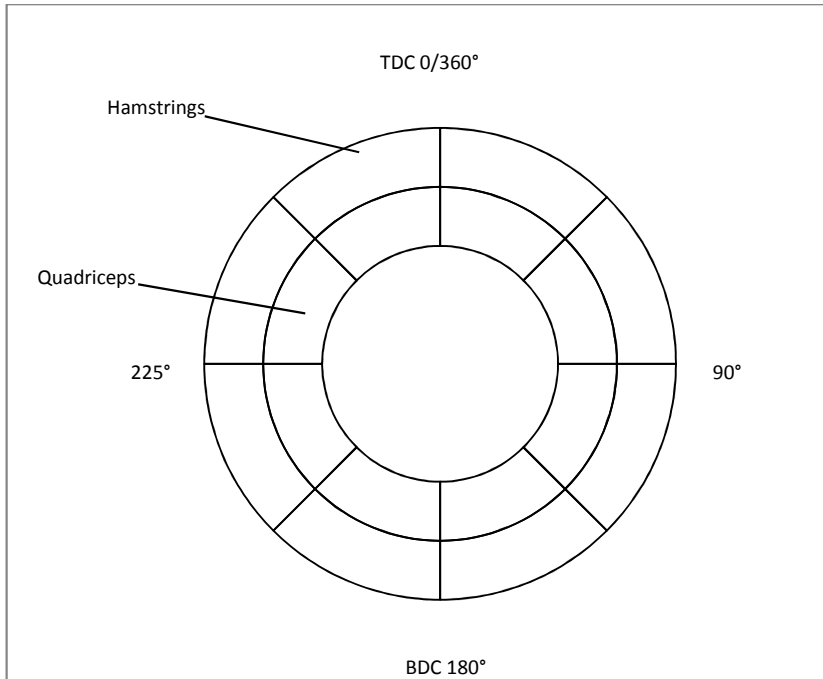


Figure 14a: Phase diagram; PED07, baseline affected leg (right), demonstrating no activity in quadriceps or hamstrings above resting baseline.

Participant scores: Days=9, FAC=0/5, MI=33/100, S-Ped=0.012, J (aff leg)=no activity above baseline, J (unaff leg)=0.038

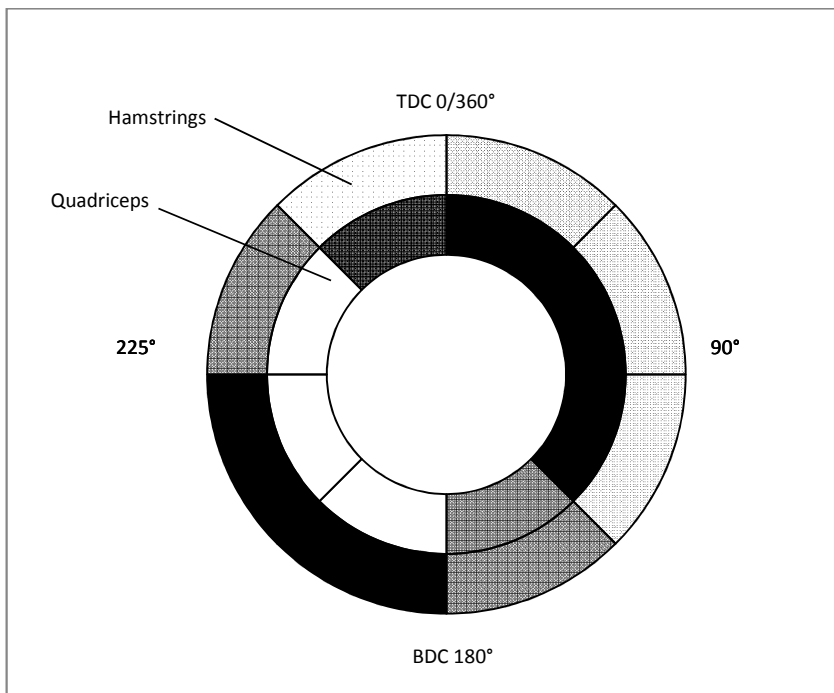


Figure 14b: Phase diagram; PED07, baseline unaffected leg (left), demonstrating onset/offset of quadriceps and hamstrings muscle activity according to angle.

Key: Outer circle= hamstrings, Inner circle= Quadriceps; Dark= Muscle on, Pale= Muscle off, Mixed shade= partially on/off graded shading; TDC= top dead centre, BDC= bottom dead centre. Abbreviations: Days=days since stroke onset, FAC=Functional Ambulatory Categories MI=Motricity Index lower limb, S-Ped=smoothness J aff=reciprocity affected leg, J unaff=reciprocity unaffected leg

Figures 14a and 14b depict very different movement strategies that led to very smooth pedalling. A high level of smoothness was achieved ($S\text{-Ped}=0.012$) but with no activity above baseline in either muscle group for the affected limb. However, quadriceps and hamstrings in the unaffected limb worked reciprocally throughout the pedalling cycle to achieve the movement ($J=0.038$). Due to the coupled crank, the affected leg was being moved cyclically and smoothly but without measurable muscle activity.

Figures 15a and 15b provide clear depiction of less smooth pedalling ($S\text{-Ped}=0.068$), but where muscles were active in both the unaffected and affected limbs. Here, a degree of co-contraction is evident throughout the pedalling cycle in both limbs.

Figures 16 and 17 are scatter plots of the activity for each wheel position bin for those participants where baseline data were available ($n=6$). Heterogeneity of activity patterns is demonstrated in quadriceps, there is no clearly defined phase in which the muscle is either fully active or off for all participants (figure 16).

In hamstrings (figure 17), whilst the data are largely scattered, some patterning is evident contrary to that which might be expected during pedalling- higher activity levels are demonstrated in the earlier i.e. extensor phases of the wheel, with less activity in the later phases.

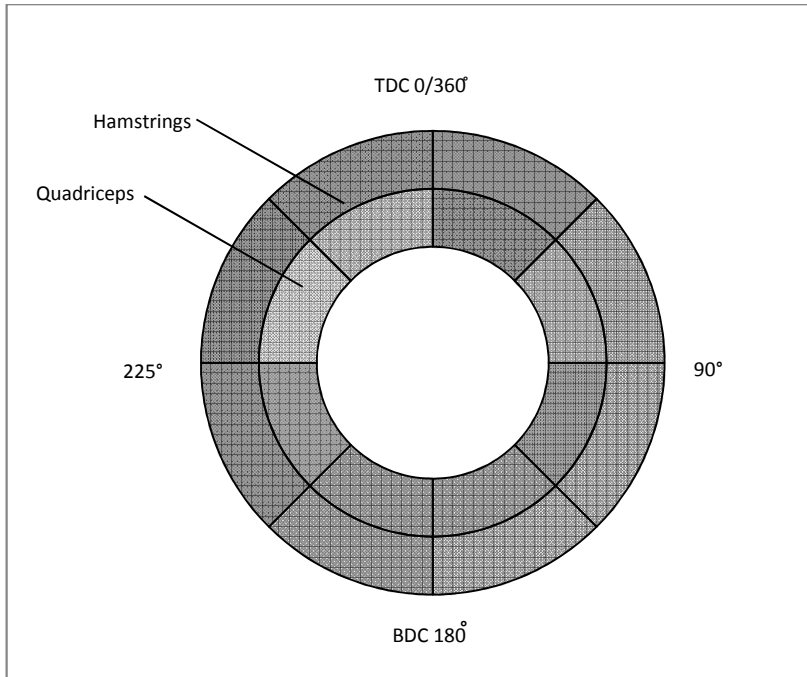


Figure 15a: Phase diagram; PED09, baseline affected leg (left), demonstrating onset/offset of quadriceps and hamstrings muscle activity according to angle.

Participant scores: Days=4, FAC=0/5, MI=70/100, S-Ped=0.068, J (aff leg)=0.288, J (unaff leg)=0.531

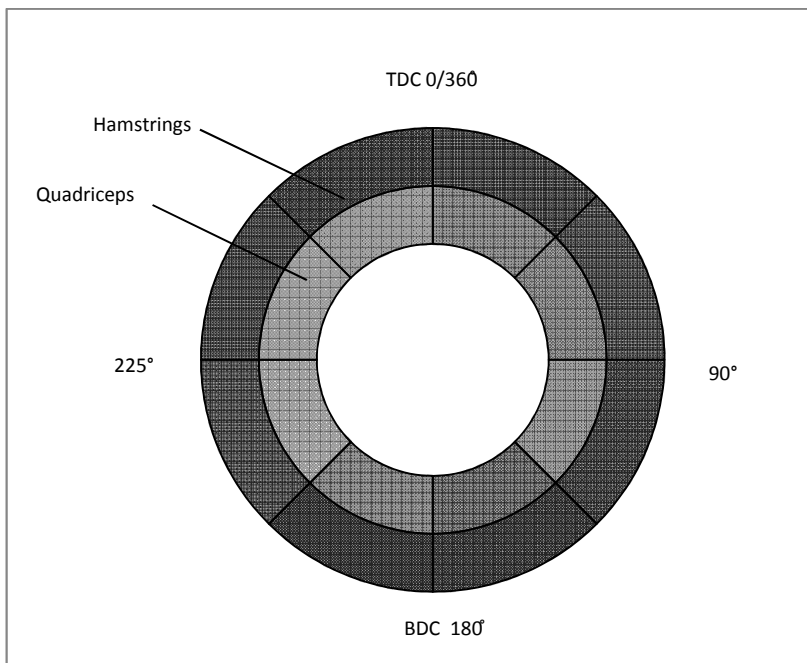


Figure 15b: Phase diagram; PED09, baseline unaffected leg (right), demonstrating onset/offset of quadriceps and hamstrings muscle activity according to angle.

Key: Outer circle= hamstrings, Inner circle= Quadriceps; Dark= Muscle on, Pale= Muscle off, Mixed shade= partially on/off graded shading; TDC= top dead centre, BDC= bottom dead centre. Abbreviations: Days=days since stroke onset, FAC=Functional Ambulatory Categories MI=Motricity Index lower limb, S-Ped=smoothness J aff=reciprocity affected leg, J unaff=reciprocity unaffected leg

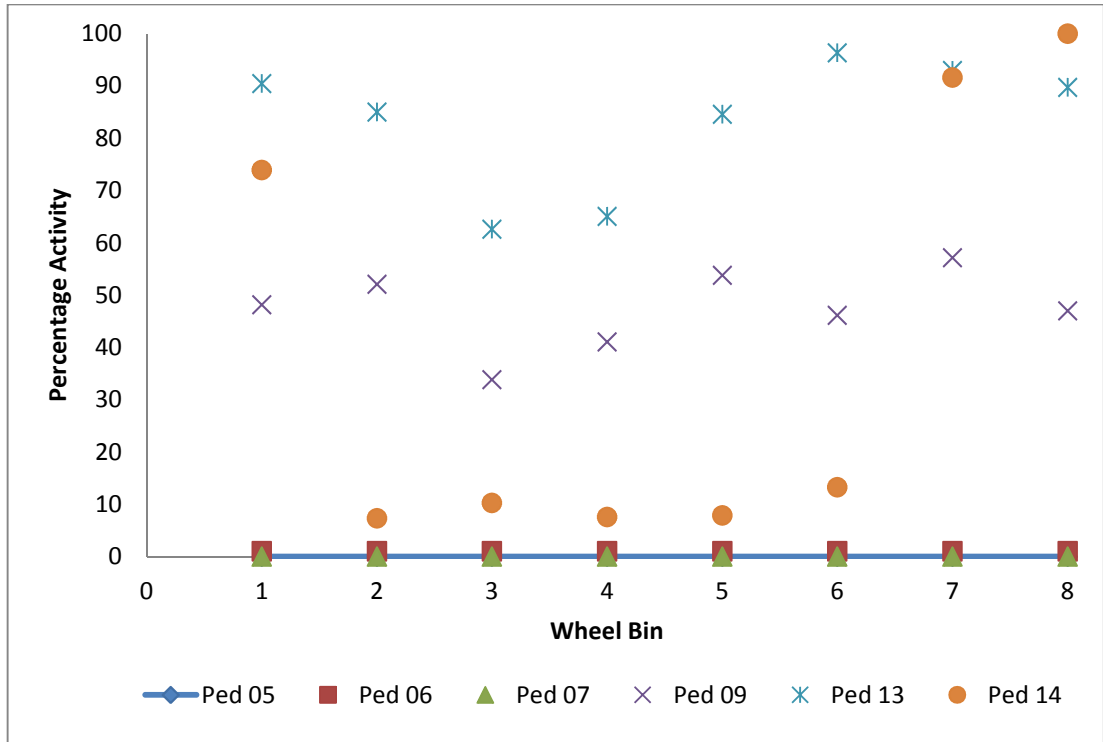


Figure 16: Scatter plot (n=6 participants) demonstrating percentage activity at baseline for affected limb quadriceps muscles according to wheel position bin

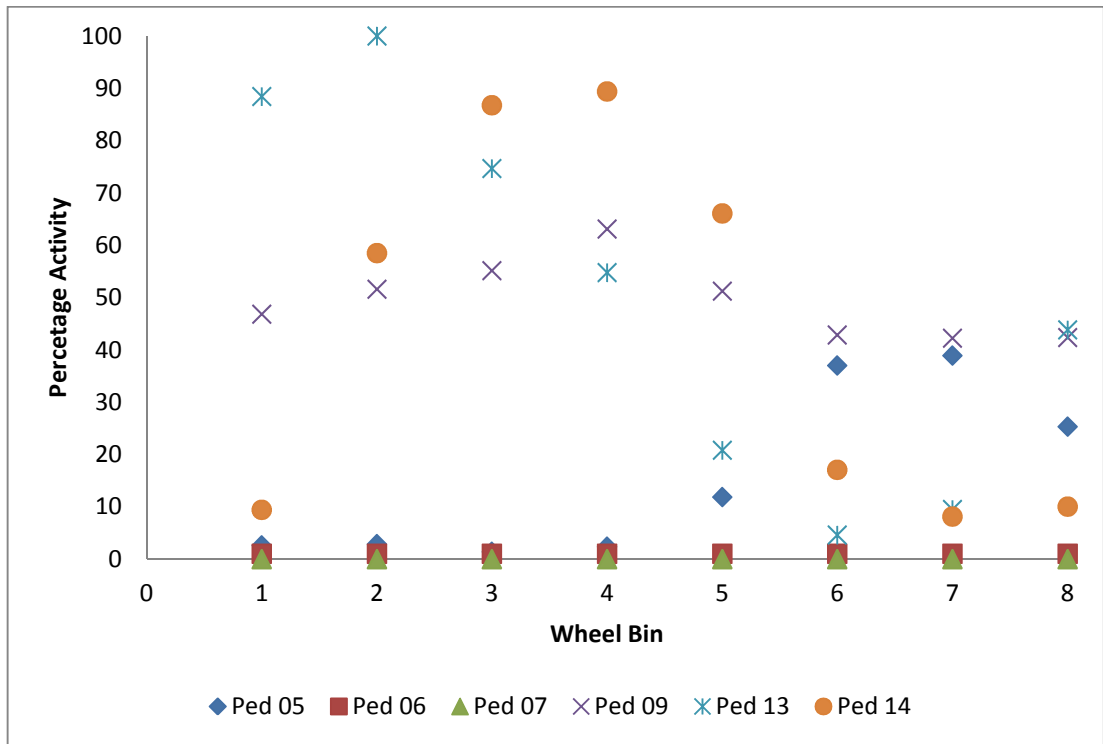


Figure 17: Scatter plot (n=6 participants) demonstrating percentage activity at baseline for affected limb hamstring muscles according to wheel position bin

5.11.7 Determining whether there is sufficient evidence for UP to justify proceeding to a larger clinical trial; including investigation of potential clinical efficacy, potential prognostic indicators and adverse events for early stroke survivors using UP (aims 3c, 3e, 3f.)

In this feasibility study, 4.6 % (n=19) of those early stroke survivors screened were eligible to participate. Only 2.2 % (n=9) were randomised with no participants taking part in UP on ten consecutive days in the acute stroke unit setting. No adverse events were recorded in the group of early stroke survivors participating in this study.

There was, therefore, insufficient data available from the study to address aims 3c and 3e, either to examine potential prognostic indicators or potential efficacy.

Clinical measures scores and measures of muscle onset/offset, reciprocity of muscle activity and smoothness were available for a small number of participants in both control and intervention groups at a variety of time points (tables 15a and 15b, 16a and 16b, 17a and 17b)

For smoothness of pedalling (S-Ped), baseline and outcome data were available for only one intervention group participant (PED 09: baseline S-Ped=0.068, outcome S-Ped=0.052) and one control participant (PED 03: baseline S-Ped=0.016, outcome S-Ped=0.018) (table 15b).

Some patterns do emerge from the data in tables 15a and 15b. For example, smoothness scores were higher at higher pedalling cadences. For sessions where cadences were above 40rpm, mean smoothness scores were higher (n=8 pedalling sessions; S-Ped= 0.028), than sessions where cadences were below 40rpm (n=10 pedalling sessions; S-Ped=0.058). The lowest smoothness score was achieved at the lowest cadence (PED13; S-Ped 0.164, rpm=18.0).

For reciprocity of muscle activity, quantified using Jaccard's correlation, these data were available at baseline and outcome for only one participant (PED 09: baseline J affected leg=0.288, J unaffected leg =0.531; outcome J affected leg=0, J unaffected leg=0.074) (table 16b). The affected leg demonstrated an improvement following the intervention. At both measurement points here the unaffected leg

demonstrated less reciprocal activity than the affected leg. Indeed, for the only three baseline data sets for which J was calculable, this was the case (PED 09: J unaffected leg=0.531, J affected leg=0.288; PED 13: J unaffected leg=0.608, J affected leg=0.468; PED 14: J unaffected leg=0.245, J affected leg=0.053) (tables 16a and 16b)

Clinical measures were recorded at outcome for four control and two intervention participants (tables 17a and 17b). This amount of data is insufficient to contribute to evaluations of potential efficacy.

5.11.8 Summary

In summary of this section of the research, despite the challenges faced in relation to attrition during this clinical research, sufficient data were collected during the study to address aims 2a, 3a, 3b and 3d and hence to establish that:

- 4.6% (n=19) of those early stroke survivors screened were eligible to participate in the study.
- 84.6% (n=11) of early stroke survivors that made an initial attempt (n=13) could take part in Upright Pedalling (aims 3a and 3b)
- 2.2 % (n=9) of those early stroke survivors screened were randomised, with no participants taking part in UP on ten consecutive days in the acute stroke unit setting.
- U-PeD could be instrumented to enable derivation of measures during reciprocal pedalling early after stroke (aim 2a)
- lower limb movement could be characterised during UP and provide physiological insights into the movement strategies adopted by early stroke survivors during pedalling (aim 3d)
- it was not possible to provide the intervention for ten days on the acute unit where this research was sited (aim 3b)
- It was not possible to establish whether there were any clinical characteristics that indicated which individuals were able to take part in UP nor whether there was sufficient evidence of efficacy to justify proceeding to subsequent trials at this stage (aims 3c and 3e).

- No adverse events were recorded in this group of early stroke survivors (aim 3f)

Table 15a: Baseline and Outcome smoothness scores and pedalling cadence, where available, for participants randomised to control group.

Participant	Randomised	Baseline		Day 1		Day2		Day3		Day4		Outcome	
		Smoothness	Rpm	Smoothness	Rpm	Smoothness	Rpm	Smoothness	Rpm	Smoothness	Rpm	Smoothness	Rpm
Ped 03	Control	0.016	41.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.018	41.5
Ped 05	Control	0.136	20.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Not available	Not available
Ped 08	Control	Not available	Not Available	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.007	66.0
Ped 13	Control	0.164	18.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Not available	Not available

Table 15b: Baseline and Outcome smoothness scores and pedalling cadence, where available, for participants randomised to intervention group.

Participant	Randomised	Baseline		Day 1		Day2		Day3		Day4		Outcome	
		Smoothness	Rpm	Smoothness	Rpm	Smoothness	Rpm	Smoothness	Rpm	Smoothness	Rpm	Smoothness	Rpm
Ped 04	Intervention	0.047	39.5	Not Available	Not available	0.014	38.04	2 days Only	2 days only	2 days only	2 days only	Not available	Not available
Ped 06	Intervention	0.012	53.2	0.028	36.7	0.035	36.4	0.033	36.7	0.018	30.8	Not available	Not available
Ped 07	Intervention	0.012	43.1	No intervention	No intervention							Not available	Not available
Ped 09	Intervention	0.068	37.5	0.051	47.1	0.055	43.3	2 days Only	2 days Only	2 days only	2 days only	0.052	44.6
Ped 14	Intervention	0.065	28.1	No intervention	No intervention							Not available	Not available

Abbreviations: n/a: not appropriate as control group participant. Not available: data not available, see table 11. Ped 10 and 11 unable to pedal; Ped 12 no attempt as unwell

Table 16a: Baseline and Outcome reciprocity scores, expressed as J- values, where available, for participants randomised to control group

		J value score												
Participant	Randomised	Baseline		Day1		Day2		Day3		Day4		Outcome		
		Aff leg	Unaff leg	Aff leg	Unaff leg	Aff leg	Unaff leg	Aff leg	Unaff leg	Aff leg	Unaff leg	Aff leg	Unaff leg	
Ped 05	Control	No qds activity	0.005	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Not available	Not available
Ped 08	Control	Not available	Not available	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	No quads activity	0.034
Ped 13	Control	0.468	0.608	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Not available	Not available

Table 16b: Baseline and Outcome reciprocity scores, expressed as J- values, where available, for participants randomised to intervention.

		J value score												
Participant	Randomised	Baseline		Day1		Day2		Day3		Day4		Outcome		
		Aff leg	Unaff leg	Aff leg	Unaff leg	Aff leg	Unaff leg	Aff leg	Unaff leg	Aff leg	Unaff leg	Aff leg	Unaff leg	
Ped 04	Intervention	Not available	Not available	Not available	Not available	No qds activity	0.039	2 days only	2 days only	2 days only	2 days only	2 days only	Not available	Not available
Ped 06	Intervention	No muscle activity	No hams activity	No quads activity	No hams activity	No quads activity	0.0004	1.0	0.595	1.0	1.0	1.0	Not available	Not available
Ped 07	Intervention	No muscle activity	0.038	No intervent	No intervent.	No intervent	No intervent	No intervent.	No intervent.	No intervent.	No intervent.	No intervent.	Not available	Not available
Ped 09	Intervention	0.288	0.531	0	0.118	No hams activity	0.0008	2 days only	2 days only	2 days only	2 days only	2 days only	0	0.074
Ped 14	Intervention	0.053	0.245	No intervent.	No intervent.	No intervent	No intervent	No intervent.	No intervent.	No intervent.	No intervent.	No intervent.	Not available	Not available

Abbreviations: where table states no muscle activity, this is no recorded muscle activity above baseline; No intervent= no intervention, reasons as per table 11; n/a= not appropriate as control group participant

Table 17a: Baseline and Outcome Motricity Index and Functional Ambulatory Categories scores, where available, for participants able to pedal; control group

Participant	Randomised	MI (/100)		FAC (/5)	
		Baseline	Outcome	Baseline	Outcome
Ped 03	Control	29	39	0	1
Ped 05	Control	38	70	0	0
Ped 08	Control	38	48	0	0
Ped 13	Control	29	39	0	0

Table 17b: Baseline and Outcome Motricity Index and Functional Ambulatory Categories scores, where available, for participants able to pedal; intervention group

Participant	Randomised	MI (/100)		FAC (/5)	
		Baseline	Outcome	Baseline	Outcome
Ped 04	Intervention	59	76	0	0
Ped 06	Intervention	78	Unwell	0	Unwell
Ped 07	Intervention	33	Transferred	0	Transferred
Ped 09	Intervention	70	76	0	2
Ped 14	Intervention	64	Transferred	0	Transferred

Chapter 6.0: Reliability, Validity and Discriminative Ability of Measures derived during Instrumented Upright Pedalling

6.1 Introduction

Results of the clinical pedalling study (Chapter 5.0) demonstrated that it was possible to derive measures of lower limb motor impairment during instrumented UP activity; and to use these measures to assess and characterise lower limb movement early after stroke. Therefore, the measures under investigation in this section of the thesis were those derived for, and first used in, the earlier feasibility study. Indeed, the development and testing of measures for subsequent trials evaluating complex interventions is one recognised objective of such feasibility work (Craig et al. 2008).

The reliability, validity and discriminative ability of these measures between stroke survivors and older adults without brain lesions, have not been explored to date.

The purpose of this chapter is, therefore, to investigate the test-retest repeatability, concurrent validity and discriminatory ability of the pedalling measures. This chapter presents the methods and results of the investigation of aims 2b, 2c, and 2d.

6.2 Design and Setting

This was a clinical observational measurement study in a university laboratory. It was not considered necessary to move the equipment to a clinical setting for this development stage of the potential measure; the feasibility of the use of this equipment for data collection in an acute clinical setting was explored in Chapter 5.0.

6.3 Participant inclusion criteria

6.3.1 Stroke survivor volunteers

To be included in the study, all participants were required to:

- *be adults aged 18+*
- *have sustained a unilateral stroke resulting in a motor hemiplegia*
- *have a resting heart rate of 90 beats per minute or less and systolic blood pressure of 100-160 mmHg.* This was set according to the safe limits decided upon for the previous clinical study in liaison with a stroke physician and the Principal Investigator
- *Score 1, 2, 3, 4 or 5 on the Functional Ambulation Categories (Holden et al. 1984).* Clinically, this means participants might require firm continuous or intermittent support of one person assisting with weight and balance; can ambulate on a level surface with standby assistance; can ambulate independently on a level surface but need assistance with non-level surfaces or can ambulate independently including on stairs and inclines. A wide range of ambulatory function was purposefully chosen in order that the reliability and validity of the measures be explored across as broad a range of stroke survivors as possible to enhance generalisability of findings
- *be able to sit unsupported for 30-seconds on the edge of a bed with feet on the floor.* This enabled safe transfer on and off the bike
- *be able to follow a one-stage command* i.e. sufficient communication, orientation and memory to participate in the measurement sessions. This ensured that participants had sufficient communication to participate in this cycling measures sessions without excluding those with aphasia

Participants were excluded if:

- *their GP indicated that participation is not appropriate*
- *they had co-existing pathology contributing to substantial impairment in the paretic lower limb e.g. osteoarthritis leading to deformity in the lower limb*

6.3.2 Healthy Volunteers

To be included in the study, all participants were required to:

- *be adults 50 years of age or over*
The majority of strokes continue to occur in the older population (British Heart Foundation Coronary Heart Disease Statistics 2010), therefore this criterion optimised comparisons made with stroke survivors
- *be independent in community ambulation*
This ensured that those volunteering did not have any obvious mobility limitation that might influence data collected
- *have a resting heart rate of 90 beats per minute or less and systolic blood pressure of 100-160 mmHg*
- *Have no underlying condition that might limit participation in the measurement session*

Participants were excluded if:

- *they had pathology contributing to substantial impairment in the paretic lower limb e.g. osteoarthritis leading to deformity in the lower limb*

6.4 Recruitment process

6.4.1 Recruitment process: stroke survivor volunteers

To ensure that the potential new measure was relevant across the stroke population, it was important that reliability and validity of the proposed tool was explored in a group of stroke survivors who were clinically stable and with a broad range of clinical characteristics. Stroke survivors were therefore recruited from across the local community.

6.4.1i Strategy One

A number of stroke survivor support groups exist in Norfolk. The Chief Investigator (the author of the thesis) contacted the administrators of the groups, and, with their consent, presented study information at their meetings. Participant information sheets (*Appendix II*) were left with the administrator and those stroke survivors who expressed an interest after the presentation of information. Telephone contact was then made with them no less than seven days later. If they were still interested in participating, either a) a home visit was arranged to discuss the study further and seek informed consent; or, b) the researcher returned to the next stroke group meeting to answer any questions and seek informed consent; according to the potential participant's choice. At this point, the screening characteristic of Functional Ambulation was also assessed to avoid an unnecessary visit to the laboratory. However, it was anticipated that the majority of participants would meet this criterion as the category was purposefully broad (see inclusion criteria section 6.3.1).

Immediately following provision of informed consent, an information letter and study summary (*Appendix II*) was sent to the participant's GP. Seven days were allowed for the GP to express any medical concerns about participation.

Participants were then given an appointment to attend the laboratory. A wide range of measurement session days were available to ensure that participants could attend at their convenience as far as was possible.

6.4.1ii Strategy Two

In addition to the above procedure, recruitment posters were designed in collaboration with the UEA Faculty of Medicine and Health Enterprise and Engagement team (*Appendix II*). These posters were placed in public areas of the local community including libraries and religious institutions, in order to broaden opportunities for participation. Potential participants were invited to contact a member of the research team to express interest in the study.

6.4.1iii Strategy Three

Approximately half way through the study period, it was recognised that most local stroke groups had been spoken to and posters were not yielding new participants.

A minor amendment was submitted to Norfolk REC requesting permission to contact stroke survivors who had completed another rehabilitation trial being undertaken by the Restorative Neurology Group at UEA, the *FesTivaLS* trial (09/H0308/147). The amendment was approved and involved the research assistant on the *FesTivaLS* trial making initial contact with potential participants. Those expressing interest were then sent information sheets and telephone contact was made with them seven days afterwards by the Chief Investigator of the measurement study. Questions were answered and, if definite interest was expressed, consent forms were posted out to this set of participants. On receipt of the completed consent forms, contact was made with the participant's GP and the process continued exactly as 6.4.1i

6.4.2 Recruitment process: Healthy Volunteers

Posters (*Appendix II*) were placed around the University of East Anglia (UEA) site, as well as the venues in 6.4.1ii, inviting expressions of interest in the study. Potential volunteers were then sent information sheets and the researcher contacted them one week later. If they remained interested in participating, the researcher offered to visit them at a location on the UEA site convenient to them in order to seek informed consent. Some volunteers expressed a wish to sign consent on their visit to the laboratory for the measurement session and this was accepted.

Again, a wide range of measurement session days were available to ensure that participants could attend at their convenience as far as is possible.

6.5 Sample size

Previous work on the reliability of pedalling derived measures, that might have informed a sample size estimate, is extremely limited. At the outset of the study design, only Dorel et al. (2008) and Laplaud et al. (2006) had explored repeatability of EMG pedalling measures; Dorel et al. (2008) recruited eleven tri-athletes and Laplaud et al. (2006) recruited eight young cyclists. Whilst these were clearly small observational measurement studies, neither study made any attempt to justify sample size or to use the data collected to suggest sample sizes for other studies.

In determining sample size for this study, the pragmatics of time constraints were balanced with statistical requirements i.e. the need for a sufficient sample size to yield a precise estimate of the reliability coefficient, with sufficiently narrow confidence intervals, in a reasonably short data collection period. In consultation with a Professor of Medical Statistics, it was estimated that 30 participants would be the minimum number required to meet statistical requirements. This closely concurs with the view of Eilasziw et al. (1994) on appropriate methodology for assessing reliability of rehabilitation instruments. The sample size for the stroke survivors group was therefore set at 30 over a data collection period of three to six months. It was anticipated that the sample would be divided into three groups of ambulatory ability for data analysis- those with an FAC of 1 and 2, those with an FAC of 3 and 4 and the most mobile with an FAC of 5.

Ten age-matched (>50 years) healthy volunteers were recruited for the comparison group.

6.6 Overview of Procedure

6.6.1 Procedure for stroke survivors

Common procedures for the measurement sessions were described in section 6.7.

On arrival, participants were shown the research equipment and the procedure explained in full again.

The researcher then measured the participant's heart rate and blood pressure to ensure that they were within the safe limits set for the study on the measurement day.

Participants were helped to position themselves comfortably on the bike and EMG electrodes attached. Following recording of resting data, they were asked to pedal for one minute to familiarise themselves with the equipment. They were then asked to pedal for a further minute whilst EMG data was recorded.

It was anticipated that stroke survivors with a variety of clinical characteristics would demonstrate various comfortable pedalling speeds and therefore a fixed pedalling cadence was not set for this study with participants who were later after stroke. However, participants were asked to replicate the comfortable speed achieved in the initial measurement session during the second measurement session as closely as possible.

Following an initial minute of pedalling, and allowed to rest comfortably in the lab for 30 minutes to an hour.

They were then helped back onto the bike and the measurement session above repeated exactly. A single rater was responsible for placing the electrodes and recording both measurement sessions.

6.6.2 Procedure for healthy volunteers

On arrival, and following provision of informed consent, participants were shown the research equipment and the procedure explained in full.

The researcher then measured the participant's heart rate and blood pressure to ensure that they were within the safe limits set for the study on the measurement day.

Participants were positioned comfortably on the bike, electrodes placed and resting data collected.

Participants were then asked to pedal at their comfortable speed, for one minute, to familiarise themselves with the equipment and testing procedure. They were then asked to pedal for one minute at each of five different speeds from 10-50 rpm, with a short rest in between each minute. EMG data was recorded for each pedalling speed.

A range of different cadences was chosen for the healthy volunteer group in order that comparisons might be made with possible cadences used by stroke survivors. In the experimental study 2 presented in Chapter 7.0, participants were asked to pedal at up to 50rpm; at baseline, cadences were demonstrated from 18 to 54rpm and so a range of 10rpm to 50rpm was adopted for the current study. It was anticipated that a range of cadences in older healthy adults might better inform the interpretation of possible movement strategies adopted by stroke survivors during UP; and, a more accurate interpretation of discriminative ability could be made by assessing at different speeds. Furthermore, it is noteworthy that the only previous studies examining reliability of EMG measures during pedalling used young adults and tri-athletes at high cadences, challenging generalisability to an older participant group.

Heart rate was monitored to ensure it did not exceed 85% age predicted maximum $((220 - \text{age}) \times 0.85)$.

Participants were then asked to rest for 30 minutes to an hour, and the pedalling session at the five speeds above repeated exactly.

6.7 Measurement battery

6.7.1 Stroke survivor participant characteristics

- age,
- gender,
- time since stroke onset,
- ambulatory ability, as measured by the FAC; degree of motor impairment of the hemiplegic lower limb, as measured by the Motricity Index.

6.7.2 Healthy volunteer participant characteristics

- age
- gender

6.7.3 Clinical measures:

6.7.3i The Motricity Index was selected as the commonly used clinical measure for examination of concurrent validity. Evidence for it being a commonly adopted clinical measure has been published (Turner-Stokes and Turner-Stokes, 1997).

6.7.3ii The Functional Ambulation Categories (Holden et al. 1984) were used to assess walking ability. It is not currently known whether upright pedalling measures might reflect a stroke survivor's current ambulatory status.

Lower limb motor impairment during upright pedalling was characterised using surface EMG of quadriceps and hamstring muscles in the following manner:

6.7.3iii Onset and offset of EMG activity of antagonistic muscle groups during pedalling: this measure, and the processing carried out to derive of the calculations of onset and offset of activity were as described in detail in sections 6.4.3iii 6.5.1.

6.7.3iv Reciprocal activation of antagonistic muscle groups during pedalling: this measure and the statistic used to quantify reciprocity were as described in detail in section 4.5.2.

6.7.3v Smoothness of pedalling (S-Ped): this measure and the processing carried out to quantify S-Ped were as described in detail in section 4.5.3

Outcomes for this study were therefore: degree of discriminatory ability for UP measures between stroke survivors and healthy volunteers; test/retest repeatability of UP as a measure of motor impairment after stroke; degree of agreement between the Motricity Index and UP as a measurement of motor impairment after stroke (concurrent validity); degree of agreement between upright pedalling after stroke and current ambulatory status.

6.8 Analysis

Intra-class Correlation Coefficients plus 95% confidence intervals together with limits of agreement were used for end analysis of test-retest repeatability. This is an accepted method for evaluating measurement repeatability (Bland et al. 1990).

Two-sample t-tests with 95% confidence intervals (or analogous non-parametric methods) were used for discriminating differences between stroke survivors and healthy volunteers, for the measures of reciprocity and smoothness; and for the measures of muscle activation according to wheel position bin, a repeated measures ANOVA was initially used, followed by a Principal Components Analysis (PCA). The use of the PCA is described more fully in the study results.

Spearman's rank correlation coefficient was used to quantify association between each UP measure and the Motricity Index and Functional Ambulatory Categories.

6.9 R&D governance

The research study received the approval of the Norfolk Research Ethics Committee, UK (11/EE/0002; *Appendix II*)

6.10 Financial Implications for participants

Participants were reimbursed for travel costs to and from the laboratory.

Taxis were booked and funded for those participants who are unable to travel by other means.

Funding was available through a small amount of general research monies previously allocated to the Restorative Neurology Group at UEA.

6.11 Adverse Reactions

Adverse reactions were considered highly unlikely in this study, but there was the possibility that participants might experience an adverse reaction of aching/discomfort in the lower limb during pedalling- this was monitored for throughout each test session and it was planned that testing would cease immediately if the participant and/or researcher made such an observation and deemed it necessary to stop.

6.12 Potential risks and benefits

Potential risks for participants and researchers in this study were considered very small.

All staff were trained in the appropriate manual handling procedures required for the study and a current risk assessment and appropriate insurances were in place for the use of the exercise bike in the measurement laboratory. The bike had been used safely with early stroke survivors in two previous feasibility studies (unpublished, Wandsworth local REC, UK, 03.0102 and Essex 1 REC, UK, 09/H0301/52; Hancock et al. 2011).

There were no specific benefits for participants excepting their inclusion in a novel research trial that might influence future stroke rehabilitation research and practice.

6.13 Results

The purpose of this section is to present the results of the experimental measurement study.

The measurement of motor impairment by UP was expressed by reciprocal activation of antagonistic muscle pairs, muscle activation timing (onset and offset of activity) and smoothness of pedalling. The derivation of these measures from EMG data and kinematic data recorded during UP is described fully in Chapter 4.0.

Where comparisons have been made between data sets for healthy volunteers and stroke survivors, data collected at 40rpm for the healthy volunteers was used as this most closely reflected the mean pedalling cadence of the stroke survivors (41.4 rpm)

Data collected from the right leg of the healthy volunteers was used in the analysis except for one session in which external noise affected the right leg channels during data collection and hence the data from the participant's left leg were used (HV08). Data collected from both the affected and unaffected legs was used for the stroke survivors.

According to the algorithms presented in sections 4.4.3i & 4.4.3iii, for the stroke survivor group, one data set required additional filters to be applied and one data set required the resting threshold to be raised. For the healthy volunteer group, one data set required additional filtering and two required the resting threshold to be raised.

Analyses were carried out in Statistical Analysis System (SAS) version 9.2.

6.13.1 Participant Characteristics

It was intended that 30 stroke survivors be recruited to the study; 26 were actually recruited during the study period. Ten healthy older adults were recruited as planned.

Participant characteristics are as detailed in Tables 18 and 19.

One stroke survivor participant did not attend their appointment as arranged; the final number attending was therefore 25.

Following initial measurement of blood pressure and heart rate as per inclusion criteria, six (24%) were unable to take part due to blood pressure recorded as above study limits.

One participant felt unwell at the beginning of a session and measures were not pursued.

Ten male and eight female stroke survivors were measured in the study, with a mean age of 60.78 years (range 41.25 to 75.83) (table 18). The Motricity Index lower limb scores ranged from 38 up to 92 and Functional Ambulatory Categories ranged from 1 to 5.

All eighteen participants who were eventually included successfully pedalled the upright bike for at least one minute during each of two measurement sessions. No adverse reactions were recorded.

Six (60%) of the healthy volunteer group were male and the mean age of participants was 58 years (table 19). Data were successfully recorded for all ten participants. For one participant (HV03), data were re-recorded at a later date due to excessive external noise displayed on all channels of the EMG recording equipment during the first session.

Table 18: Baseline Characteristics Stroke survivors

Abbreviations: M= male, F=female,R=right, L=left, BP= blood pressure, ASL= above study limits

Participant	Age (years)	Time since stroke onset (years)	Gender	Weaker side	MI Score (lower limb /100)	FAC Score(/5)	Measurements completed (Y or N; if N reason stated)
RePed, STK 01	58	1.5	M	Right	92	5	Y
RePed, STK 02	70	3.0	F	Left	84	4	Y
RePed, STK 03	58	4.3	M	Right	48	1	Y
RePed, STK04	63	-	F	-	-	-	N: BP ASL
RePed, STK 05	70	1.2	M	Left	84	4	Y
RePed, STK 06	71	12.7	F	Left	78	4	Y
RePed, STK 07	66	22.6	F	-	-	-	N: Felt unwell
RePed, STK 08	66	17.6	M	-	-	-	N: BP ASL
RePed, STK 09	41	19.8	F	Left	65	4	Y
RePed, STK 10	57	5.8	M	Right	49	2	Y
RePed, STK 11	75	10	M	Right	38	1	Y
RePed, STK 12	69	3.5	M	Right	53	5	Y
RePed, STK 13	58	5.8	M	Right	43	2	Y
RePed, STK 14	47	9.3	F	Right	65	4	Y
RePed, STK 15	51	10.7	F	Left	76	4	Y
RePed, STK 16	53	6.0	F	Right	51	1	Y
RePed, STK 17	79	14.3	M	-	-	-	N: BP ASL
RePed, STK 18	82	2.1	F	-	-	-	N: BP ASL
RePed, STK 19	62	4.6	M	Right	92	3	Y
RePed, STK 20	-	-	-	-	-	-	N: Did not attend appointment
RePed, STK 21	85	2.1	M	-	-	-	N: BP ASL
RePed, STK 22	51	1.7	M	Right	60	2	Y
RePed, STK 23	71	5.2	M	Left	65	4	Y
RePed, STK 24	47	2.8	F	Right	73	5	Y
RePed, STK 25	75	6.1	F	Left	76	2	Y
RePed, STK26	62	1.8	M	-	-	-	N: BP ASL
Mean (range)	61 (41 to 75)	6.3 (1.2 to 19.8)	10/18 M	11/18 R	66.2 (38 to 92)	3 (1 to 5)	18 completed session

Table 19: Baseline Characteristics, Healthy volunteers

Participant	Age (years)	Gender (M=male, F=female)	Measurements completed (Y or N; if N reason stated)
RePed, HV01	56	M	Y
RePed, HV02	52	F	Y
RePed, HV03	54	M	Y*
RePed, HV04	59	F	Y
RePed, HV05	62	F	Y
RePed, HV06	56	M	Y
RePed, HV07	53	M	Y
RePed, HV08	64	M	Y
RePed, HV09	68	F	Y
RePed, HV10	51	M	Y
Summary	Mean 58 (range 51 to 68)	4/10 F	10 completed

*During first attempted measurement session date, excessive external noise on the EMG signal was detected across all channels; hence the participant re-attended at a later date to repeat the measures, successfully

6.13.2 Discriminative ability between stroke survivors and healthy volunteers (aim 2c.)

Table 20 presents the results of the test for discriminatory ability of the measures of reciprocity and smoothness of pedalling, between healthy volunteers and stroke survivors. Where data was normally distributed, a two-sample t-test was used, otherwise a two-sample Wilcoxon test was used.

Whilst 18 data sets were recorded from the stroke survivors, for the reciprocity measure, 15 sets were available after processing for the affected limb and 17 for the unaffected limb. This was due to marked external noise during one measurement session, and in two cases for the affected limb, there was no muscle activity above baseline from which to calculate the J-value.

Table 20: Results of analysis of discriminatory ability between stroke survivors and healthy volunteers for the measurement of lower limb motor impairment by UP: reciprocity and smoothness

Measurement expressed by:		Healthy Volunteers	Stroke survivors	Difference (95%C.I) p-value
Reciprocity (affected limb)	N	10	15	-0.249
	Mean	0.248	0.500	(-0.491 to -0.010)
	StdDev	0.081	0.305	P=0.044 ¹
Reciprocity (unaffected limb)	N	10	17	-0.146
	Mean	0.248	0.393	(-0.379 to 0.087)
	StdDev	0.081	0.298	P=0.208 ¹
Smoothness	N	10	18	-0.003
	Median	0.014	0.017	P=0.367 ²
	Semi IQR	0.0015	0.0050	

1: two-sample *t*-test 2: two-sample Wilcoxon test

The only measure that was significantly different between the healthy volunteers and the stroke survivors was reciprocity of movement in the affected limb of the stroke survivors ($p=0.044$). Muscle activity in the affected limb of the stroke survivors was significantly less reciprocal than in the measured limb of the healthy volunteers.

There were no significant differences between reciprocal activity in the unaffected limb of the stroke survivors and the measured limb of the healthy volunteers ($p=0.208$).

There were no significant differences between stroke survivors and healthy older adults in terms of smoothness of activity ($p=0.367$); in fact, mean smoothness values in each group were very similar, though standard deviations around the mean in the stroke survivors were wider.

Table 21 presents the results of the test for discriminatory ability for the measure of muscle activation timing.

From analysis with repeated measures ANOVA, using mean percentage of activity across wheel bins for both healthy volunteers and stroke survivors, no difference was demonstrated for either quadriceps ($p= 0.111$) or hamstrings ($p= 0.347$).

Table 21: Results of analysis of discriminatory ability between stroke survivors and healthy volunteers for the measurement of lower limb motor impairment by UP: muscle activation timing

Muscle	Wheel Bins	Percentage activity on		p-value ¹
		Healthy volunteers N=10	Stroke Patients N=17	
Quadriceps	1	84.3	71.7	Group: p = 0.111 Bins: p = 0.034 Bin*Group: p = 0.084
	2	74.7	68.3	
	3	58.8	69.4	
	4	27.7	76.4	
	5	37.2	77.7	
	6	62.2	82.2	
	7	89.4	83.0	
	8	98.5	79.6	
Hamstrings	1	32.3	56.8	Group: p = 0.347 Bins: p = 0.202 Bin*Group: p = 0.240
	2	36.8	60.8	
	3	47.9	68.3	
	4	58.5	70.3	
	5	63.6	68.9	
	6	44.0	68.5	
	7	35.5	51.4	
	8	34.0	50.9	

¹ Based on Wilk's Lambda from a Multivariate Analysis of Variance; **Group**=between-groups comparison of mean activity across each turn, **Bins**=difference between percentage activity 'on' between bins. i.e. comparison of activity in each position bin; **Bin*Group**=significance of pattern of activity, between groups.

However, for differences expressed over the eight different wheel bins across the two groups, a significant difference was found for quadriceps muscle (p= 0.034). This demonstrates that the percentage of muscle activity 'on' was dependent on the wheel position bin. Hence, across the two groups of participants, there was heterogeneity when examining quadriceps activity per wheel bin.

Analysing the interaction between wheel bin and group i.e. the pattern of activity over specific wheel bins between groups, a non-significant, though borderline, difference was found between the pattern of quadriceps activity for stroke survivors and healthy volunteers (p=0.084).

Due to this suggestion of discriminatory ability according to the ANOVA, an additional analysis was carried out using Principal Components Analysis (PCA) to further explore these data. PCA seeks patterns in correlated data sets using orthogonal transformations. It attempts to reduce the data to a smaller number of variables accounting for as much of the variation as possible. These results are presented in table 22.

For both quadriceps and hamstrings, 81.4% of the variance in the data was accounted for in principal components one and two (table 22). Adding a third component accounted for only another 10.8% of the variance (92.2% total).

Interpretation of component one of the analysis, which represents the general level of activity during pedalling, demonstrates that there was no significant between groups difference, suggesting similarity of activity level between the groups for both quadriceps ($p=0.493$) and hamstrings ($p=0.178$).

Interpretation of principal component two for quadriceps muscle demonstrates a contrast between bins. There are definite positive and negative loadings for the healthy volunteers, suggested by the positive mean component score when this component is applied across all healthy volunteers (mean component score 1.112). There is a pattern of positive loading, muscle activity, in bins 1, 2, 7 and 8 and negative loading, or little activity in bins 3, 4, 5, and 6. This pattern is illustrated in figure 18, demonstrating a pattern of activity across the wheel bins for quadriceps indicating increased activity at the end of the flexor phase of the movement and into the early extensor phase.

For the stroke survivors' data in this component, the mean component score is negative (-0.654), suggesting that the level of activity for bins 1,2,7 and 8 are relatively higher than for bins 3,4,5, and 6 in stroke survivors compared to healthy volunteers. This difference is highly significant ($p=0.001$). This significant difference is consistent with the analysis using repeated measures ANOVA (table 21), confirming indications of discriminatory ability between healthy volunteers and stroke survivors for the measure of muscle activation timing during UP for quadriceps muscles.

Table 22: Results of PCA analysis of discriminatory ability between stroke survivors and healthy volunteers for the measurement of lower limb motor impairment by UP: muscle activation timing, demonstrating components one and two.

	Position Bin	Component 1	Component 2
Quadriceps	1	0.362	0.358
	2	0.407	0.173
	3	0.416	-0.140
	4	0.281	-0.517
	5	0.345	-0.434
	6	0.393	-0.166
	7	0.332	0.256
	8	0.260	0.520
Variance (%)		54.6%	26.8%
Healthy volunteers mean component score when column component applied to data (SD)		-0.368 (2.12)	1.112 (0.918)
Stroke survivors mean component score when column component applied to data (SD)		0.217 (2.11)	-0.654 (1.334)
p-value(between groups comparison of mean component score)		p=0.493	p=0.001
Hamstrings	1	0.351	-0.433
	2	0.380	-0.266
	3	0.385	0.058
	4	0.347	0.404
	5	0.312	0.520
	6	0.373	0.300
	7	0.351	-0.126
	8	0.323	-0.456
Variance (%)		63.5%	19.3%
Healthy Volunteers mean component score when column component applied to data (SD)		-0.771 (1.902)	0.143 (1.411)
Stroke survivors mean component score when column component applied to data (SD)		0.453 (2.372)	-0.084 (1.167)
p-value(between groups comparison of mean component score)		p=0.178	p=0.656

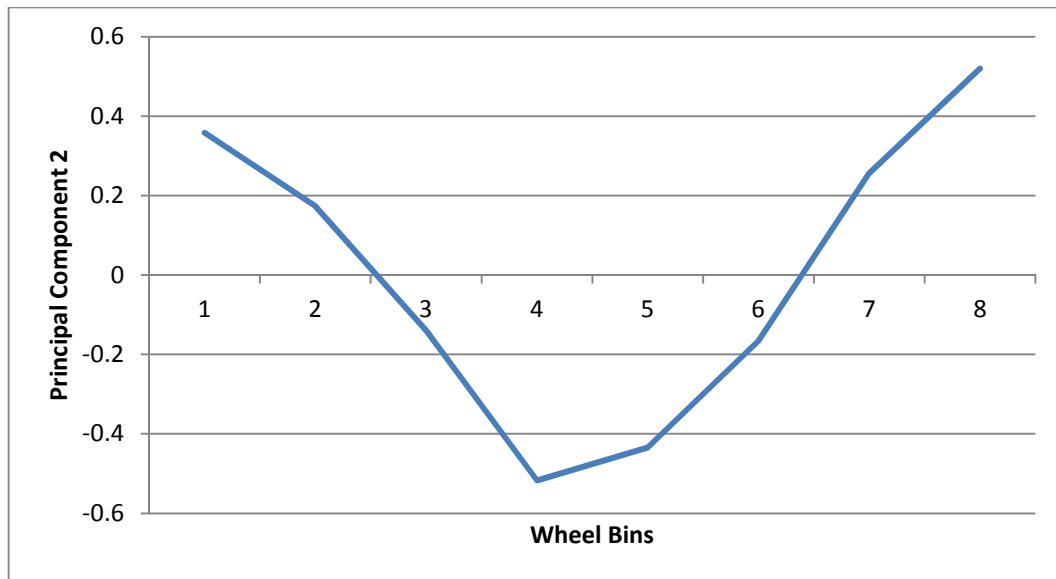


Figure 18: Plot illustrating principal component 2 for quadriceps (combined data), demonstrating contrast in activity levels between wheel position bins

6.13.3 Test-retest repeatability of the measurement of motor impairment by UP (aim 2b.)

Interpretation of the ICC values was guided by methods employed by Eliasziw et al. (1994); 0.0-0.20=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial, 0.81-1.00=almost perfect. The lower limit of the 95% confidence interval was used to delineate the category.

6.13.3i Test-retest repeatability of measurement of muscle activation timing

Table 23: Results of analysis of test-retest repeatability for muscle activation timing

	N (bins)	ICC	95% C.I.
Healthy Volunteers			
Quadriceps	10 (80)	0.76	(0.65, 0.84)
Hamstrings	10 (80)	0.56	(0.39, 0.69)
Stroke Patients			
Unaffected Quadriceps	17 (136)	0.67	(0.56, 0.75)
Unaffected Hamstrings	17 (136)	0.21	(0.05, 0.37)
Affected Quadriceps	17 (136)	0.46	(0.32, 0.58)
Affected Hamstrings	17 (136)	0.43	(0.28, 0.56)

Table 23 presents the results of the analysis of test-retest repeatability for the measure of muscle activation timing using intra-class correlation coefficients (ICC) with 95% confidence intervals.

Some agreement between measurement sessions was demonstrated for stroke survivors and healthy volunteers in both quadriceps and hamstrings. Unaffected quadriceps in the stroke survivors demonstrated moderate correlation between sessions (ICC=0.67; 95% CI: 0.56, 0.75) and for quadriceps in the healthy volunteers, the correlation was substantial (ICC=0.76; 95% CI: 0.65, 0.84). Fair correlations were observed between test sessions for both affected quadriceps (ICC=0.46; 95% CI: 0.32, 0.58) and affected hamstrings in the stroke survivors (ICC= 0.43; 95% CI: 0.28, 0.56). The lowest value was for unaffected hamstrings in the stroke survivors, with only a slight correlation and wide confidence intervals in this muscle group between measurement sessions (ICC=0.21; 95% CI: 0.05, 0.37).

6.13.3ii Test-retest repeatability of measurement of reciprocal activation

Table 24 presents the results of the analysis of test-retest repeatability for the measure of reciprocal activation.

Table 24: Results of analysis of test-retest repeatability for reciprocal activation

	N	ICC	95% C.I.
Healthy Volunteers			
Cadence 10rpm	10	0.28	(0, 0.75)
Cadence 20rpm	9	0.18	(0,0.73)
Cadence 30rpm	9	0	(0, 0.63)
Cadence 40rpm	9	0.61	(0.10, 0.90)
Cadence 50rpm	9	0.72	(0, 0.85)
Stroke Patients			
Unaffected Limb	10	0.38	(0, 0.80)
Affected Limb	17	0.35	(0, 0.70)

The confidence intervals for all results of the analysis of test-retest repeatability of the measure of reciprocal activation were very wide. Despite ICC point estimates taken alone suggesting fair correlations for both the unaffected and affected limb of stroke survivors, and substantial correlations at faster speeds for the healthy volunteers, the wide confidence intervals illustrate imprecision in the ICC's, with lower limits of agreement at zero. This reflects the relatively low sample size and leads to an inability to reliably determine test-retest repeatability of this measure for this sample.

6.13.3iii Test-retest repeatability of measurement of smoothness of pedalling activity

Table 25 presents the results of the analysis of test-retest repeatability of the measure of smoothness of pedalling activity

Table 25: Results of analysis of test-retest repeatability for smoothness of pedalling activity

	N	ICC	95% C.I.
Healthy Volunteers			
Cadence 10rpm	10	0.46	(0, 0.83)
Cadence 20rpm	10	0.59	(0.01, 0.88)
Cadence 30rpm	10	0.12	(0, 0.67)
Cadence 40rpm	10	0.64	(0.10, 0.90)
Cadence 50rpm	10	0.52	(0, 0.85)
Stroke Patients	18	0.28	(0, 0.65)

The confidence intervals for all results of the analysis of test-retest repeatability of the measure of smoothness were very wide. ICC point estimate values taken alone suggest generally moderate correlations for healthy volunteers, except for 30rpm which, similarly to the measurement of reciprocity of activity, was low; and for stroke survivors, the ICCs suggest fair repeatability. However, the wide confidence intervals with the lower limits close to or equalling zero, illustrate imprecision in the ICCs; again, this reflects the relatively low sample size and leads to an inability to reliably determine test-retest repeatability of this measure for this sample.

6.13.4 Association between of the measurement of motor impairment by UP and the Motricity Index and Functional Ambulatory Categories (FAC)(aim2d)

Tables 26a and 26b present the results of the analysis of correlation between the pedalling measures and existing clinical measures of motor impairment and current walking ability for the stroke survivors.

Table 26a: Results of analysis of association with the Motricity Index and with current walking ability as measured by the FAC, for smoothness and reciprocity

Measure	Smoothness	Reciprocity affected limb	Reciprocity unaffected limb
Motricity Index	r=-0.375 p=0.130 N=18	r=0.278 p=0.316 N=15	r=0.075 p=0.775 N=17
FAC	r=-0.165 p=0.513 N=18	r=0.030 p=0.916 N=15	r=-0.136 p=0.604 N=17

Table 26b: Results of analysis of association with the Motricity index and with current walking ability as measured by muscle activation timing (% activity “on”)

Measure	Affected quadriceps %on	Affected hamstrings %on	Unaffected quadriceps %on	Unaffected hamstrings %on
Motricity Index	r=-0.153 p=0.06 N=17	r=0.033 p=0.899 N=17	r=0.156 p=0.549 N=17	r= -0.03 p=0.922 N=17
FAC	r=-0.223 p=0.390 N=17	r= -0.180 p=0.490 N=17	r=-0.117 p=0.656 N=17	r= 0.266 p=0.302 N=17

Using Spearman’s rank correlation coefficient, no significant associations were demonstrated between any UP measures and existing measures of impairment or walking function (tables 26a and 26b). Hence, there was no significant correlation between the EMG derived measures nor the smoothness measure and a commonly used measure of impairment, the Motricity Index. However, for the measurement of muscle activation timing (percentage of activity “on” within each position bin) in the affected quadriceps, the correlation approached statistical significance (p=0.06).

There was no significant association between the EMG derived measures nor the smoothness measure and the participants' current ambulatory status as measured by the FAC.

6.13.5 Summary of findings

In addressing aims 2b, 2c, and 2d, this study found that:

- There are indications that the measurement of lower limb motor impairment as expressed by changes in muscle activation timing has a) some discriminatory ability between stroke survivors and healthy volunteers for the quadriceps muscle; b) fair test-retest repeatability for affected side quadriceps and hamstrings in stroke survivors; c) substantial test-retest repeatability in quadriceps and fair test-retest repeatability in hamstrings in healthy older adults; and d) demonstrates a borderline significant association with a commonly used clinical measure of lower limb motor impairment, the Motricity Index
- There are indications that the measurement of lower limb motor impairment as expressed by reciprocity of muscle activity has discriminatory ability between stroke survivors (for the affected limb) and healthy volunteers
- It was not possible to make reliable estimates of the magnitude of the test-retest repeatability of the measurement of lower limb motor impairment as expressed by changes in reciprocal activation and smoothness of pedalling in this sample of stroke survivors
- There was no relationship between the measurement of lower limb motor impairment as expressed by changes in reciprocal activation and smoothness of pedalling and commonly used measures of motor impairment and walking ability.

Chapter 7.0: Discussion

7.1 Introduction

This chapter will present a critical interpretation of the findings of the studies presented in this thesis and will conclude with recommendations for future work. The discussion will be framed around the statement of aims (Chapter 2.0) and will, where appropriate, provide commentary on how the findings relate to existing published work.

7.2 Assessing the current state of the evidence about pedalling exercise after stroke

7.2.1 Summary of findings

This study investigated aims 1a and 1b, which were derived from question one, **“Does reciprocal pedalling exercise enhance motor function after stroke?”**

The synthesis indicated that there was some, but limited, support for pedalling exercise benefiting muscle activity, muscle strength, balance, and functional independence after stroke, from early phase studies. However, inter-study heterogeneity, small sample sizes, wide confidence intervals for effect sizes, and the risks of potential biases suggested that the evidence was not sufficiently robust to support or refute the use of reciprocal pedalling exercise to enhance recovery of motor function after stroke. These findings support the conclusion of a narrative review by Fujiwara et al. (2005), that while pedalling might have potential to enhance motor function in people with central nervous system disorders, further research is needed before use in clinical practice.

7.2.2 Discussion of findings

The smaller, exploratory studies included in this review showed the feasibility of using pedalling interventions after stroke (e.g. Brown et al. 2005; Perell et al. 2001, 2000). These studies also found some trends towards benefit from pedalling on measures of motor impairment, including lower limb muscle activity and muscle strength. These findings provide proof-of-concept, but insufficient evidence to support or refute the clinical use of pedalling. Risks of potential biases were high for these studies, often as a direct reflection of study design, though reports of results according to design were generally clear. However, it was this set of studies, plus one small randomised pilot study (Katz-Leurer et al. 2006) that specifically aimed to examine the effects of pedalling activity on motor function. All of the larger studies included in the review used pedalling as a form of aerobic exercise, though did include some secondary outcomes of motor function, evaluated generally using activity level measures. No large-scale study specifically designed to evaluate the effects of pedalling activity on motor function after stroke was found in this review process. Hence, evidence from the smaller studies in this review might provide precursors for later phase studies of clinical efficacy, incorporating measures of both impairment and activity.

While meta-analysis was not indicated for the RCTs, single study examination revealed large effect sizes for beneficial effects of a pedalling intervention on balance and functional independence, immediately (PASS total, effect size 1.50 [0.61, 2.43]; FIM motor, effect size 1.60 [0.69, 2.55]) and six-weeks after the intervention (PASS total, effect size 1.50 [0.60, 2.42]; FIM motor, effect size 1.47 [0.59, 2.41]; Katz-Leurer et al. 2006). However, the large effect sizes should be interpreted with caution as the sample size for this pilot study was small with 10 participants in the intervention arm and 14 in the control, confidence intervals were wide and a moderate risk of bias was evident. A small beneficial effect on balance was also demonstrated in a study of aerobic pedalling exercise immediately (Berg Balance Score, effect size 0.22 [-0.42, 0.85]) and eight weeks after the intervention (Berg Balance Score, effect size 0.27 [-0.37, 0.91] (Quaney et al. 2009), but again,

sample sizes were small with 19 in each trial arm with very wide confidence intervals that crossed zero. This study also demonstrated a lack of clarity of reporting on key elements (e.g. sequence generation). Therefore, despite these trends towards benefits, definitive, generalisable conclusions cannot be drawn about effects of pedalling on balance and functional independence.

It is noteworthy that one of the larger studies with the lowest risk of bias demonstrated small, positive, but non-significant, effects on lower limb muscle strength, (effect size 0.18 [-0.57, 0.94]) and endurance (effect size 0.16 [-0.60, 0.93]) from a pedalling intervention in 54- to 72-year olds with chronic stroke (Lee et al. 2008). A small positive effect for lower limb muscle strength possibly supported observations in the smaller studies (e.g. Perell et al. 2001, 2000). However, again, the wide confidence intervals suggest imprecision and hence a lack of generalisability for these findings. Findings of small, beneficial though non-significant, effects of pedalling exercise on muscle strength after stroke were therefore in no way definitive.

It is of interest that the mean participant age of 63 years was non-representative of the UK stroke population, where 75% of first strokes occur in those aged 65 and over (British Heart Foundation Coronary Heart Disease Statistics, 2010). Older stroke survivors may present different research and rehabilitation challenges than younger survivors. For example, the likelihood of multiple pathologies alongside the stroke may be higher, leading to extraneous reasons why participation in rehabilitation activities and research trials might be limited. Further research into pedalling exercise in an older participant group is indicated to ensure generalisability of findings to the stroke survivor population.

Over half of the included studies recruited participants greater than three months since stroke onset. It is possible that such patients are easier to recruit to exercise trials, as they are likely to be more medically stable and with less fluctuation in their abilities. However, current evidence suggests that early therapeutic intervention might optimise potential for recovery. As identified in Chapter 1.0, clinical studies

support the concept that early rehabilitation is important for improving outcomes. This review has identified that current research into pedalling as a potential therapeutic intervention has not exploited this important window, and thus results cannot be generalised to early stroke survivors. Opportunities therefore exist for further exploration of the effects of pedalling exercise in stroke survivors early after onset.

Studies included in this review used variable doses of pedalling interventions. Evidence on optimal dose of rehabilitation interventions after stroke remains equivocal (Cooke et al. 2010). Although the number of repetitions of an activity needed to facilitate brain reorganization has not been established in human studies, animal model studies suggest that 300–400 repetitions in a 30-minute session might be needed (Kleim et al. 1998). Pedalling exercise has the potential to provide high numbers of repetitions of lower limb flexion and extension in reasonable therapeutic time frames, and there are opportunities for future research to explore optimal, tolerable doses in stroke survivors.

The equipment used in the studies was rarely described in detail, but in the majority of cases, a recumbent or semi-recumbent pedalling posture was adopted using leg cycle ergometers. Ease of use of such equipment is clear: patients may be seated or reclining in a chair or wheelchair and carry out cyclical lower limb activity. Seated pedalling negates the need for the substantial concentration and physical effort required to stay upright. However, this concentration and effort are components inherent in learning to walk early after a stroke; and upright pedalling postures are more likely to replicate the walking-like activity necessary to ensure that a pedalling task offers opportunities for functional movement. This is important, as previous research has demonstrated that functionally related activity can strengthen generalisability to tasks such as walking (e.g. Salbach et al. 2004; Dean et al. 2000). Hence, an upright pedalling device, enabling activity in a walking-related posture, might more appropriately replicate functional walking-like activity.

More generally, the review findings are unsurprising in the light of the state of the current evidence on specific rehabilitation interventions after stroke. Studies assessing potential rehabilitation therapies can provide conflicting evidence and be poorly conducted and reported, with insufficient interpretation of clinical significance (Dobkin, 2007). Indeed, recently, Santaguida et al. (2012) carried out a 'review of (systematic) reviews' of stroke rehabilitation therapy and exposed important methodological flaws, in categories including randomisation, allocation concealment and blinding, leading to conclusions that improvements in both research methods and reporting are required. A further review concluded that reporting of some key design features in stroke rehabilitation studies was lacking, particularly in areas such as timing of therapy and justification of outcome instruments used (Oremus et al. 2012). In congruence with these findings, the systematic review presented here described a lack of transparent reporting of key elements of studies.

It is likely that these findings reflect that, whilst considerable advances have been made in the last half-century in understanding the potential for restoration of function after central nervous system damage, rehabilitation research is still in its infancy. Hence, as was found in the presented systematic review, studies tend to be developmental in nature, and large-scale controlled trials of robust quality remain less common (Pomeroy et al. 2011).

Consequently, it was important that key messages from the systematic review presented here informed the development of the protocol for study two, investigating Upright Pedalling early after stroke. In particular, four findings helped to shape the research design: there was very limited investigation of pedalling early after stroke in acute settings, over half the studies were designed to assess aerobic capacity with motor function only as secondary outcomes, only one of the five randomised studies adopted impairment level outcome measures and the majority of equipment used in the studies enabled pedalling in recumbent or semi-recumbent postures.

A discussion of the ensuing feasibility study follows.

7.3 The feasibility of participating in reciprocal pedalling (Upright Pedalling) activity early after stroke

7.3.1 Summary of findings

This section of the work addressed study aims 2a and 3a, 3b, 3c, 3d, 3e and 3f.

Sufficient data were collected during the study to address aims 2a, 3a, 3b and 3d and hence to establish that:

- 4.6% (n=19) of those early stroke survivors screened were eligible to participate in the study.
- 84.6% (n=11) of early stroke survivors that made an initial attempt (n=13) could take part in Upright Pedalling (aims 3a and 3b)
- 2.2 % (n=9) of those early stroke survivors screened were randomised, with no participants taking part in UP on ten consecutive days in the acute stroke unit setting.
- U-PeD, the upright pedalling device, could be instrumented to enable derivation of measures during reciprocal pedalling early after stroke (aim 2a)
- lower limb movement could be characterised during UP (aim 3d) and provide a detailed physiological insight into the variety of movement strategies adopted by early stroke survivors during reciprocal pedalling
- it was not possible to provide the intervention for ten days on the acute unit where this research was sited (aim 3b)
- No adverse events were recorded in this group of early stroke survivors (aim 3f)

It was not possible to establish whether:

- there were any clinical characteristics that indicated which individuals were able to take part in UP (aim 3c)

- there was sufficient evidence of efficacy to justify proceeding to subsequent trials at this stage (aim 3e)

7.3.2 Discussion of findings

This section of the discussion will be presented according to the study aims.

7.3.2i Ability to take part in Upright Pedalling early after stroke (aims 3a and 3b)

The majority of participants recruited to the study were able to take part successfully in UP. No adverse reactions were recorded. It was promising to find that eleven early stroke survivors, 84.6% of those who made an attempt, all with substantial weakness, and unable to walk, were able to take part in UP. The feasibility of taking part in UP, early after stroke, was therefore demonstrated in this small sample of stroke survivors. This concurs with findings for the feasibility of use of BWSTT with early stroke survivors. Recent work reported positive findings for safety and feasibility of BWSTT for people within four weeks of stroke (Ada et al. 2010) and within 45 days of stroke onset (Franseschini et al. 2009). However, challenges to the further pursuit of BWSTT as a possible intervention to improve walking early after stroke, have recently been made (e.g. Dobkin and Duncan, 2012) so the relevance of its feasibility early after stroke might reasonably be challenged.

Whilst there is some evidence that successful pedalling can occur with profound deficit later after stroke (Kautz & Brown, 1998; Fujiwara et al. 2005), there has been no work to date demonstrating similar findings, in upright postures, early after onset. As established in Chapter 3.0, there are scant opportunities for repetitive practice of functional, reciprocal movement of the lower limbs, in upright postures akin to walking, for those otherwise unable to mobilise early after stroke. This study demonstrated the potential for early stroke survivors to take part in just such an activity. These data suggest that future pilot investigations of potential clinical efficacy of UP in this participant group are indicated.

Only two participants were not able to pedal the bike. It is possible that those unable to pedal were generally de-conditioned, as both were longer since stroke

onset than the study mean and had faced multiple medical challenges with little therapeutic input up to being considered fit to participate. Field notes also indicated that one had severe sensory inattention and difficulty with forward propulsion of the pedal which was a likely contributory factor. Both were transferred prior to further pedalling attempts so no further assessment of their ability was possible. It is possible that familiarity with the task and general improvements in the participants' conditions may have led to them being able to participate at a later date within the first 31 days after stroke and this element of the study design should be pursued in a future pilot study.

Whilst numbers in the study assessing the ability to pedal were too small for definitive conclusions to be made, it is important to examine the participant characteristics in order to determine if they were representative of the stroke population. Such data is important to determine any indications for generalisability of findings and, perhaps more importantly in this very early phase work, to shape future protocols.

Of those recruited to this study and proceeding to the baseline pedalling attempt, 69% were male, broadly representative of the UK stroke population, as stroke incidence is currently 25% higher in men than women (Stroke Association: Stroke Statistics 2013).

The age of participants (mean 70.8 years) was, however, slightly lower than in the general population (mean age 75 years; Stroke Association: Stroke Statistics 2013). It is possible that older stroke survivors were more unwell, as they are likely to have multiple pathologies; hence they were less likely to meet inclusion criteria for this pedalling study.

The mean number of days from stroke onset was 12.5 at baseline, and the wide range of 4 days to 26 days for those able to pedal indicated successful participation in UP at a broad number of time points within the bracket of "early after stroke." This is particularly promising for planning a future pilot trial of the intervention in people early after stroke.

7.3.2ii Investigation of the possibility of taking part in UP daily on an acute stroke unit and determining prognostic indicators and efficacy (Aims 3a, 3b, 3c and 3e)

The primary finding from the study indicated that the majority of stroke survivors recruited early after stroke were able to participate in UP. However, challenges were faced in reaching this point and progressing onwards from it, in terms of both recruitment and attrition. These factors contributed to findings about the proportion of patients on this acute stroke unit able to take part in the activity and the number of days for which this was possible; hence must be discussed when considering aims 3a and 3b. Recruitment and attrition data also affected the possibility of investigating prognostic indicators for and clinical efficacy of the intervention (aims 3c and 3e). Understanding and interpreting these challenges is also an essential component in considering future research into the intervention.

This developmental stage study, of a possible rehabilitation intervention for use early after stroke, necessitated recruitment of participants from an acute stroke unit. This proved to be challenging to the research team; indeed, it is more widely known that participant recruitment to stroke rehabilitation studies is one of the most difficult aspects of conducting the research (Lloyd et al. 2010; Blanton et al. 2006). Potential participants for the feasibility study were screened by stroke unit staff and 4.6% of those admitted to the unit were considered eligible for potential participation and hence approached by the researcher.

Finding that 95.4% of potential participants were screened as ineligible was initially surprising in the light of data from a recent early intervention lower limb rehabilitation trial, where 16% of people screened were found to be eligible (Cooke et al. 2010). However, this phase I study considered that the period “early after stroke” extended up to three months after onset, where the current study included participants only in the first month after stroke. Limiting the current study to including only stroke survivors in the first month after onset was important to meet one of the scientific challenges identified in Chapter 2.0; that of investigating possible interventions for use in the important early period after stroke. But, it is likely that, in this very early phase after onset, it was more challenging to find

participants who were considered medically appropriate to participate. Indeed, in the current study, over 35% of those screened were too unwell to be considered for participation; conversely, over 27% were independently mobile and thus insufficiently impaired to take part. These findings are not dissimilar to Ada et al. (2010), who investigated BWSTT in the first four weeks after stroke and recruited only 7.7% of those screened, with over 50% of exclusions due to medical instability, or conversely, participants being too mobile. It is inevitable that, immediately following onset of stroke, patients present with a wide range of needs. One fifth of strokes are fatal (Stroke Association: Stroke Statistics, 2013). Of those surviving, some people remain very unwell and in need of ongoing medical support whilst others make rapid recoveries to independent function, with a broad range of deficits in between.

Additionally, inclusion criteria for the current study were necessarily tightly controlled, to ensure that participants were early after stroke and with substantial weakness, but well enough to attempt pedalling. Stringent criteria are important, to improve scientific rigour and to ensure study aims are addressed safely; but are known to influence the number of participants potentially available for involvement in rehabilitation trials (Blanton et al. 2006). Indeed, Blanton et al.'s (2006) review of recruitment to a major, funded phase III study of an upper limb intervention after stroke (the EXCITE trial, results reported in Wolf et al. 2010), returned an average of only 6.1% recruitment following initial screening across multiple centres. This low "enrolment ratio" (Blanton et al. 2006) was considered to be due partly to the stringent inclusion criteria, the intensive nature of the upper limb intervention and to the multiple measurement points required. Though ratios were low, it is of note that the criteria on time since stroke onset was, at three to nine months, relatively wide ranging in comparison to the current study.

Meeting such challenges to recruitment during this feasibility study should not, however, deter further attempts at recruitment of early stroke survivors to rehabilitation studies from acute centres. Though initial screening may mean that the majority cannot be engaged in rehabilitation research at this stage, such centres do provide a one-location bank of potential participants in the crucial period early

after stroke when the brain is most responsive to extrinsic therapies. They offer possible research locations that avoid the potential cost of moving participants and researchers. Furthermore, they provide a potential interface for rehabilitation research and clinical practice, where therapists and researchers can work in tandem. Clinical site research offers the potential for an 'osmosis of understanding' between clinicians and researchers; such integration between practice and research is recognised as essential in improving the "translational research pipeline" of research findings into practice (Cumberland Consensus Working Group, 2009).

Numbers providing informed consent after initial screening provide important additional information for planning future studies, and in this case were promising. Once approached as potential participants and having received detailed study information, 84.2% (n=16) provided informed consent. Of those attempting to pedal the upright bike (n=13), all wished to remain involved in the study and those unable to pedal (n=2) both expressed a wish to return and try again. These findings suggest both positive engagement in the research in this participant group and that the practical procedures involved in using the bike were acceptable to those participating. The findings make an encouraging contribution to the foundations for a future pilot trial of the intervention. They also suggest that formal assessment of participant acceptance and opinion of the intervention might make a useful contribution to future protocols.

At the outset of the study, it was intended that the second part of the design would yield results determining whether a further, larger clinical trial was indicated. The study was developed in close collaboration with a consultant stroke physician and it was considered possible to involve the planned numbers of stroke survivors for up to the intended ten days of the study period. However, following the initial pedalling trial, attrition rates were high and insufficient data was collected to address this aim. The high rates of attrition were due to unforeseen changes in local systems of stroke care that had a considerable impact during the year of recruitment. The rapid development of both a new hyper-acute stroke service at the hospital site and an off-site early rehabilitation unit resulted in a dramatic reduction in length of stay on the acute stroke unit and patients were largely

transferred or discharged as soon as they were medically stable. Hence, those eligible for, or just enrolled in, the study were frequently transferred off site. Nine participants reached randomisation with none remaining in the study for the proposed ten days.

Half way through the recruitment period, and as the difficulties became apparent, consideration was given to moving the only available prototype pedalling device to the off-site rehabilitation unit. However, a number of factors led to a decision to pursue the study at the initial site: as this was a transitional period for the service, there were no data available regarding possible numbers of early stroke survivors to be transferred; a large rehabilitation study was already recruiting participants within six weeks of stroke at the new site; and the current study had no additional funding beyond the PhD studentship so extending the recruitment period was not possible.

It was not possible, therefore, to collect sufficient data to address aims 3c and 3e. However, whilst it was not possible to pilot the study in its entirety in this acute hospital setting, there is no evidence that such a design might not be successfully run in an alternative setting, or across different settings, as participants move on throughout the rehabilitation process. Piloting the study in an early rehabilitation unit might offer the potential for assessing the intervention with those stroke survivors who have remained in-patients because they have the substantial deficit required by the inclusion criteria. There is some, therefore, justification for a further pilot study of the new intervention early after stroke in different settings. Assessment of average length of stay data would be required prior to implementing a study in alternative locations and ideally, more than one U-PeD would be required to address these aims.

The challenges faced in addressing these aims also made it difficult to compare and contrast findings from this work with other possible rehabilitation tools for use early after stroke, such as body weight-supported treadmill training, BWSTT. Some comparison in terms of feasibility of use early after stroke has been noted in section 7.3.2i. However, insufficient data on efficacy of UP was collected to enable useful

comparisons to be made to the existing body of work on BWSTT, which is largely centred on efficacy and does not include the biological measures presented here. Important findings from this developmental work on UP enabled assessment and description of movement during UP and this is not directly comparable to the existing work on BWSTT.

Findings on characterisation of movement are discussed in the next section.

7.3.2iii Assessment and characterisation of lower limb movement during Upright Pedalling early after stroke (aims 2a and 3d)

It has been demonstrated that stroke survivors can take part in this upright pedalling activity early after onset (section 7.3.2i). Furthermore, the U-PeD was successfully instrumented to enable derivation of measures that were then used to characterise lower limb movement during UP.

Despite some of the challenges discussed in 7.3.2ii, data collected provided a detailed foundation for considering how the pedalling movement might be assessed and described. This section will discuss and interpret these data.

Two of the measures used to assess the pattern of lower limb activity during UP were derived from EMG data. Such data is collected as raw output of muscle energy and as such, is open to various methods of processing and interpretation. As a result of careful analysis of previous published work in this area, rigorous, clearly described methods were elucidated for the current studies. This enabled maximum confidence in the data presented; and clearly defined methods that might be used to assess muscle onset and offset and the phasic nature of muscle activity in future studies, allowing for possible comparisons across both participants and studies.

Data from the feasibility study demonstrated that eleven of the thirteen early stroke survivors tested could pedal. Where measurable, smooth pedalling was frequently observed; particularly in those participants pedalling at cadences of above 40rpm. However, patterns of muscle activity underlying the functional movement varied between participants, both in terms of activity according to wheel position and the reciprocity between muscle groups in both the affected and unaffected limbs.

Implications from data suggesting that early stroke survivors can generate steady pedalling for a short time are considerable. The ability of stroke survivors to generate constant, rhythmic pedalling activity early after stroke has been demonstrated to predict their capability to be community walkers at three months after onset (Katz-Leurer and Shochina, 2005). However, this study used only observation of the ability to pedal only rhythmically and constantly for one minute, it did not examine any kinematics or physiological measures of the muscle activity contributing to the movement. Hence, unlike the current study, the manner in which the activity was achieved was not assessed.

Recorded patterns of muscle activity during UP early after stroke were heterogeneous across participants. This finding was unsurprising, as stroke does not have uniform effects on neural networks. Indeed, high inter-participant variability of muscle activity patterns during pedalling has been previously demonstrated in stroke survivors during investigation of impaired muscle activation timing, using adapted ergometer pedalling in upright postures (Kautz and Brown, 1998); though in this study participants were more than six months from stroke onset. These findings contrast to published data for older adults without stroke, where consistent patterns of activity through four wheel position bins were demonstrated across participants (Kautz and Brown, 1998; Brown and Kautz, 1998). Whilst variability was high in stroke survivors, these authors noted that a later and prolonged onset of quadriceps muscles frequently occurred. A similar pattern of muscle activity was observed in the first illustrative case in the study presented here: reciprocity of activity was reasonable, as areas of higher percentage onset in quadriceps and hamstring muscles were in opposition; however, affected quadriceps demonstrated activity prolonged throughout the pedalling cycle to some extent, with no “off” periods. This might indicate a prolonged “extensor thrust” to propel the crank through the complete turn with reduced ability to selectively deactivate extensor activity.

In contrast, in the second illustrative case, the participant achieved smooth pedalling activity despite there being no measurable activity above baseline in either muscle group in the affected leg. This indicates pedalling by the unaffected

limb alone and only passive movement of the affected limb. The importance of characterising activity in both limbs early after stroke is demonstrated here as the unaffected limb clearly makes a contribution to the complete coupled cyclical movement. These findings, however, are not necessarily detrimental to the suggestion of UP for rehabilitation of bilateral lower limb movement. In an investigation of unilateral pedalling, Kautz et al. (2006) discovered that sensorimotor activity in one leg activated rhythmic motor activity in the other leg in stroke survivors, but this did not occur in a control group without neurological impairment. Furthermore, the effects were more marked in those most severely impaired after stroke and in bi-articular muscles such as rectus femoris and biceps femoris. The authors suggest that there might be some up-regulation of ipsilateral excitatory pathways assisting the hemiplegic leg as the unaffected leg pedals. The functional implication here is that, even single limb pedalling, as recorded in one of the illustrative examples in the feasibility study, might make beneficial contributions to bilateral motor patterns post-hemiplegia.

It was of interest that, where data were available at baseline, scatter plots of percentage activity for each wheel phase demonstrated heterogeneity of pattern for quadriceps, but a pattern of increased activity in the *extensor* phase of the wheel in hamstrings. These findings concur with those of Brown et al. (1997) in their assessment of pedalling patterns in healthy elderly volunteers and stroke survivors. They noted that activity in biceps femoris in the stroke survivors predominated in wheel phases equivalent to bins three and four in the study presented here; not in the early phases of the upstroke extensor phases (bins five and six) as demonstrated in their healthy volunteers. However, whilst the observations were similar, these data were reported for a single muscle not the generic group from which recordings were made in the current study, and were recorded during horizontal pedalling, not pedalling in vertical postures.

It is possible that the U-PeD pedal design may have contributed here- foot straps were used to ensure safe placement of the foot to the pedal; this enabled participants to “pull” up on the straps to assist the wheel in the transition from the flexor to extensor phases of the wheel, thus generating hamstrings activity towards

the top of the wheel which may have persisted in the early wheel phases to grade the descent. In generating such a “thrust” at the top of the wheel, it was conceivable that momentum was then used in the later phases to finish the cycle and thus less hamstrings activity was needed to complete the flexor phase. It was not possible, using surface EMG used here, to determine whether muscle activity generated was concentric or eccentric and, therefore, difficult to determine whether these major muscle groups were being used for propulsion or were providing a “braking” effect. Surprisingly, few studies have investigated the effects of the foot and pedal interface during cycling (Hug and Dorel, 2009). It is likely that any such equipment used in the rehabilitation of stroke survivors will require some manner of stabilising the foot in the pedal to ensure safe pedalling. Future research grant applications being explored to develop the current work, including seeking monies for a redesign of the cycling equipment and testing of various pedal designs.

The broader implications of heterogeneous muscle activity patterns must be considered when proposing UP as a possible tool for rehabilitative training of functional activity. Using different underlying movement strategies to achieve the same goal might be considered detrimental, as abnormal patterns might drive abnormal, maladaptive brain activity. Conversely, however, data demonstrating that early stroke survivors can adopt different movement strategies in order to achieve the smooth, coupled movement might be seen as beneficial, in the light of the identified need for rehabilitation interventions to include repetition of functional activity. Indeed, it might not be reasonable to assume homogeneity of activity this early after the onset of stroke; stroke survivors might need to adopt a variety of strategies to achieve functional movement that can then be refined with on-going therapy support. This suggests that setting parameters for responses to lower limb rehabilitation and recovery for groups of early stroke survivors might be challenging; particularly as current clinical measurement systems do not give therapists sufficient information to make those judgments. It is known that commonly used clinical assessments are unlikely to quantify impairment at such a detailed level as the assessment presented here; for example, it is possible that an individual stroke survivor who demonstrates no change on the Motricity Index,

therefore classified clinically as making no progress, could be demonstrating changes in underlying muscle activity which might contribute to future functional change. The practice of making early clinical decisions on currently available clinical tools, that do not include a detailed understanding of movement after stroke, might reasonably be challenged.

It is also reasonable to propose that the practice of rhythmic pedalling movement, by whatever strategies are available to the individual, might contribute to more normal underlying patterns at a later stage, after regular practice. Data from this study was insufficient to carry out measurement of muscle activity during and after ten days of pedalling intervention as planned, but there is scope for the measures here to be extended over further intervention days in the next phase study. This would then enable definitive decisions about correlations between improvement in underlying muscle activity patterns and clinical change during a programme of UP, to be made.

It is unremarkable that smoothness of movement in the current study was observed to be lowest at lower pedalling cadences (below 40rpm). Ansley and Cangle (2009) examined the determinants of optimal cadence in a review of sports medicine literature, and concluded that there is not a single recommended optimal pedalling cadence. Considerations of what is optimal vary according to multiple factors, both internal and external to the individual, including demands such as crank resistance and fatigue and muscular effort. Demands on stroke survivors pedalling early after onset are likely to be considerable as they attempt to re-establish coordinated movement patterns following damage to motor control systems. If able to achieve higher cadences, motor units are required that can rapidly activate and deactivate to meet the increasing frequency of the task (Ansley and Cangle, 2009) but at slower speeds it is possible that agonist/antagonist co-contraction, with its associated negative work, contributes to less smooth movement. This is reflected in the patterns observed in the third illustrative case from the feasibility study, where co-contraction is evident in both affected and unaffected legs and one of the least smooth pedalling sessions was observed, at a speed of less than 40rpm. Indeed, here and in the two other cases for which reciprocity was calculable for both legs,

increased co-contraction was evident in the unaffected limb. It is possible here that, as observed in previously published data, the affected limb might be increasing negative work done throughout the cycle which in turn puts increased work on the unaffected limb of stroke survivors (Kautz and Brown, 1998). Again, measurement over a number of days of intervention is further indicated in order to establish if there was any improvement in reciprocity of the unaffected leg correlating with improvements in the affected leg.

7.3.3 The feasibility of participating in reciprocal pedalling (Upright Pedalling) activity early after stroke: limitations

The small numbers of stroke survivors included in the feasibility study necessitated cautious interpretation of all data. Numbers were insufficient to inform decisions about potential prognostic indicators or clinical efficacy of the newly developed intervention. Observations relating to characterising movement related largely to single participants pedalling during single sessions. Additionally, though EMG methods were the same for each participant for whom movement characteristics were reported, for hamstrings, the use of the technique with very early stroke survivors necessitated a slight adaptation to published guidelines which may have led to less reproducible methodology (*Appendix III*). However, the interpretation to this point has not suggested definitive answers, but, it is hoped, has made reasonable, justified proposals for moving forward with this programme of research in the future.

7.3.4 The feasibility of participating in reciprocal pedalling (Upright Pedalling) activity early after stroke: conclusions and recommendations

Results discussed to this point indicate that it is feasible for people early after stroke, with considerable weakness and unable to walk, to take part in Upright Pedalling.

The current study was not able to determine potential clinical efficacy of the intervention due to high attrition but was able to indicate that it would be possible to carry out a pilot randomised controlled trial of the intervention in alternative settings early after stroke.

Additionally, these data have demonstrated the importance of assessing muscle performance at a detailed physiological level in order to understand the movement patterns underlying functional activity. This study, incorporating the methods developed for processing and analysing EMG data in Chapter 6.0, has elucidated scientific methodology for assessing movement during functional activity after stroke, advancing methods of analysing human movement after stroke in functionally relevant postures. The foundations for future study investigating potential benefits have been laid down and work is currently underway to pursue further research funding.

7.4 Investigating measures of lower limb impairment after stroke made during Upright Pedalling

7.4.1 Summary of findings

This section of the work addressed study aims 2b, 2c and 2d by using a clinical measurement study.

The study found that:

- There are indications that the measurement of lower limb motor impairment as expressed by changes in muscle activation timing:
 - a) has some discriminatory ability between stroke survivors and healthy volunteers for the quadriceps muscle (aim 2c);
 - b) has fair test-retest repeatability for affected side quadriceps and hamstrings in stroke survivors (aim 2b);
 - c) has substantial test-retest repeatability in quadriceps and fair test-retest repeatability in hamstrings in healthy older adults (aim 2b);
 - d) demonstrates a borderline significant relationship with a commonly used clinical measure of lower limb motor impairment, the Motricity Index (aim 2d)

- There are indications that the measurement of lower limb motor impairment as expressed by reciprocity of muscle activity has some discriminatory ability between stroke survivors and healthy volunteers (aim 2c)
- It was not possible to make reliable estimates of the magnitude of the test-retest repeatability of the measurement of lower limb motor impairment as expressed by changes in reciprocal activation and smoothness of pedalling in this sample of stroke survivors (aim 2b)
- There was no relationship between the measurement of lower limb motor impairment as expressed by changes in reciprocal activation and smoothness of pedalling and commonly used measures of motor impairment and walking ability (aim 2d)

A simple summary of key findings from the investigation of psychometric properties according to each measure is presented in table 27, with reference to the original data table in each column heading.

7.4.2 Discussion of findings

It is important that measurement studies are carefully designed to ensure that interpretations can be made with confidence. For example, it is essential that the psychometric properties of measures are investigated in a suitable number of participants with a wide range of deficits to improve generalisability of findings (Barack and Duncan, 2006). Hence, before discussing the findings directly related to the study aims, consideration will be given to the recruitment and characteristics of the study sample.

Table 27: Summary of key findings from investigation of psychometric properties of Upright Pedalling derived measures (chapter 6.0)

Psychometric properties				
Measurement expressed by:	Discriminatory ability: HV and StrS (tables 20 & 22)	Test-retest repeatability* (tables 23, 24 & 25)	Association: FAC (StrS only) (tables 26a & 26b)	Association: MI (StrS only)(tables 26a & 26b)
Muscle activation timing	PCA demonstrated significant difference in component 2 scores- quadriceps activity pattern according to wheel bin: evidence of discriminatory ability. Non-significant difference in hamstrings activity: no evidence of discriminatory ability	StrS: Fair for affected quadriceps [ICC=0.46 (0.32, 0.58)] and affected hamstrings [ICC=0.43 (0.28, 0.56)] HV: substantial for quadriceps [0.76 (0.65, 0.84)], fair for hamstrings [0.56, (0.39, 0.69).	No association	No association any parameter, though borderline significant relationship with affected quadriceps
Reciprocity (affected limb)	Significant difference: evidence of discriminatory ability	Unable to reliably determine for either group, very wide confidence intervals around ICC point estimates	No association	No association
Reciprocity (unaffected limb)	Non-significant difference, no evidence of discriminatory ability	Unable to reliably determine for either group, very wide confidence intervals around ICC point estimates	No association	No association
Smoothness	Non-significant difference, no evidence of discriminatory ability	Unable to reliably determine for either group, very wide confidence intervals around ICC point estimates	No association	No association

Abbreviations: FAC: Functional Ambulatory Categories; MI: Motricity Index; StrS: stroke survivors; HV: healthy older adult volunteers.*Repeatability: **fair** when the ICC **lower limit 95% CI**= 0.21 to 0.40, **substantial** when ICC **lower limit 95% CI**= 0.61 to 0.80

The main recruitment strategy adopted, which involved presentation of study information at local stroke groups, proved largely successful, with 26 out of the intended sample size of 30 stroke survivors providing informed consent. It was not possible, within the study timeframe, to recruit the final four participants. Recruitment of healthy older adults from the local community was successful with ten participants providing informed consent as per the protocol.

Numbers of stroke survivors actually measured were reduced as six participants had blood pressure above study limits on the day of measurement. These data should be considered when planning further pedalling studies recruiting community dwelling stroke survivors. Blood pressure limits to participation are necessarily cautious for activity based studies; but, as demonstrated in the current study, such limits might reduce the sample size by over 20%. Hence, intended samples for future studies might need to be larger than sample size calculations from measurement effects alone would suggest. In the current study, data according to study aims (sections 7.4.2i-iv) have been interpreted and recommendations made with due caution as the number of participants eventually taking part in the measurement sessions was less than the intended sample size.

However, two key elements of the study design were met by those eighteen participants successfully taking part in the measurement sessions:

Firstly, stroke survivors had a broad range of walking ability and lower limb activity (FAC range 1 to 5; Motricity Index mean score 66.2, range 38 to 92). This enabled the reliability and validity to be explored in a representative sample of stroke survivors, who commonly demonstrate a wide range of motor and ambulatory abilities. It is important when examining the results of evaluations of rehabilitation measurement tools that the performance of the measure is interpreted with reference to the population sample used for its assessment (Salter et al. 2005). Reliability, for example, is only an indicator of how reliably a measurement tool functioned within the sample on whom it was tested; hence an investigation of the psychometric properties of a measure in a sample with varied characteristics, such as was illustrated in the study here, might improve clinical applicability.

Secondly, whilst at 60.1 years (range 41.25 to 75.83 years), the mean age of the stroke survivors was below the mean age of stroke onset in the UK (75 years), age-matching to the healthy volunteers (mean 58 years, range 51.92 to 68.67 years) was broadly successful. It would, therefore, have been unlikely that any non-stroke related effects of ageing on muscle function during pedalling would have had an impact on activity recorded. It was unsurprising that the range of ages of healthy

volunteers was narrower than that of the stroke survivors, as the majority of the healthy volunteers were staff working at UEA and hence had not reached retirement age.

Therefore, recruitment to and participation in the study had mixed success- whilst initial numbers providing informed consent were good, some did not meet inclusion criteria and hence numbers actually participating were reduced by 20%. Additionally, the intended strategy of recruiting participants with a broad range of characteristics, and age-matched to the healthy older adults, was successful, increasing the possible clinical relevance and generalisability of findings.

A discussion of results according to specific study aims now follows.

7.4.2i Discriminatory ability of UP measures after stroke (aim 2c): measurement of reciprocal activity

Differences between measures of reciprocal activity recorded for stroke survivors and healthy volunteers pedalling at 40rpm, the closest pedalling cadence to that adopted by the stroke survivors, were quantified using two-sample t tests.

A significant difference was found for reciprocity of the affected limb of the stroke survivors as compared to the test limb of the healthy volunteers ($p=0.044$) but the difference was non-significant for the unaffected limb ($p=0.208$). The significant difference is suggestive of discriminatory ability for the measure of affected limb reciprocity in comparison with lower limb activity of healthy older adults.

The non-significant difference between the unaffected limb of the stroke survivors and the test limb of the healthy volunteers is a finding with potential clinical interest. It is possible that this is indicative of a lack of altered, compensatory activity in these later stage stroke survivors' unaffected limbs during pedalling. This is in contrast to the findings from a small number of earlier stroke survivors (discussed in 7.3.2ii&7.3.2iii) where considerably altered reciprocal activity in the unaffected limb was demonstrated. However, it is likely that in the very early stroke survivors, none of whom could walk, recruitment strategies for muscle activity were variable due to the early stages of neural recovery, whereas in the later participants muscle activity patterns were established. The later stage participants had

repeatedly practised reciprocal bilateral lower limb activity as a result of being mobile to some extent, with or without assistance. They were able to demonstrate phasic activity in their unaffected limb which was not significantly different to the test limb of healthy volunteers.

With reference to the aims of the current study, there is therefore some evidence that measuring reciprocity in the affected limb of stroke survivors has discriminatory ability in comparison to the same measure in healthy older adults. Additionally, there may be wider implications here for the possible use of UP as a clinical rehabilitation tool- if later stage stroke survivors are able to generate phasic activity in the unaffected limb similar to that observed in healthy volunteers during pedalling, despite weakness in the affected limb, then UP might provide a targeted therapy for the affected limb without non-phasic, compensatory activity in the unaffected limb.

Therefore, alongside findings of possible discriminatory ability for this measure, it is possible that, as proposed early in this thesis, more normal movement patterns might be facilitated using UP.

7.4.2ii Discriminatory ability of UP measures after stroke (aim 2c): measurement of smoothness of pedalling

Differences between measures of smoothness of movement in stroke survivors and healthy volunteers were quantified using a two-sample Wilcoxon test.

There was no significant difference observed between groups; mean smoothness measures were similar, with healthy volunteers pedalling only slightly more smoothly than the stroke survivors (S-Ped stroke survivors =0.017 [SD 0.005]; S-Ped healthy volunteers=0.014 [SD 0.0015]). Standard deviations for the stroke survivor group were wide, suggesting heterogeneity in the stroke survivor group possibly reflective of their broad range of abilities. Indeed, it is possible that the reason that there were no clear differences between the healthy volunteers and the stroke survivors is that the spectrum of ability across the stroke survivors was broad.

However, whilst this finding suggests that the measurement of smoothness might not be discriminatory between the two groups, it is another finding with

implications for UP as a potential clinical rehabilitation tool. The observation that stroke survivors can pedal in a similarly smooth manner to healthy older adults, suggests that UP might be providing, in terms of smoothness, a repetitive movement experience that is close to normal for the stroke survivors, at cadences of 40rpm and above. Similarly to 7.4.3i, the implication here is that the movement experience is more normal and hence provides an opportunity for the targeted behavioural activity required to drive beneficial brain change after stroke, identified as a principal underpinning stroke rehabilitation in the background to this thesis (Chapter 1.0).

Such an interpretation is, however, made with caution. Due to the coupled nature of the activity, it is of course possible that the unaffected limb is responsible for much of the smoothness of the movement. This might be reinforced by the findings discussed in section 7.4.2i; that the unaffected limb of later stage stroke survivors moves in a similar reciprocal manner to the test limb of healthy volunteers. However, this is not necessarily detrimental, as the end result of this coupled activity is the repetitive practice of a smooth, bilateral movement, using skilled and not compensatory movement in the unaffected limb.

Findings of similarities of smoothness of pedalling in stroke survivors and healthy volunteers contrast to the only other data available for such a measure (Chen et al. 2005). This small study found that smoothness was significantly lower in subjects with hemiplegia (n=13) than those without (n=8). However, closer inspection of Chen et al.'s (2005) analysis revealed that smoothness was calculated in a different way to the current study, using instantaneous velocity over four simple wheel phases, making direct comparisons with the current study difficult. Additionally, data were collected during semi-recumbent cycling; it may be that the upright posture used in the current study enabled stroke survivors to achieve more normal movement and hence similar smoothness to healthy older adults. Finally, the subjects without hemiplegia in Chen et al.'s (2005) study were considerably younger than those in the stroke survivor group; hence, unlike the current study, comparisons of performance did not consider age-related contributory factors.

In the current study, whilst smoothness of pedalling did not demonstrate discriminatory ability between stroke survivors and healthy volunteers, measurement of this parameter across the two groups illustrates possibly clinically important similarity of movement performance which might support the further development of UP as a potentially beneficial rehabilitation tool.

7.4.2iii Discriminatory ability of UP measures after stroke (aim 2c): measurement of muscle activation timing

Differences between stroke survivors and healthy volunteers for the measurement of muscle activation timing required careful analysis as these data were expressed over multiple wheel phases during pedalling. The studies presented here used a very detailed system of analysing activity using percentage “on” within each of eight wheel bins (section 4.5.3iii). Previous studies, whilst emphasising the importance of activation timing over muscle activity levels for evaluating movement patterns, have only used four wheel phases and have generally decided “muscle on” or “muscle off” within each phase (e.g. Brown et al. 1997; Brown and Kautz, 1999). It was appropriate to design and adopt such a more comprehensive system in this developmental work, to ensure that movement was characterised in the most detail possible to capitalise on knowledge acquired for future studies. A multivariate Analysis of Variance was used to quantify any differences here between stroke survivors and healthy volunteers.

A significant difference was observed for the activation pattern for quadriceps over the eight wheel bins, but not for hamstrings. Hence, this was suggestive of discriminatory ability of muscle activation timing measures between stroke survivors and healthy volunteers for quadriceps muscles. An additional Principal Components Analysis confirmed this suggestion, with a significant difference between loadings for each wheel bin for stroke survivors and healthy volunteers, in the second component.

The possibility of the measurement of quadriceps activation timing being a useful, discriminatory impairment measure after stroke is particularly pertinent, as quadriceps is a primary producer of the extensor forces required during recovery of

walking function. Hence a measure that might be sensitive to underlying changes in quadriceps muscle activation during a walking-like activity has potential clinical, as well as physiological, importance.

7.4.2iv Repeatability of UP measures after stroke (aim 2b)

It was essential to quantify the test-retest repeatability of the pedalling measures, as, in clinical practice, such measures are used across multiple treatment visits and thus need to accurately measure change over time in the same participant. Furthermore, it is well known that variability in EMG derived measures can originate during measurement (Hug and Dorel, 2009) and that measurement can be affected by factors such as skin impedance and electrode placement. Natural variability in muscle is likely to be higher in stroke survivors. The current study was designed to minimise these effects as far as was possible- skin preparation and electrode placement were done by the same therapist, and the testing sessions were carried out on the same day with a rest period in between, avoiding day to day variability in muscle performance and allowing for a more confident interpretation of findings. An adaptation from published guidelines to participant positioning for electrode placement and placement of electrodes for hamstrings was necessitated when working with stroke survivors taking part in U-PeD (*Appendix III*) but this was a consistent adjustment across all participants.

7.4.2v Test-retest repeatability of UP measures in healthy volunteers and stroke survivors (aim 2b): reciprocal activation and smoothness

It is important to note here that 95% confidence intervals around the intra-class correlation coefficient (ICC) values were very wide for both measures in both the healthy volunteers and the stroke survivors, at times crossing zero. This is likely to be a result of the small sample size here (n=17) but it is also possible that there was considerable heterogeneity within the populations tested. Hence, any observations of agreement or otherwise between sessions from the calculations of intra-class correlation coefficients cannot be substantiated with any precision, and remain, from this data set, simply observations. Had the predicted sample size of 30 been achieved, more precise results and hence more meaningful conclusions might have been attained. These data are insufficient to recommend or reject the clinical use of

the measure but might enable sample size calculations for future studies aiming to definitively quantify the magnitude of any test-retest variance.

The observation of possibly improved test-retest repeatability at higher pedalling cadences in healthy volunteers is of note, though the interpretation is made with caution in the light of the wide confidence intervals already noted. It is likely that the higher pedalling cadences were more comfortable for this group of older adults. Optimal cadence pedalling cadence is known to be affected by both individual and external factors and is very challenging to determine, though 50 to 70 rpm is considered metabolically optimal (Ansley and Cangle, 2009); hence the higher cadences in this study may have been more naturally achievable for this group. A cadence of 50rpm, the cadence at which the point estimate for the ICC suggested substantial repeatability of reciprocal activation for the healthy volunteers, is analogous to normal walking pace (100 steps per minute; Katz-Leurer and Shochina, 2005); suggesting that these measures might be more repeatable at cadences similar to walking pace. However, this is an observation which cannot be fully substantiated from the current data due to the wide confidence intervals.

At lower cadences, it was likely that some “grading” of activity to control the momentum of the crank was occurring and healthy older adult participants had to constantly moderate their muscle activity to meet the challenge of keeping to the target speed. Such constant fluctuation possibly led to less phasic and smooth movement patterns, which may have been difficult to repeat between sessions.

Stroke survivors certainly found a higher cadence easier to achieve- they adopted close to 40rpm as their comfortable pedalling speed. ICCs for this group were observed to be lower than for the healthy older adults for measures of both reciprocity and smoothness, an interpretation again made with necessary caution due to the wide confidence intervals. This potentially reduced repeatability is possibly related to the fact that the stroke survivors were participating in an activity that was challenging to them and a degree of acquisition of motor skill was required across sessions, which may have made phasic activity and smooth pedalling less repeatable.

Further work is indicated to determine the magnitude of any test-retest variability with improved precision.

7.4.2vi Test-retest repeatability of UP measures in healthy volunteers and stroke survivors (aim 2b): muscle activation timing

Repeatability for the measurement of muscle activation timing was substantial in quadriceps of healthy volunteers and moderate in the unaffected quadriceps of stroke survivors. In the affected leg of stroke survivors, only fair correlations were observed. These data were supported with more precise 95% confidence intervals than those of the preceding two measures. Whilst they are insufficient to recommend the clinical use of the measure from this small sample size, they might enable sample size calculations for future studies aiming to definitively quantify the magnitude of any intersession variance.

Measurement of muscle activation timing parameters are particularly relevant when studying impairments, as they provide indications of the underlying strategies adopted to achieve a movement. It is therefore surprising to find that little work has been done to explore the psychometric properties of these measures in healthy volunteers, and to the best knowledge of the author here, there has been no work quantifying their repeatability in stroke survivors. Dorel et al. (2008) examined repeatability of muscle activation patterns in 10 lower limb muscles of eleven tri-athletes, before and after a 53 minute training session. In general, muscle activation timing parameters were found to have good repeatability before and after the session, though repeatability for Vastus Medialis was weak in terms of onset of activity. These authors used a simple burst onset and offset point to define activation timing. In contrast, the repeatability work reported in this thesis used actual percentages of activity above a pre-determined baseline within each wheel bin to define activation; hence quantifying the activation in considerable detail, which may have also increased the likelihood of variability over and above that likely to occur with simple “on/off” decisions.

Jobson et al. (2012) also note the lack of investigations in this area and recently expanded Dorel et al.’s (2008) work. They explored both intra- and inter-session

reliability of muscle activation patterns using a group of experienced cyclists and one of non-cyclists. Inter-session repeatability of timing parameters was found to be good in both groups, better than intra-session repeatability.

Whilst both of these reliability studies provide an interesting bank of data on muscle activation timing in healthy adults, data from elite athletes and younger volunteers is in no way comparable to that from healthy older adults or stroke survivors. In fact, the study presented in this thesis provides the first set of test-retest data for the measures derived during upright pedalling in stroke survivors and older adults, and it is hoped it will provide a platform for future work.

Other observations from Jobson et al. (2012) are of further relevance to the methods employed in the current study. One conclusion of their work is that systems to advance the evaluation of muscle activity patterns might employ more advanced analysis techniques to avoid arbitrary selection of threshold for defining patterns. It is hoped, that for both the studies presented in this thesis, careful consideration was given to this matter and justifiable, transparent and repeatable methods of EMG processing and analysis were adopted, strengthening the foundations for future work.

7.4.2vii Associations with commonly used measure of motor impairment (aim 2d)

Using Spearman's rank correlation coefficient, there were no significant correlations between the derived measures of reciprocal activation or smoothness of pedalling and the Motricity Index as a measure of motor impairment or the Functional Ambulatory Categories as an indication of walking ability. These findings suggest that it would not necessarily be appropriate to use the UP derived measures interchangeably with the MI to measure impairment nor to predict walking capability and, therefore, the measures have not demonstrated concurrent validity with the chosen clinical measures in this study. However, this lack of correlation might indicate that the measures recorded during UP are measuring a different aspect of motor function to the commonly used clinical tools.

Correlations of borderline significance ($p=0.06$) were demonstrated between the measures of muscle activation timing in the affected quadriceps of stroke survivors and the Motricity Index. As for the other measurement properties (repeatability and discriminatory ability), it is the measurement of an aspect of quadriceps function that demonstrates (borderline) significance. In this case, it is possible that there this borderline correlation reflects that one third of the MI scale consists of measurement of knee extension and the measure of muscle activation captures percentage of quadriceps activity on during the extensor phase of pedalling, so some similarity of activity was represented. However, it should be noted that even if of borderline significance, any correlation was not strong, with $r=0.153$ for this measure.

However, the above findings were only of borderline significance and there were non-significant relationships for all other aspects of the derived measures. In general, this lack of significant association with the MI is possibly due to the nature of the derived measures. The EMG measures and the smoothness measure were derived from very detailed analysis of physiological behaviour underlying the production of movement during pedalling. The MI, whilst still regarded as an impairment measure, is a rudimentary, “hands-on” tool for measuring the end output of that physiological function- voluntary muscle contraction. It may be that the measures derived during pedalling are indicative of “pre-clinically-observed change.” Hence, it is possible that this level of measurement could provide indications of beneficial change before such change is observed with clinical measurement. As discussed during the interpretation of data from study two, this contention needs exploring in future studies that adopt these measures over a number of time points as participants take part in a further pilot study of UP.

7.4.3 Investigation of measures of lower limb impairment after stroke made during Upright Pedalling: limitations

The discussion and interpretation of the results from study three have been made with appropriate caution; the anticipated sample size for the stroke survivors was not met, and hence, in particular for the analyses of test-retest repeatability for two of the measures, confidence intervals were extremely wide. This seriously limits the

application of current findings to wider practice and, as such, the measures require further investigation to establish the magnitude of variance between testing sessions.

7.4.4 Investigation of measures of lower limb impairment after stroke made during Upright Pedalling: conclusions and recommendations

There were some indications that instrumented UP could be used to discriminate between stroke survivors and healthy age-matched volunteers in the both the timing of onset and offset muscle activation and reciprocal activation in quadriceps during pedalling. Thus further work is justified.

Subsequent research is also indicated in order to determine the magnitude of intra- and inter-participant variance between testing sessions and data from this study could be used to inform sample size calculations for definitive investigation of test-retest repeatability.

Additionally, findings from the measurement study have also provided some possibly important indications for the use of UP as a potential rehabilitation tool; in particular, in terms of demonstrations of both similarity of smoothness of pedalling between stroke survivors and healthy volunteers and of reciprocal activation of the unaffected leg of stroke survivors and healthy volunteers.

Chapter 8.0: Thesis Conclusions, Limitations and Directions for Future Work

8.1 Introduction

The purpose of this final chapter is to summarise the conclusions arising from the studies presented in this thesis; and to indicate possible directions for future work.

8.2 Conclusions

The conclusions are presented according to the chapters of the thesis.

8.2.1 Conclusions: Background review (Chapter 1.0)

The background to this work highlighted that investigating stroke rehabilitation interventions is a current UK research priority, due to the considerable impact of this life-altering condition on individuals, those who care for them and on wider society. Stroke survivors identify recovery of walking as an important goal and physiotherapists need evidence based interventions that might help people to achieve this goal.

It was recognised that stroke rehabilitation research programmes should incorporate the identified underlying principles of rehabilitation, including investigating the effects of functional, repetitive interventions for the lower limb in the important early period after stroke.

It was further elucidated that reciprocal pedalling exercise might incorporate the identified principles and offer opportunities for the promotion of walking-like activity early after stroke. Furthermore, it was proposed that reciprocal pedalling exercise might allow detailed characterisation of movement to better understand the muscle activity underlying the functional movement and the possible effects of the intervention. It was illustrated that opportunities for such characterisation of functional, reciprocal movement early after stroke were very limited. It was also suggested that UP might enable the derivation of sensitive measures of lower limb

motor impairment to inform important clinical decisions on progress, again with illustration that opportunities for recording of such measures during functional movement after stroke are few.

8.2.2 Conclusions: Systematic Review (Chapter 3.0)

During preparation of the background to the work, it became apparent that, whilst there were some suggestions in the current literature that pedalling might be a beneficial intervention for the recovery of motor function after stroke, there had been no comprehensive synthesis of available data. Hence, the first study in the thesis (Chapter 3.0) was a systematic review of the current studies investigating the effects of reciprocal pedalling exercise on motor function after stroke (Hancock et al. 2012), carried out according to Cochrane methodology.

A narrative synthesis, including both randomised and non-randomised studies, indicated that there was some, but limited, support for pedalling exercise benefiting muscle activity, muscle strength, balance, and functional independence after stroke, from early phase studies. However, inter-study heterogeneity, small sample sizes, wide confidence intervals for effect sizes, and the risks of potential biases suggested that the evidence was not sufficiently robust to support or refute the use of reciprocal pedalling exercise to enhance recovery of motor function after stroke. However, proof-of-concept for pedalling interventions was demonstrated.

Importantly for the ensuing studies in the thesis, the systematic review also found that the devices most favoured for pedalling interventions were recumbent or semi-recumbent ergometers; studies did not incorporate pedalling in upright postures, which might improve task-specificity for walking training. Additionally, there was limited investigation of pedalling interventions in early stroke survivors in acute settings and less than half the included studies were designed to primarily investigate effects on motor function after stroke. Hence, these conclusions from the review provided an evidence-based platform for the design of the ensuing feasibility study.

8.2.3 Conclusions: Establishing methods for investigation of reciprocal pedalling after stroke (Chapter 4.0)

The work presented in this thesis was in the early, developmental phase and as such, it was considered particularly important to justify and describe transparently the methods adopted. Clearly described decisions in early phase work can provide more solid foundations from which to build future research and hence increase opportunities for resultant work to translate to clinical practice. This chapter therefore presented justification of the tools, techniques, measures and procedures adopted for the studies presented in chapters 5.0 and 6.0, using published work where appropriate.

Firstly, current evidence indicated that equipment enabling pedalling in upright postures might allow movement experience in a more normal, functional posture and hence provide greater task-specificity for walking training. An upright pedalling device (U-Ped), incorporating postural support and adjustable seating enabling pedalling in an upright posture, was therefore selected for use. Additionally, as the importance of characterisation of movement during this functional activity had been established (chapter 1.0), an instrumented system for capturing muscle activity according the crank angle, within 45 degree segments, or “wheel position bins” was incorporated.

Secondly, chapter 4.0 exposed some challenges in using previously published work to inform methods for processing and analysing the EMG signal. A critique of twelve pedalling studies that incorporated measures derived using surface EMG, exposed inconsistent reporting of justification for use of filters, integrating EMG data, establishing a resting signal and quantifying activity bursts. No clear set of procedures for adoption for use in the current work was apparent. A lack of clarity of such procedure was not considered acceptable in this developmental work and hence clearly described, replicable procedures for EMG processing and analysis were presented for the studies herein. Algorithms were designed with clearly defined pathways for the use of additional filtering, and for any alteration to the pre-defined system for deciding “ons” and “offs” of activity bursts. A novel method

for precisely quantifying “ons” above the established baseline was presented, using percentage of time “on” for each of the 45 degree position bins within each turn.

Finally, the chapter presented the measures chosen and procedures common to the experimental studies. A range of measures were selected to best explore both the movement underlying the pedalling activity and its potential effects on function, from biological measurement of muscle activity including reciprocity and muscle activation timing, through to functional ambulation.

8.2.4 Conclusions: Investigating the feasibility of participating in reciprocal pedalling (Upright Pedalling) early after stroke (Chapter 5.0)

A feasibility study, investigating participation in UP early after stroke, was carried out in an acute hospital setting (Chapter 5.0).

The findings from this first experimental study indicated that it was feasible for people early after stroke, with considerable weakness and unable to walk, to take part in Upright Pedalling. 84.6% (n=11) of early stroke survivors that made an initial attempt (n=13) could take part in Upright Pedalling. No adverse events were recorded. No participants chose to withdraw from the study.

However, recruitment rates on the acute stroke unit where this research was situated were low, with 4.6% (n=19) of those early stroke survivors screened eligible to participate in the study. Additionally, only 2.2 % (n=9) of those early stroke survivors screened were eventually randomised to the relevant part of the study, with no participants taking part in UP on ten consecutive days in the acute stroke unit setting. The high attrition was due to a major reconfiguration of local stroke services during the period of study. No participants chose to withdraw themselves from the study, one was unable to continue due to a serious unrelated event.

Whilst the study was not able to determine potential clinical efficacy of the intervention due to high attrition but was able to indicate that it would be possible to carry out a pilot randomised controlled trial of the intervention in alternative settings early after stroke.

Though attrition rates were disappointing, they provided, along with every other aspect of carrying out this type of research in an acute stroke unit, tremendous learning opportunities for the author's future research career and the experience gained will be used in developing future protocols. For example, detailed assessment of length of stay data at potential sites, development of more than one prototype U-Ped and sufficient research staff to enable possible data collection at more than one site, might all be indicated as future protocols are developed.

However, important data were collected during the study, particularly that which demonstrated the importance of assessing muscle performance at a detailed physiological level, in order to understand the movement patterns underlying functional activity. The study, incorporating the methods developed for processing and analysing EMG data in Chapter 4.0, elucidated scientific methodology for assessing movement during functional activity early after stroke, advancing methods of analysing human movement early after stroke in functionally relevant postures.

The study provided foundations for future work investigating potential benefits of UP early after stroke.

8.2.5 Conclusions: Investigation of measures of lower limb impairment after stroke made during Upright Pedalling

A prospective measurement study was carried out in a university laboratory, in an attempt to establish aspects of the validity and reliability of measures made during instrumented UP. The measures investigated were: muscle activation timing, reciprocity of lower limb movement, and smoothness of movement. Participants included stroke survivors (n=18) with a broad range of clinical characteristics and a group of age-matched healthy volunteers (n=10).

The study concluded that there were some indications that instrumented UP could be used to discriminate between stroke survivors and healthy age-matched volunteers in both the timing of onset and offset muscle activation and reciprocal activation in quadriceps during pedalling. Also for the measurement of muscle activation timing, fair test-retest repeatability for the affected quadriceps and

hamstring muscles was demonstrated in the stroke survivors, and substantial test-retest repeatability for the affected quadriceps was demonstrated in the healthy older adults. Whilst clinical recommendations about measurement of muscle activation timing could not be made at this stage, due to the low sample size, these data indicate that further research into this measure is indicated.

There was no evidence of discriminatory ability for reciprocity of movement of the unaffected limb of stroke survivors in comparison with the test limb of healthy older adults, nor for smoothness of movement between stroke survivors and healthy older adults. Additionally, it was not possible to determine the magnitude of intra- and inter-participant variance between testing sessions for the measurements of reciprocity or smoothness of movement with sufficient precision to make clinical recommendations. This was most likely due a low sample size. However, it will be possible to use data from this study to inform sample size calculations for future definitive investigation of test-retest repeatability.

It was especially interesting to the over-arching theme of this thesis that some findings of the measurement study also provided possibly important indications for the use of UP as a potential rehabilitation tool. In particular, there were demonstrations of both similarity of smoothness of pedalling between stroke survivors and healthy volunteers and of reciprocal activation of the unaffected leg of stroke survivors and the test limb of healthy volunteers. These findings might suggest that UP is providing opportunities for lower limb activity similar to that experienced by healthy older adults without abnormal compensatory activity in the unaffected lower limb. This finding feeds back into the aims established for the feasibility study and further justifies future investigation of the efficacy of the intervention.

This work has therefore provided early indications for the use of U-PeD as a rehabilitation, assessment and measurement tool after stroke. Further work is indicated and planning for this work is underway (section 8.4).

8.3 Limitations and strengths of the work

8.3.1 Limitations

The main limitation of the systematic review was, due to resource constraints, a lack of completely independent data extraction by a second reviewer. Extraction was carried out by the lead reviewer, leading to potential bias. However, the independent reviewer was consulted on any queries and monthly supervision of the review was undertaken by an experienced third party.

It is also possible that there was some influence by a publication bias as the search was limited to studies written only in English. However, studies included were carried out across a variety of international centres.

In general, both experimental studies were limited by reduced sample size. For the acute clinical study, this was due to necessarily stringent inclusion criteria for this very early rehabilitation study and ensuing high attrition due to service reorganisation. For the measurement study, the sample size initially recruited in the given timeframe was reasonable, but with reduced participation in the measurement sessions themselves predominantly due to participants not meeting one of the inclusions criteria on the measurement days (blood pressure).

Some more specific limitations must be considered when concluding this body of work, and these are outlined below:

- The aims of the studies did not include qualitative investigation of the acceptability of taking part in UP. Whilst it was very promising that 84.2% (n=16) of those approached (n=19) provided informed consent to participate, and no-one attempting to pedal chose to withdraw from the study, a future mixed-methods design could provide a deeper understanding of the acceptability of participation in UP. Data collected from the feasibility study has provided a platform for a future pilot protocol to include working

iteratively with stroke survivors, their carers and therapists, to investigate their perceptions of the acceptability of UP (section 8.4)

- The U-PeD is a prototype and hence studies were limited by the availability of only one such device. The challenges faced in terms of reorganisation of local stroke services might have been more manageable with increased availability of upright pedalling equipment; however, the overarching nature of work presented herein is developmental and initial studies using only the existing prototype were justifiable at this stage
- Accessibility to the prototype U-PeD and positioning on the device required use of a hoist and two staff members to assist early stroke survivors. For the more mobile stroke survivors in the investigation of UP derived measures, use of a step to access the device was sufficient. Accessibility to the device for future studies and potential clinical use needs further consideration.
- Randomisation in blocks of four was used for the feasibility study; this method is likely to lead to the researcher being able to predict group allocation and introduce potential bias. This method needs reconsideration for future protocols.
- Work with stroke survivors with substantially reduced mobility necessitated some minor adaptations to published guidelines on participant position for electrode placement and to positioning of electrodes for data collection from hamstrings. Such adaptations were pragmatic when working with this participant group and the same adaptations were made for every participant so that data might be compared across participants. However, if more than one researcher at more than one research site were to be involved in future, training would be required to minimise potential biases from these changes.

The impact of limitations has been documented where relevant throughout the thesis and, where appropriate, results were interpreted with reference to those limitations.

8.3.2 Strengths

The studies presented in this thesis are novel investigations of a new potential rehabilitation intervention for use after stroke. New knowledge has been delivered, on the ability of early stroke survivors to take part in UP and the potential discriminatory ability and test retest repeatability of UP measures of impairment. The work has been demonstrated to be of publishable quality, including international, scientific peer reviewed journal articles (Hancock et al. 2012 & Hancock et al. 2011) and abstracts/poster presentations at national and international conferences (e.g. the UK Stroke Forum & The American Society of Rehabilitation Medicine).

As such, there are a number of important strengths which should be summarised as part of the conclusions to the work:

- The background to the studies used existing evidence to clearly identify an opportunity to develop a lower limb rehabilitation tool that enables repetitive, functional movement early after stroke.
- The systematic review of current evidence on reciprocal pedalling after stroke adopted methodology recommended by the Cochrane Collaboration and hence its findings were considered to provide a reliable, evidence-based platform for the development of a protocol for the feasibility study
- The study investigating the use of Upright Pedalling by early stroke survivors was developmental in nature; a feasibility study of a small group of participants. A prototype device was investigated in a group of stroke survivors with clearly justified inclusion criteria, using a range of measures, in an acute stroke unit setting. Such exploratory work is considered to be the foundation step in the development of complex rehabilitation interventions, and, without investigations beginning at this level, interventions are less likely to be adopted for use in clinical settings (Craig et al. 2008). Hence, this study has provided a platform for future iterative studies of design and implementation of UP.

- The feasibility study demonstrated that a group of early stroke survivors were able to participate in UP in an acute stroke unit setting, despite substantial paresis and the inability to walk. There was evidence of reciprocal, smooth movement even in some participants with severe motor impairment. Additionally, later stage stroke survivors were also able to participate in UP, demonstrated during the measurement study.
- Both the feasibility and measurement studies demonstrated that it was possible to characterise UP movement in detail and derive measures of impairment, during a functional activity in an upright posture with similarities to walking.

8.4 Future directions and concluding statement

The conclusion to this point is that UP is a technology worthy of future investigation. Hence, the following future work is suggested:

- Collaboration with an engineering team to enable development of the prototype U-PeD device to include: consideration of accessibility on and off U-PeD, an alternative pedal design possibly to include force plates, more easily adjustable seat height and trunk support to facilitate optimum upright postures in a variety of stroke survivors.
- Further feasibility work with a new prototype would then be required, using a mixed-methods design, and to include: a qualitative investigation of the acceptability of the device, using stroke survivors, carers and therapists; assessment of prognostic factors to provide possible indicators of response, a dose-finding investigation to assess optimal dose for response in early stroke survivors.
- Subsequently, a pilot study of the efficacy of taking part in UP early after stroke is expected to be conducted, in alternative locations (early rehabilitation units). Pedalling data recorded over a number of days of the

intervention would be needed and it is likely that more than one U-PeD would enable the work to progress more efficiently.

- Due to the lack of definitive findings in key areas of the prospective investigation of UP derived measures, further work on the repeatability of instrumented UP measures is also indicated . The design adopted for the study herein could be repeated, using a newly developed UP prototype, but with a larger group of stroke survivors, requiring a longer data collection period

The author is currently preparing post-doctoral fellowship applications to support the proposed work.

Concluding statement

This thesis has presented a new, promising technology that can be used by people with severe paresis early after stroke and that can enable reciprocal, lower limb movement in functional walking-like posture. It offers the potential for task-orientated training that might best talk to the brain in a language it understands in the crucial early period after stroke onset, to best promote functional recovery.

Upright Pedalling is a technology worthy of future investigation.

Appendix I
Systematic Review Documentation

Proforma for Identifying Eligible Studies for Systematic Review

Reference No. & Author			
Title:			
Full Reference:			
Retrieved From:			
Design (describe):			
Criteria: Add notes as necessary	Yes	No	Unsure
Participants: <ul style="list-style-type: none"> • Adults • Stroke • Paretic lower limb 			
Intervention: <ul style="list-style-type: none"> • Recip pedalling ex designed to enhance motor recovery in the lower limb • (One-off or over time) 			
Primary Outcomes: <ul style="list-style-type: none"> • Motor Impairments inc muscle function Secondary Outcomes: <ul style="list-style-type: none"> • Disability • Participation • Adverse ev/side effects 			

Notes:

Studies included in the Systematic Review

Brown, D.A., Nagpal, S., & Chi, S. Limb-loaded cycling program for locomotor intervention following stroke. *Physical Therapy* 2005; 85(2): 159-168

Fujiwara, T., Liu, M. & Chino, N. Effect of pedalling exercise on the hemiplegic lower limb. *American Journal of Physical Medicine & Rehabilitation* 2003; 82: 357-363

Holt, R., Kendrick, C., McGlashan, K., Kirker, S. & Jenner, J. Static bicycle training for functional mobility in chronic stroke- case report. *Physiotherapy* 2001; 87 (5): 257-260

Katz-Leurer, M., Carmeli, E. & Shochina, M. The effect of early aerobic training on independence six months post stroke. *Clinical Rehabilitation* 2003; 17: 735-741

Katz-Leurer, M., Sender, I., Keren, O. & Dvir, Z. The influence of early cycling training on balance in stroke patients at the sub-acute stage: results of a preliminary trial. *Clinical Rehabilitation* 2006; 20: 398-405

Lee, M., Kilbrath, S.L., Singh, M.F., Zeman, B., Lord, S.R., Raymond, J. & Davis, G.M. Comparison of effect of aerobic cycle training and progressive resistance training on walking ability after stroke: A randomised sham exercise-controlled study. *Journal of the American Geriatric Society* 2008; 56: 976-985

Perell, K.L., Gregor, R.J & Scremin, A.M. Muscle strength and gait-speed changes after bicycle exercise in participants with unilateral CVA. *Journal of Aging and Physical Activity* 2001; 9: 386-397.

Perell, K.L., Gregor, R.J., Scremin, E., Bicycle pedal kinetics following force symmetry feedback training in subjects with unilateral cerebrovascular accident. *Journal of Applied Biomechanics* 2000; 16: 124-141

Potempa, K., Lopez, M., Braun, L.T., Szidon, P., Fogg, L. & Tincknell, T., Physiological outcomes of aerobic exercise training in hemiparetic stroke patients. *Stroke* 1995; 26: 101-105

Quaney, B.M., Boyd, L.A., McDowd, J.M., Zahner, L.H., He, J., Mayo, M.S. & Macko, R.F. Aerobic exercise improves cognition and motor function post-stroke. *Neurorehabilitation and Neural Repair* 2009; 23(9): 879-885

Seki, K., Sato, M. & Handa, Y. Increase of muscle activities in hemiplegic lower extremity during driving a cycling wheelchair. *Tohoku Journal Experimental Medicine* 2009; 219: 129-138

Tang, A., Sibley, K., Thomas, G., Bayley, M., Richardson, D., McIlroy, W. & Brooks, D. Effects of an aerobic exercise program on aerobic capacity, spatiotemporal gait parameters and functional capacity in subacute stroke. *Neurorehabilitation and Neural Repair* 2009; 23(4): 398-406

Data extraction for included studies

Study:

Trial Setting:

Subject characteristics (inc age, gender, type stroke, time since stroke, inc/exc criteria)

Methods:

Trial Design:

Randomisation:

Allocation concealment

Generation of allocation sequence

Experimental group:

Category/ treatment description

Dose

Co-interventions

Control group:

Type

Dose

Co-interventions

Data extraction for included studies (contd.)

Blinding:

Subjects

Providers

Assessors

Dropouts:

Numbers

Reasons

Other potential confounding factors:

Intention to Treat Analysis:

Outcomes:

Timepoints for measures

Outcome measures used

Outcomes for which data is provided in the paper

Systematic Review Methodological Quality Assessment- risk of bias

Ref No	Author & Date	Sequence Generation		Blinding			Incomplete Outcome data	Selective result reporting	Other potential biases
		Allocation concealment?	Adequate sequence generation ?	Blinding participants?	Blinding providers?	Blinding Assessors?	Where relevant, incomplete outcome data addressed?	Free of selective reporting?	Free of other biases?
Comments:									
Comments:									

YES: LOW risk of bias; NO: HIGH risk of bias; UNCLEAR: unclear; UNABLE: not possible e.g. participant blinding in trial where pedalling was the key intervention

Ref: Higgins, J & Green, S (Eds) Cochrane Handbook for Systematic Reviews of Interventions; 2008, pp187-241 Wiley-Blackwell, Chichester

Appendix II

Research Governance, study information and consent



National Research Ethics Service

Essex 1 Research Ethics Committee

Level 9
Terminus House
The High
Harlow
Essex
CM20 1XA

Telephone: 01279 413136

Facsimile: 01279 419246

27 August 2009

Mrs Nicola Hancock
Post-graduate research student
University of East Anglia (studentship)
The Queen's Building,
University of East Anglia
Norwich NR4 7TJ

Dear Mrs Hancock

Study Title: Clinical efficacy and prognostic indicators for lower limb pedalling exercise early after stroke: A phase 1 randomised controlled trial with observer blinding.
REC reference number: 09/H0301/52
Protocol number: 1

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

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

Confirmation of ethical opinion

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

Ethical review of research sites

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

Conditions of the favourable opinion

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

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

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

This Research Ethics Committee is an advisory committee to East of England Strategic Health Authority

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

Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

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

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

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

Document	Version	Date
Participant Consent Form	1	17 June 2009
Participant Information Sheet	1	17 June 2009
Compensation Arrangements		19 June 2009
Summary/Synopsis	1	17 June 2009
Covering Letter		
Protocol	1	17 June 2009
Investigator CV		17 June 2009
REC application		18 June 2009
Supervisors CV		17 June 2009
Participant Information Sheet	2	05 August 2009
Participant Consent Form	2	05 August 2009
Response to Request for Further Information		

Statement of compliance

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

After ethical review

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

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

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

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

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

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

09/H0301/52

Please quote this number on all correspondence

Yours sincerely



 **Dr Alan Lamont**
Chair

Email: liz.wrighton@eoe.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: Ms Tracy Moulton
Research Contracts Manager
Research & Business Services
University of East Anglia
Norwich NR4 7TJ

Ms Kathryn Andrews
R&D Dept
Norfolk and Norwich University Hospital NHS Trust

East Norfolk and Waveney Research
Governance Committee



Mrs Nicola Hancock
Post-Graduate Research Office
The Queens Building
University of East Anglia
Norwich
NR4 7TJ

Please reply to: Research Governance Committee Office
Research and Development Department
Level 3, East Block, Room 032
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY
Direct Dial: 01603 287408
Internal: 3408
Direct Fax: 01603 289800

24 September 2009

e-mail: rdooffice@nnuh.nhs.uk
Website: www.norfolkhealthresearch.nhs.uk

Dear Mrs Hancock

Re: 2009MFE04 (158-09-09) Clinical efficacy and prognostic indicators for lower limb pedalling exercise early after stroke: A pilot randomised controlled trial with observer blinding.

Thank you for submitting the above project to the East Norfolk and Waveney Research Governance Committee for approval. On behalf of the Committee I am pleased to inform you that your project has been given full approval and you may begin your research.

Please note that this approval applies to the following sites:

- Norfolk and Norwich University Hospitals NHS Foundation Trust

I have enclosed two copies of the Standard Terms and Conditions of Approval. Please sign and return one copy to the Research Governance office. Failure to return the standard terms and conditions may affect the conditions of approval.

Please note, under the agreed standard terms and conditions of approval you must inform this Committee of any proposed changes to this study and to keep the Committee updated on progress.

If you have any queries regarding this or any other project please contact Julie Dawson, Research Governance Administrator, at the above address. Please note, the reference number for this study is **2009MFE04 (158-09-09)** and this should be quoted on all correspondence.

Yours sincerely

Dr Richard Reading
Chair
Consultant Paediatrician – NHS Norfolk

Enc



National Research Ethics Service

Norfolk Research Ethics Committee

Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Telephone: 01223 597733
Facsimile: 01223 597645

11 March 2011

Re-issued 04 April 2011 – to correct text underlined in the first paragraph

Ms Nicola Hancock
Associate Tutor/Post-graduate research student
University of East Anglia
The Queen's Building
University of East Anglia
Norwich
NR4 7TJ

Dear Ms Hancock

Study Title: Developing a clinical measure of motor impairment after stroke: Test-retest reliability and concurrent validity of upright pedalling.
REC reference number: 11/EE/0002
Protocol number: 1

Thank you for your letter received 08 March 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

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

Confirmation of ethical opinion

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

Ethical review of research sites

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

The favourable opinion applies to the following research site(s):

Research Site	Principal Investigator / Local Collaborator
University of East Anglia, Stroke and Rehabilitation Research Laboratory	Professor Valerie Pomeroy

Conditions of the favourable opinion

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

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

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

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

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

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

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

Document	Version	Date
Covering Letter	Nicola Hancock	
REC application	68601/18022/1/116	18 January 2011
Non-NHS SSI	68601/179951/7/906/8935 4/202070	14 January 2011
CV for PI/academic supervisor	Valerie Pomeroy	17 January 2011
Advertisement	1	17 January 2011
GP/Consultant Information Sheets	V1, Healthy Volunteers	17 January 2011
GP/Consultant Information Sheets	V1, Stroke Survivors	17 January 2011
Evidence of insurance or indemnity	Zurich Municipal	16 June 2010
Investigator CV	Nicola Hancock	17 January 2011
Summary/Synopsis	V1, Figure 2 of protocol	17 January 2011
Letter from Sponsor	UEA	14 January 2011
CV for Med Statistician	Prof. Lee Shepstone	17 January 2011
Protocol	2	01 March 2011
Response to Request for Further Information	from Nicola Hancock	08 March 2011
Participant Information Sheet: Stroke Survivors Group	2	01 March 2011
Participant Information Sheet: Healthy Volunteers	2	01 March 2011
Participant Consent Form: Stroke Survivors Group	2	01 March 2011
Participant Consent Form: Healthy Volunteers	2	01 March 2011

Statement of compliance

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

After ethical review

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

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

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

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

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

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

11/EE/0002

Please quote this number on all correspondence

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

Yours sincerely



pp **Michael Sheldon MA, PhD**
Chair

Email: Anna.Bradnam@eoe.nhs.uk

Enclosures: "After ethical review – guidance for researchers"



National Research Ethics Service
NRES Committee East of England - Norfolk

Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Tel: 01223 596907
Fax: 01223 597645

25 May 2011

Ms Nicola Hancock
Associate Tutor/Post-graduate research student
The Queens Building
Health and Social Sciences Research Institute
University of East Anglia
Norwich
NR4 7TJ

Dear Ms Hancock

Study title: Developing a clinical measure of motor impairment after stroke: Test-retest reliability and concurrent validity of upright pedalling.

REC reference: 11/EE/0002

Protocol number: n/a

Amendment number: Amendment #1

Amendment date: 10 May 2011

Amendment detail: Information relating to volunteers GPs being contacted by the research group has been removed from the consent form for healthy volunteers

Thank you for your letter of 10 May 2011, notifying the Committee of the above amendment.

The Committee does not consider this to be a 'substantial amendment' as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	Version	Date
Notification of a Minor Amendment	Amendment #1	10 May 2011
Participant Consent Form: Consent form: healthy volunteers	3	10 May 2011

Statement of compliance

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

11/EE/0002:

Please quote this number on all correspondence

Yours sincerely

A handwritten signature in black ink, appearing to read 'Peter Drew', is written over a horizontal line. The signature is enclosed within a hand-drawn circle.

Peter Drew
Assistant Committee Co-ordinator

E-mail: peter.drew@eoe.nhs.uk

Copy to:

R&D Department
Registry
University of East Anglia
Norwich
NR4 7TJ

06 October 2011

Ms Nicola Hancock
Associate Tutor/Post-graduate Research Student
Restorative Neurology Group
Faculty of Medicine
University of East Anglia
Norwich Research Park
Norwich
NR4 7TJ

Dear Ms Hancock

Study title: Developing a clinical measure of motor impairment after stroke: test-retest reliability and concurrent validity of upright pedalling

REC reference: 11/EE/0002

Protocol number: n/a

Amendment number: Amendment #2 (minor)

Amendment date: 06 October 2011

Amendment detail: The current study recruitment period, due to end in December 2011, has been extended to March 30 2012 in order to meet sample sizes and hence study aims

Thank you for your letter of 06 October 2011, notifying the Committee of the above amendment.

The Committee does not consider this to be a "substantial amendment" as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	Version	Date
Covering Letter	Nicola Hancock	06 October 2011
Notification of a Minor Amendment	Amendment #2 (minor)	06 October 2011

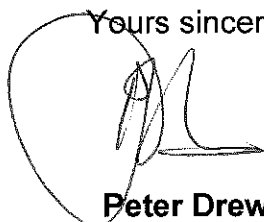
Statement of compliance

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

11/EE/0002:

Please quote this number on all correspondence

Yours sincerely

A handwritten signature in black ink, appearing to be 'Peter Drew', written over a large, faint circular stamp or watermark.

Peter Drew
Assistant Committee Co-ordinator

E-mail: peter.drew@eoe.nhs.uk

Copy to:

Ms Tracy Moulton
Research Contracts Manager
Research & Business Services
University of East Anglia
Norwich
NR4 7TJ

Professor Valerie Pomeroy
The Queen's Building
University of East Anglia
Norwich
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National Research Ethics Service
NRES Committee East of England - Norfolk

Victoria House
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25 October 2011

Ms Nicola Hancock
Associate Tutor/Post-graduate research student
University of East Anglia
The Queen's Building
University of East Anglia
Norwich
NR4 7TJ

Dear Ms Hancock

Study title: Developing a clinical measure of motor impairment after stroke: Test-retest reliability and concurrent validity of upright pedalling.

REC reference: 11/EE/0002

Amendment number: Substantial Amendment 1

Amendment date: 04 October 2011

Amendment Summary: We propose an amendment to the current recruitment strategy for this study We are currently recruiting stroke survivors via contact with local stroke groups. We propose that stroke survivors who have completed study 09/H0308/147 are telephoned by the research associate and asked whether they would be interested in receiving information about study 11/EE/0002.

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Cover letter to participants	1	05 October 2011
Protocol	3	05 October 2011
Notice of Substantial Amendment (non-CTIMPs)	Substantial Amendment 1	04 October 2011

Covering Letter		
email reassuring the Committee that it will be made very clear to participants that this is an entirely new study		25 October 2011

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

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

11/EE/0002:	Please quote this number on all correspondence
--------------------	---

Yours sincerely

PP 

Michael Sheldon MA, PhD
Chair

E-mail: lynda.mccormack@eoe.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms Tracy Moulton
Research Contracts Manager
Research & Business Services
University of East Anglia
Norwich
NR4 7TJ

Professor Valerie Pomeroy
The Queen's Building
University of East Anglia
Norwich
NR4 7TJ

NRES Committee East of England - Norfolk

Attendance at Sub-Committee of the REC meeting on 17 October 2011

<i>Name</i>	<i>Profession</i>	<i>Capacity</i>
Michael Sheldon MA, PhD	Retired Clinical Psychologist	Lay
Dr Robert Stone	General Practitioner	Expert

Also in attendance:

<i>Name</i>	<i>Position (or reason for attending)</i>
Mrs Lynda McCormack	REC Co-ordinator

Hancock Nicola Mrs (AHP)

From: Hancock Nicola Mrs (AHP)
Sent: 25 October 2011 11:35
To: 'McCormack Lynda'
Cc: Pomeroy Valerie Prof (AHP)
Subject: RE: Research ethics application 11/EE/0002

Dear Lynda

Thank you for raising this excellent point- I can reassure the committee that it will indeed be made very clear to the participants from the earlier study that this is an entirely new study. We will make this very clear on the initial approach to them and can also ensure again that this is fully understood at the point of seeking informed consent .

I hope this answers the query and am happy to further any other information that might be required.

Kindest regards

Nicola

Nicola Hancock
PG Cert (ClinEd), BSc (Hons) MCSP
Associate Tutor/Post-Graduate Research Student
Restorative Neurology Group
School of Allied Health Professions
Faculty of Medicine and Health Sciences
University of East Anglia
Norwich Research Park
Norwich
NR4 7TJ

n.hancock@uea.ac.uk
07717133178

From: McCormack Lynda [<mailto:lynda.mccormack@eoe.nhs.uk>]
Sent: Tuesday, October 25, 2011 11:15 AM
To: Hancock Nicola Mrs (AHP)
Subject: Research ethics application 11/EE/0002

Dear Ms Hancock

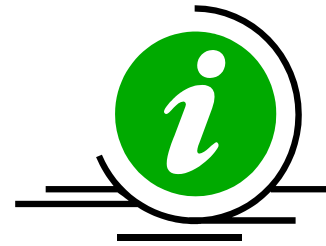
I am emailing regarding your request for a substantial amendment to study 11/EE/0002.

The Sub-committee have reviewed your request and would like reassurance that when the participants in the earlier study are approached it is made very clear that it is a new study that they are being invited to participant in.

Please can you email me your comments regarding this so that I can forward to the members.

Regards, Lynda

Lynda McCormack | Committee Co-ordinator
Norfolk REC



Participant information sheet

Date:

Study title: Clinical efficacy and prognostic indicators for lower limb pedalling exercise early after stroke: A pilot randomised controlled trial.

Researchers: Professor Valerie Pomeroy, Nicola Hancock (Lead Researcher), Dr Phylo Mynt (Local NHS Collaborator), Rebecca Stuck, Leo Earl

You will have been approached by a member of the **hospital clinical staff** about this research. This clinical staff member **will not be involved in any other part of the research.**

It is **important that you understand the purpose** of the project.

It is **important that you understand what it will involve.**

Discuss the project with others if you wish. If you **need more information**, ask the lead researcher, Nicola Hancock. Her contact details are on **page 10** and she is **very happy to be contacted.**

Part 1 describes the **purpose of the study** and **what will happen** if you decide to take part.

Part 2 answers some common questions patients have about research

Please take time to read the information carefully. Thank you for reading this.

Part 1

1. What is the purpose of this study?

Weakness in the leg is common **after stroke** and this can affect the ability to walk. **Physiotherapists** use lots of **techniques to help people** strengthen their legs but we do not always know **which techniques work for which patients**. It is also difficult for therapists to help people in the **early stages after their stroke** when they are very weak. This is because **muscles may not be able to work** well enough to do exercises and **more than one therapist** may be needed to help one patient to move.

Because we **do not know** what works for which patients, we are **carrying out some research** into a particular therapy:

We want to find out if **pedalling on an upright exercise bike** can help recovery in the leg early after a stroke. We also want to know **which particular patients** might be able to pedal and **who might benefit**.

This research forms part of an educational qualification, namely a PhD, for the lead researcher Nicola Hancock.

2. About the bike

The exercise bike has been used before for patients who have had a stroke.

It is a **sturdy piece of equipment** with a frame around it to help **support the body and arms** whilst sitting on the seat. There are **straps** for the hips and feet. The bike has a mechanism called a **UNICAM** which means that it can be **adjusted** so that the weaker leg moves in a smaller circle than the stronger one. This is useful for people who might **not manage to pedal normally** and means that they **can still take part**.

Here is a picture of the bike:



**A video of someone being moved onto the bike and pedalling
it is also available for you to look at if you wish**

3. Why have I been asked to take part?

You have been asked to take part as you have had a stroke in the last 30 days. If you decide to take part you will be one of around 24 people in the study.

We are looking for people who:

- **Have weakness in their leg** following a stroke within the last month
- Are **current patients** on the stroke unit
- Were **mobile independently before** their stroke
- **Are well enough** to take part this soon after their stroke

Do I have to take part?

NO. It is **up to you** to decide. Taking part is **entirely voluntary** and your decision will in **no way affect** any other parts of your **treatment.**

You are **free to withdraw at any time** and **do not have to give a reason.**

4. What happens if I decide to take part?

Once you are happy that you **want to take part** , a member of the research team will visit you on the ward. You will be asked to **sign a consent form** to show you **agree to take part.**



Remember that you can **stop at any time without giving a reason** and this will **not affect your treatment now or ever**.

5. Some information for you about each stage of the research study

Stage 1: On your first visit:

A member of the research team will **assess you** to see if you are suitable to take part in the study. This will take around **30 minutes**. **We will** assess your ability to move your leg, to move around the bed e.g rolling, to sit up and to stand.

Remember that we are looking for **people who are very weak** early after a stroke, so **not being able to do a movement does not mean you cannot take part**. However, if you are **not suitable** to participate in the study, you will be told at this point and will **not be asked to take any further part** in the study.

At this assessment stage we will also need to access some information about your clinical condition from your medical notes and scans. This information will only be accessed by relevant members of the research team.

Stage 2: If you are suitable:

You will be asked to do some more short **tests** of your **ability to move**. **Then**, you will be **shown the exercise bike** and if **happy to proceed**, you will be assisted onto the seat and **positioned securely**. Only when you feel **comfortable** and **safe**, will you be asked to **pedal the bike for one minute**. We will record whether you **can** or **cannot** pedal.

If you can pedal:

You will proceed to the next stage of the study

If you cannot pedal:

You will be given another opportunity to try every three days. This is because you may have felt tired or anxious at first or your muscles were still too weak after the stroke. If you can pedal for one minute at any of these attempts, you will proceed to the next stage of the study.

If you still cannot pedal:

You will not be suitable to continue with the study.

This is **unlikely** as our previous work shows that **many people are able to use this bike after stroke.**

If you cannot pedal, it does **not mean** you have **failed**- it is just that this pedalling therapy is **not the right treatment for you**. Everyone has different problems after a stroke and you will **continue** to work with the **usual therapies** recommended by the clinical team to help you. You have **helped the research team** by helping us to know which stroke patients might or might not be able to take part in future studies.

Stage 3:

If you are **suitable and able to pedal**, you will then have some more measures taken. These will be **similar to those taken before** you tried to pedal but will also **include some recordings of how active your leg muscles are** using **electromyography** or **EMG**. There is a section on page 8 describing this.

Stage 4:

You will be allocated to a **treatment group** or **control (no treatment) group at random**. The **allocation** will be by an **independent administrator** not part of the research team. He or she will open a **sealed envelope** containing a number and will tell the research team **what group** you are in. We will then tell you. You will be **identifiable only by a number** in this process, none of your personal details are used.

You **cannot choose** your group. This has to be at **random** to allow us to **find out whether the treatment is effective or not**. The researcher doing the assessments at the end of the study will **not know which group you are** in and so cannot influence the findings. This is called a **“blind”** study. Please do **not tell the assessor** which group you are in.

Stage 5:

If you are allocated to the **control (no treatment) group**:

You will **continue with your usual therapy** and not be asked to take part in the pedalling exercise.

After **two weeks**, we will **visit you again** to repeat the measures taken in stage 3 so that we can **compare the results** with those patients in the treatment group

If you are allocated to the **treatment group**:

You will attend **each weekday for 2 weeks** and try to pedal on the bike for **10 minutes**. It does not matter if you cannot manage 10 minutes, we will just **record what you can manage**.

Before you get onto the bike, we will be **sticking some electrodes** onto the muscles at the **back and front of your thigh** so that we can record the muscles' activity. This will happen each day and there are some more details on this below.

We will also be using a **heart rate monitor** and a monitor telling us about the **oxygen levels in your blood**. These will be connected to your finger on your unaffected arm.

Stage 6:

We will take some **outcome measures** at the end of the two week period for patients in **both groups**. These will consist of the **same measures taken before you were allocated to a group**.

Measuring your muscle activity

We need to know how **active your muscles are** and **when they are working** whilst you pedal. We can get this information using **electromyography or EMG**. This is a very **safe process commonly used** in rehabilitation research.

Before you are assisted onto the bike, we will **stick two electrodes** on each thigh, one at the front and one at the back.

Here is a picture of the electrode (green) and its connector:



We will stick them on after ensuring that your skin is clean. You will **feel nothing** from the electrodes after this. They are **connected to a box by some wires**. The box records the messages from the electrodes and this information is then stored on a laptop computer. You **will feel nothing at all** from this process.

6. Some other points about your possible involvement 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 leg during pedalling. This will be **closely monitored** and we will pace the pedalling to your level of ability.

Therapy can be stopped at any time. If you want to stop being

involved you simply tell us.

What are the possible benefits of taking part in the study?

- You will get a very **thorough assessment** of your ability to move after your stroke and **if in the treatment group** will receive **additional daily exercise**. However, **we do not know the possible benefits** of pedalling exercise early after stroke, which is **why we are doing the research**.

What happens when the study stops?

- This is the first study on pedalling early after stroke on this bike and it would be **inappropriate for you to continue** with this potential therapy after the study stops.

We will send you a leaflet when the study has been analysed, informing you of the results

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.13).

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** (p12-14).

Contact details for lead researchers:

Professor Valerie Pomeroy: v.pomeroy@uea.ac.uk

01603 591724

Nicola Hancock: n.hancock@uea.ac.uk

07717 133178

Rebecca Stuck: r.stuck@uea.ac.uk

01603 597316

End of Part 1

Part 2: Some common questions and answers

What happens if new information about the research therapy comes along?

- Sometimes in research, new things are found out about new therapies. Few studies have been done about this pedalling therapy and this study is partly 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.

Will anyone else know I am doing this?

- It is sensible for other **key members of the stroke team** to be aware of your taking part **e.g the senior physiotherapist, nurse and stroke physician.**

If the Research Team are concerned at any time about your health during your participation they will **report these concerns** to the appropriate **professional**.

What if there is a problem or something goes wrong?

- If you have any **concerns** about this study, you should first contact **Nicola Hancock** or **Professor Pomeroy**, 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.

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**.
- 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 Team** 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 **20 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?

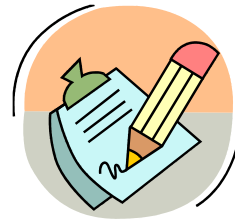
- The results of the trial will be **analysed** and used to justify **whether or not a larger scale study** is required to prove effectiveness of this therapy.
- The results will be **published in an academic journal** but individual participants will **not be identifiable**.
Participants can be sent trial report at the end of the study.

This ends 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**.

Study Title: Clinical efficacy and prognostic indicators for lower limb pedalling exercise early after stroke: A pilot randomised controlled trial.

CONSENT FORM



Researchers: Professor Valerie Pomeroy, Nicola Hancock, Dr Phyo Mynt, Professor Lee Shepstone, Professor Philip Rowe, Rebecca Stuck and Leo Earl

Please ✓

1. I understand the information sheet dated -----
and I have had the opportunity to ask questions.

2. I understand that I do not have to take part and that
I can stop at any time without giving a reason.

3. I understand that I will be given an opportunity to
pedal the bike and I may or may not be able to.

4. I understand that if I can pedal the bike I will be
allocated to either a group pedalling the bike daily
for two weeks or a group having only usual therapy.

5. I understand that the research team will have
access to my medical records and scans.

6. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the Norfolk and Norwich University Hospitals Trust, from regulatory authorities or from the NHS Trust , where it is relevant to my taking part in this research. I give permission for these individuals to have access to these records

7. I agree to take part in the study.

Signed (participant): **Date:**

Signed (researcher): **Date:**.....



Faculty of Medicine and Health Sciences

University of East Anglia

‘Just two hours of your time could help us help a stroke victim for a lifetime’

Learning to walk again is a major goal for stroke survivors trying to regain their independence. We are developing a new rehabilitation tool that might help in the measurement of lower limb movements after stroke. Our research team would like your help to validate this work

We need two groups of volunteers:

- If you're over 50, and reasonably fit and healthy, you could help our research by taking part in some lab-based gentle exercise on an upright bike. Just two five minutes cycles in a period of two hours is all we ask!
- If you're a **stroke survivor** over 18, we'd very much like to hear from you too. It doesn't matter how mobile you are, you might be able to help us with this study.

We will only need to see you once and we will pay your travel expenses.

If you're interested in helping us, together, we could help many others. Please call our research team on 01603 593959 or visit us on

www.uea.ac.uk/foh/research/Institutes/hss/stroke.





Participant Information sheet

Study Title: Developing a clinical measure of lower limb motor impairment after stroke: Test-retest reliability and concurrent validity of Upright Pedalling

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 9 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**

Note: It is the practice of our team to use enhanced communication strategies, including pictures, throughout information sheets. This is to ensure that our information is accessible to potential participants with different communication needs and is in no way designed to patronise.

Part 1

What is the purpose of this study?

After stroke, it is common to experience **weakness in one leg** which limits ability to walk and perform activities. Physiotherapists need to be able to accurately **measure this leg weakness** in order to assess abilities and plan treatment programmes. Information from such measurements is also very useful for stroke survivors to be able to see for themselves **how they are recovering**.

Accurate measurements of muscle activity are **difficult** as very **technical equipment**, often kept in **research laboratories**, is needed. Some **simple measures** are available in **clinical settings** but these do not always give the **detailed information** that might help plan treatments and monitor progress.

So there is a need to **develop detailed measures** of leg muscle activity that might be able to be **easily used** by therapists and stroke survivors in clinical settings. We are in the early stages of **developing such a measure**. This project is the **first step** in the process and involves examining the muscle patterns of people without stroke using this measure, so that useful comparisons can be made.

The new measure will consist of taking measures of leg muscle activity during **upright pedalling (UP)** on a static exercise bike. This has been

chosen as we know that **pedalling** enables people to experience **similar repetitive movement to walking**.

This bike has been used before for stroke survivors and is specially adapted. It is simple for people without stroke to use.

Here is a picture of the bike:



For a new measure to be accurately used, it must be able to demonstrate differences between stroke survivors and people without stroke. This

project will **explore these aims** and to do so, we need the **participation of some healthy adults** of 50 years and over in our rehabilitation laboratory.

Why have I been asked to take part?

You have been chosen because you are an adult 50 years of age and over and have expressed an interest. If you decide to take part you will be one of **40 participants** in this study.

We are looking for people who:

- Are **adults over the age of 50** in order to closely match the age of potential stroke survivors in the study
- Are fit and well enough to take part in a visit to our laboratory and a measurement session on the upright bike

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 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, we will visit you at UEA to ask you to sign a **consent form**.

We will then send you an appointment to attend the Stroke and Rehabilitation Research laboratory at UEA. We will only need you to **attend**

once and will try our best to find a date and time convenient to you. We will **reimburse your travel** costs.

We will show you the equipment and ask if you have any questions.

We will then record your resting heart rate and blood pressure to ensure they are within the safe limits set for this study. If we find that your blood pressure is high, we will advise you to make an appointment to see your GP.

We will ask you to put on some **shorts**.

In order to record how **active your leg muscles are** whilst on the bike, we need to use **Electromyography or EMG** of your thigh muscles. This is described more fully on page 6. To get accurate EMG readings, we will **prepare your skin** by rubbing a small area on the front and back of your thigh on each side with a **recommended gel**, then wiping and drying it.

We will then help you **onto the bike**.

You will be asked to **sit on the bike** with your **feet on a block** for up to one minute whilst we record your resting muscle activity. We will then position your feet on the pedals and ask you to **pedal at your comfortable speed** for 1 minute. When you are pedalling steadily, we will **record your muscle activity as described on page 6/7**. We will then ask you to pedal for 1 minute at each of 5 speeds, up to 50 rpm. The highest speed we will be recording at is a comfortable pace for most people.

We will also be recording the **speed and distance** you pedal whilst on the bike.

We will **monitor your heart rate** whilst on the bike to ensure it remains within **safe limits**. You will be asked to **stop immediately** if it exceeds the safe limits set but this is **very unlikely**.

You will then get off the bike and **rest** for up to an hour.

You will then be **positioned on the bike again** and we will ask you to **pedal again** exactly as you did above. We will take the **same measures**. This will help us to evaluate whether these measures can be **accurately repeated** at different times.

This will conclude the session and your participation in this research.

Measuring your muscle activity

We need to know how **active your muscles are** and **when they are working** whilst you pedal, to compare between the repeat measurements.

We can get this information using **electromyography or EMG**. This is a very **safe process commonly used** in rehabilitation research.

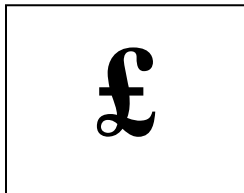
Before you are assisted onto the bike, we will **stick two electrodes** on each thigh, one at the front and one at the back.

Here is a **picture of the electrode** (green) and its connector:



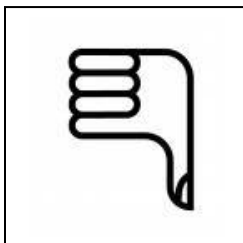
We will stick them on after ensuring that your skin is clean using a recommended gel. You will **feel nothing** from the electrodes after this. They are **connected to a box by some wires**. The box records the messages from the electrodes and this information is then stored on a laptop computer. You **will feel nothing at all** from this process.

Expenses



We will be reimbursing your travel expenses to and from the University from our research funds.

Are there any possible risks with this study?



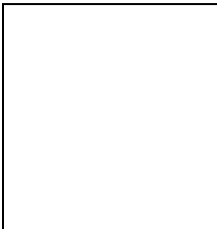
There is a **small risk** that you may experience some or discomfort if you overwork your leg during pedalling. This will be **closely monitored** but is **very unlikely** as the pedalling times are very short. **Pedalling can be stopped at any time**. If you want to stop being involved you simply tell us.

What are the possible benefits of taking part in the study?



It is not known yet whether upright pedalling might provide a useful clinical way of accurately measuring muscle function after stroke. You will be helping us by providing the important data needed to evaluate this.

What happens when the measurements are completed?



This is the first study of this potential measurement tool. The results of this study will tell us whether it might be worth using in clinical practice and in further research. We can get this information from you in one visit to our laboratory and therefore will not need you to continue after this.

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.10).

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.11).




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/Chief Investigator, **Nicola Hancock, or Valerie Pomeroy** the Principal Investigator.

Contact details:

Nicola Hancock Research Physiotherapist		The Queens Building University of East Anglia Norwich NR4 7TJ		n.hancock@uea.ac.uk		01603 593959/ 07717 133178
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Professor Valerie Pomeroy Principle Investigator		The Queens Building University of East Anglia Norwich NR4 7TJ		v.pomeroy@uea.ac.uk		01603 593959
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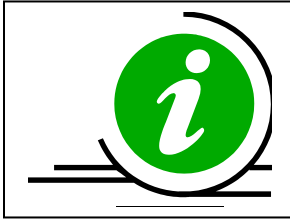
Independent Contact Details:

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, NHS Norfolk



01603 257187

Part 2



What happens if new information about the research therapy comes along?

Sometimes in research, new things are found out about new measurement tools. No studies have been done about this potential measure. 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 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.



What if there is a problem or something goes wrong?

If you have any **concerns** about this study, you should first contact **Nicola Hancock** or **Valerie Pomeroy**, 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 **University Complaints Procedure**. Details can be obtained from UEA. 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 the research?

The Research Team at the **University of East Anglia** are responsible for **organising** and **running** the research, led by **Professor Valerie Pomeroy**

The research is forms part of a **PhD** (Doctorate) qualification for **Nicola Hancock**, the Chief Investigator

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**.

You will be given a **trial number** for the purpose of **collecting and analysing data**. This means you will remain anonymous

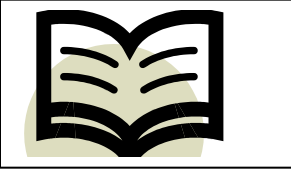
The data will only **be accessed by authorised persons** within the **Research Teams**

~~**Your
name**~~

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 this might be a **useful measure of lower limb muscle activity** after stroke

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.

Who has reviewed the study?

The development of the study has been **closely reviewed** by a supervisory team at **UEA** and an external supervisor at the **University of Strathclyde**. All were **positive** about the proposed research and **feedback** has been incorporated into this **research plan**.

The **Norfolk Ethics Committee** has approved the study

End 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**.



Study Title: Developing a clinical measure of lower limb motor impairment after stroke: Test-retest reliability and concurrent validity of Upright Pedalling

CONSENT FORM



Please initial & tick

1. I understand the information sheet dated -----
and I have had the opportunity to ask questions.

2. I understand that I do not have to take part and that
I can stop at any time without giving a reason.

3. I understand that I will be attending the STaR lab at the
University of East Anglia and will be asked to pedal an
Upright Bike whilst some measurements of muscle activity
are taken.

4. I understand relevant section of my medical notes and data
collected during the study may be looked at by individuals
from regulatory authorities or from the NHS Trust where it
is relevant to my taking part in this research. I give permission
for these individuals to have access to my records

5. I agree to take part in the study.

Signed (participant): **Date:**

Signed (researcher): **Date:**.....



Faculty of Health
Queens Building
University of East Anglia
Norwich
NR4 7TJ

Date:

Dear Dr

I am writing to you to inform you that your patient (name) has consented to take part in a study that is currently underway at the University of East Anglia. This study is called **“Developing a clinical measure of motor impairment after stroke: Test-retest reliability and concurrent validity of upright pedalling”**

We are aiming to recruit 30 participants who have had a stroke for a one-off measurement session in the Stroke & Rehabilitation Laboratory at UEA. They will be asked to pedal an upright exercise bike for a few minutes in two sessions, approximately one hour apart, and have some measures of muscle activity taken.

Please find a one page copy of the protocol attached to this letter.

We would be grateful if you could let us know of any medical reason why your patient (name) may not be included in this study. If we have not heard from you within 7 working days from the receipt of this letter, then we will understand that (name) is medically fit to participate.

If you require any further information about the study then please contact either myself (Nicola Hancock) or the Principal Investigator, Professor Valerie Pomeroy.

Nicola Hancock
n.hancock@uea.ac.uk

01603 593959
07717 133178

Yours sincerely

Professor Valerie Pomeroy
v.pomeroy@uea.ac.uk

01603 593959

Nicola Hancock
Research Physiotherapist



Participant Information sheet

Study Title: Developing a clinical measure of lower limb motor impairment after stroke: Test-retest reliability and concurrent validity of Upright Pedalling

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 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**

Note: It is the practice of our team to use enhanced communication strategies, including pictures, throughout information sheets. This is to ensure that our information is accessible to potential participants with different communication needs and is in no way designed to patronise.

Part 1

What is the purpose of this study?

After stroke, it is common to experience **weakness in one leg** which limits ability to walk and perform activities. Physiotherapists need to be able to accurately **measure this leg weakness** in order to assess abilities and plan treatment programmes. Information from such measurements is also very useful for stroke survivors to be able to see for themselves **how they are recovering**.

Accurate measurements of muscle activity are **difficult** as very **technical equipment**, often kept in **research laboratories**, is needed. Some **simple measures** are available in **clinical settings** but these do not always give the **detailed information** that might help plan treatments and monitor progress.

So there is a need to **develop detailed measures** of leg muscle activity that might be able to be **easily used** by therapists and stroke survivors in clinical settings. We are in the early stages of **developing such a measure** and this project is the **first step** in the process.

The new measure will consist of taking measures of leg muscle activity during **upright pedalling (UP)** on a static exercise bike. This has been chosen as we know that **pedalling** enables people to experience **similar repetitive movement to walking** and is something that can be done safely

after stroke. This bike has been used before for stroke survivors and is specially adapted to ensure that even very weak participants can sit upright safely and pedal. Here is a picture of the bike:



For a new measure to be accurately used, it must be **reliable** when repeated at different times, it must **agree with similar measures** already in use and it must reflect what the **stroke survivor can actually do**. This project will **explore these aims** and to do so, we need the **participation of stroke survivors on one day** in our rehabilitation laboratory.

Why have I been asked to take part?

You have been chosen because you have had a **stroke**. If you decide to take part you will be one of **40 participants** in this study.

We are looking for people who:

- Are **adults who have sustained a stroke** and have a mild, moderate or severe weakness in the leg
- Are able to walk, any distance; either with lots of help from another person or a walking aid; with a little help; or independently
- Are well enough to take part in a visit to our laboratory and a measurement session on the upright bike

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 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** or at your **stroke group meeting**.

On this visit a member of the research team will answer any further questions you may have. We will then ask you to **sign a consent form** to show you **agree to take part**.



We will then **assess your mobility on a simple scale** 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. Assessing this at this point will avoid you making an unnecessary trip to the University. However, we anticipate that most people will be able to take part as we are purposefully seeking people with a **wide range of walking ability**

This visit will take approximately **30-40 minutes**.

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 cannot take part. We will **write to your GP** and ask that they let us know within **7 days** if they have any medical concerns about your participation.

About **ten days after the home visit**, we will **post** you an **appointment** to attend the **Stroke and Rehabilitation Research (STaR) Laboratory** at the **University of East Anglia**, Norwich. If you prefer, we can **telephone** you with the appointment. We will only need you to **attend once** and will try our best to find a date and time convenient to you. We will **reimburse your travel** costs and can book you an accessible taxi if you would like us to.

What will happen on the day I attend the University laboratory?

On arrival, we will take a **measure of your heart rate and blood pressure**. This is to ensure that they are within the safe limits set for the study. If they are, we will **proceed with the measurements**. We will ask you to put on some **shorts**. **Help is available** for this if you need it.

We will then take a **simple score of your walking ability** and a **simple measure of your leg movements** in a sitting position. These measures will help us to compare the pedalling measures to those well-used in clinical practice.

In order to record how **active your leg muscles are** whilst on the bike, we need to use **Electromyography or EMG** of your thigh muscles. This is described more fully on page 7. To get accurate EMG readings, we will **prepare your skin** by rubbing a small area on the front and back of your thigh on each side with a **recommended gel**, then wiping and drying it.

We will then help you **onto the bike**. If needed, we can use a patient lifting **hoist** to help move you onto the bike, or you can simply step up onto it. You will be positioned comfortably and the **adjustable trunk support** can be placed if you and/or the research therapist assess that you need it.

You will be asked to **sit on the bike** with your **feet on a block** for up to one minute whilst we record your resting muscle activity. We will then position your feet on the pedals and ask you to **pedal at your comfortable speed** for 1 or 2 minutes. When you are pedalling steadily, we will **record your muscle activity as described on page 7**. We will also be recording the **speed and distance** you pedal whilst on the bike. We will **monitor your heart rate** whilst on the bike to ensure it remains within **safe limits**. You will be asked to **stop immediately** if it exceeds the safe limits set but this is **very unlikely**.

You will then get off the bike and **rest** for up to an hour.

You will then be **positioned on the bike again** and we will ask you to **pedal again** exactly as you did above. We will take the **same measures**. This will help us to evaluate whether these measures can be **accurately repeated** at different times.

This will conclude the session and your participation in this research.

Measuring your muscle activity

We need to know how **active your muscles are** and **when they are working** whilst you pedal, to compare between the repeat measurements. We can get this information using **electromyography or EMG**. This is a very **safe process commonly used** in rehabilitation research.

Before you are assisted onto the bike, we will **stick two electrodes** on each thigh, one at the front and one at the back.

Here is a **picture of the electrode** (green) and its connector:



We will stick them on after ensuring that your skin is prepared. You will **feel nothing** from the electrodes. They are **connected to a box by some wires**. The box records the messages from the electrodes and this

information is then stored on a laptop computer. You **will feel nothing at all** from this process.

Expenses



We will be reimbursing your travel expenses to and from the University from our research funds. If you need an accessible taxi, please tell us when we visit you at home and we can organise this.

Are there any possible risks with this study?

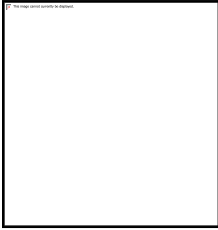


There is a **small risk** that you may experience some or discomfort if you overwork your leg during pedalling. This will be **closely monitored** but is **very unlikely** as the pedalling times are very short. **Pedalling can be stopped at any time.** If you want to stop being involved you simply tell us.

What are the possible benefits of taking part in the study?



It is not known yet whether upright pedalling might provide a useful clinical way of accurately measuring muscle function after stroke. You will be helping us by providing the important data needed to evaluate this.



What happens when the measurements are completed?

This is the first study of this potential measurement tool. The results of this study will tell us whether it might be worth using in clinical practice and in further research. We can get this information from you in one visit to our laboratory and therefore will not need you to continue after this.

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.12).

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.13).




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/Chief Investigator, **Nicola Hancock, or Valerie Pomeroy** the Principal Investigator.

Contact details:

Nicola Hancock Research Physiotherapist			 phone
	The Queens Building University of East Anglia Norwich NR4 7TJ	n.hancock@uea.ac.uk	01603 593300/ 07717 133178

Professor Valerie Pomeroy Principle Investigator			 phone
	The Queens Building University of East Anglia Norwich NR4 7TJ	v.pomeroy@uea.ac.uk	01603 593959

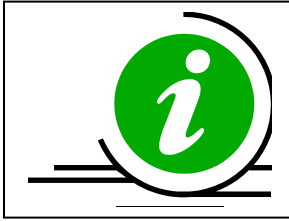
Independent Contact Details:

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, NHS Norfolk



01603 257187

Part 2



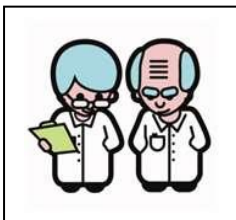
What happens if new information about the research therapy comes along?

Sometimes in research, new things are found out about new measurement tools. No studies have been done about this potential measure. 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 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.



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**



What if there is a problem or something goes wrong?

If you have any **concerns** about this study, you should first contact **Nicola Hancock** or **Valerie Pomeroy**, 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 **University Complaints Procedure**. Details can be obtained from UEA.

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 the research?

The Research Team at the **University of East Anglia** are responsible for **organising** and **running** the research, led by **Professor Valerie Pomeroy**

The research is forms part of a **PhD** (Doctorate) qualification for **Nicola Hancock**, the Chief Investigator

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**

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 **20 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 this might be a **useful measure of lower limb muscle activity** after stroke

The results will be **published in an academic journal** but individual participants will **not be identifiable**. Participants can be sent a trial report at the end of the study.

Who has reviewed the study?

The development of the study has been **closely reviewed** by a supervisory team at **UEA** and an external supervisor at the **University of Strathclyde**. All were **positive** about the proposed research and **feedback** has been incorporated into this **research plan**.

The **Norfolk Ethics Committee** has approved the study

End 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**.



Study Title: Developing a clinical measure of lower limb motor impairment after stroke: Test-retest reliability and concurrent validity of Upright Pedalling

CONSENT FORM

Please initial & tick



- 1. I understand the information sheet dated -----
and I have had the opportunity to ask questions.

- 2. I understand that I do not have to take part and that
I can stop at any time without giving a reason.

- 3. I understand that the research team will need to contact
my GP to inform them of my participation in the study

- 4. I understand that I will be attending the STaR lab at the
University of East Anglia and will be asked to pedal an
Upright Bike whilst some measurements of muscle activity
are taken.

- 5. I understand relevant section of my medical notes and data
collected during the study may be looked at by individuals
from regulatory authorities or from the NHS Trust where it
is relevant to my taking part in this research. I give permission
for these individuals to have access to my records

- 6. I agree to take part in the study.

Signed (participant): **Date:**

Signed (researcher): **Date:**.....

Appendix III

EMG methodology

Original data sets pertaining to figures 13 to 17

EMG methodology

Surface EMG is a well-established tool for the assessment of muscle activity (chapter 4.0). However, it is well-recognised that there are limitations associated with the technique, and it is important that these are minimised during experimental studies. This section of *Appendix III* details the techniques used, alongside published guidance.

In the studies presented in this thesis, activity was recorded from quadriceps and hamstrings muscles for each leg. The studies used the *Datalink EMG* system (Biometrics, UK), consisting of surface electrodes (37mm x 18mm pre-amplifiers), subject unit, base unit and software system.

The table on the following page presents the procedures used in the study, alongside the most recent European recommendations for surface electromyography (SENIAM 8, 2013).

Appendix III, Table 1: procedures used in thesis studies with comparison to European recommendations for surface EMG (SENIAM 2013)

Tool and/or technique	Procedure for thesis studies	Comparison with SENIAM recommendations: '✓' if concurs; '?' if differs, with explanatory text
Sensors	Bipolar, oval sensors with approx. 20mm between poles, details of manufacturer given.	✓
Skin preparation	Thorough preparation of skin with recommended exfoliator, manufacturer given; wiped with alcohol and alcohol allowed to vaporise so skin dry prior to placement.	✓
Starting posture	Sitting comfortably on U-PeD, feet not in pedals but resting on a block enabling approximately 15 degrees flexion.	Quadriceps: Sitting on a table with knees in flexion Hamstrings: Prone lying. ?: Neither of these positions were reasonable for stroke survivors, particularly those early after stroke, so the compromise listed in the previous column was agreed with the supervisory team and was used for all stroke survivors and healthy volunteers. Additionally, for early stroke survivors, a hoist was required, so positioning of electrodes <i>after</i> the disruption of hoisting, therefore without the risk of displacement, was considered the most rigorous
Placement & fixation	Sensor orientated to be parallel to the muscle fibres. Use of tape to secure electrode and wire to minimise movement artefact and avoid "pull" on the wire	✓
Sensor location	Reference electrode applied to the wrist	✓
	Quadriceps: sensor attached to the centre of the anterior surface of the thigh, parallel to the muscle, approximately half the distance between the iliac spine and superior patella	✓
	Hamstrings: sensor attached to the centre of the posterior surface of the thigh, parallel to the muscle, approximately half the distance from the gluteal fold to the lateral epicondyle of the tibia	?: this placement exactly follows guidelines from Cram et al. (1998). It very slightly varies from SENIAM, where it is recommended that placement is halfway on the line between the ischial tuberosity and the lateral epicondyle of the tibia. Positioning in prone and palpation of ischial tuberosity in stroke survivors was not reasonable (see "starting posture"), whereas the design of the seat enabled approx. visualisation of the gluteal fold in sitting on U-PeD

Original data sets pertaining to figures 13 to 17

Original data sets for phase diagrams figures 13a to 15b (affected leg data also used to contribute to scatter plots figures 16 & 17). Data recorded at baseline measures session.

Participant PED 14; percentage activity for each wheel bin, affected quadriceps

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	71.37	7.51	7.32	7.62	0.00	2.21	100.00	100.00
Turn 2	47.21	14.35	1.06	8.11	8.22	17.27	100.00	100.00
Turn 3	85.92	0.00	0.00	27.22	0.00	17.70	83.75	100.00
Turn 4	85.20	2.04	18.08	0.00	17.59	17.65	90.80	100.00
Turn 5	90.52	8.25	30.35	12.42	22.68	8.30	78.74	100.00
Turn 6	45.79	11.43	5.48	0.00	0.00	18.30	96.90	100.00
Turn 7	64.52	0.00	12.91	16.32	21.69	36.32	100.00	100.00
Turn 8	100.00	6.64	27.63	0.00	0.00	5.06	94.59	100.00
Turn 9	71.03	23.19	0.00	0.00	1.38	0.00	92.62	100.00
Turn 10	77.94	0.00	0.00	4.02	7.00	9.87	78.95	100.00
% on each trigger (mean)	73.95	7.34	10.28	7.57	7.86	13.27	91.64	100.00
% on each trigger (SD)	17.80	7.51	11.57	9.00	9.40	10.61	8.42	0.00

Participant PED 14; percentage activity for each wheel bin, affected hamstrings

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	66.80	98.17	96.81	50.28	23.99	0.00	0.00
Turn 2	0.00	71.30	100.00	100.00	89.12	12.05	0.00	0.00
Turn 3	0.00	81.22	95.34	100.00	72.47	27.88	0.00	0.00
Turn 4	16.33	64.29	100.00	98.97	70.99	20.81	0.00	0.00
Turn 5	0.00	58.74	98.83	100.00	76.58	37.12	1.97	0.00
Turn 6	0.00	66.67	86.64	100.00	59.50	0.43	0.00	0.00
Turn 7	0.00	49.29	100.00	93.79	94.28	9.83	0.40	0.00
Turn 8	0.00	52.13	90.46	100.00	74.01	4.22	0.00	0.00
Turn 9	0.00	74.88	98.15	100.29	66.90	24.56	0.00	0.00
Turn 10	77.94	0.00	0.00	4.02	7.00	9.87	78.95	100.00
% on each trigger (mean)	9.43	58.53	86.76	89.39	66.11	17.07	8.13	10.00
% on each trigger (SD)	24.61	22.77	30.82	30.07	24.38	11.59	24.89	31.62

Participant PED 14, percentage activity for each wheel bin, unaffected quadriceps.

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	0.00	13.41	100.00	100.00	37.64	1.39	0.00
Turn 2	0.00	0.00	8.10	100.00	98.14	48.59	1.52	0.00
Turn 3	0.00	0.00	0.00	64.17	100.00	69.91	59.58	73.71
Turn 4	0.00	0.00	0.00	92.31	96.30	58.82	7.60	0.00
Turn 5	0.00	0.00	0.00	56.67	100.00	36.24	20.87	0.00
Turn 6	0.00	0.00	0.00	71.56	100.00	46.81	27.13	0.00
Turn 7	0.00	0.00	0.00	81.61	100.00	58.55	79.37	0.00
Turn 8	0.00	0.00	0.00	56.44	100.00	66.67	35.14	6.07
Turn 9	0.00	0.00	0.00	51.86	99.31	86.84	22.54	0.00
Turn 10	0.00	0.00	3.68	70.76	100.00	76.23	57.09	5.53
% on each trigger (mean)	0.00	0.00	2.52	74.54	99.37	58.63	31.22	8.53
% on each trigger (SD)	0.00	0.00	4.66	18.12	1.24	16.60	26.53	23.03

Participant PED 14, percentage activity for each wheel bin, unaffected hamstrings

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	100.00	100.00	90.85	84.03	13.61	70.11	100.00	100.00
Turn 2	100.00	100.00	100.00	95.82	24.40	77.11	96.20	100.00
Turn 3	100.00	100.00	100.00	96.11	29.43	100.44	100.00	100.00
Turn 4	94.90	100.00	100.00	96.41	57.10	74.21	100.00	100.00
Turn 5	100.00	100.00	100.39	94.55	35.69	74.67	100.00	100.00
Turn 6	100.00	100.00	100.00	94.00	25.55	67.23	100.00	100.00
Turn 7	100.00	100.00	83.11	94.48	31.93	88.46	100.00	100.00
Turn 8	100.00	100.00	100.00	89.11	8.22	70.89	100.00	100.00
Turn 9	100.00	100.00	100.00	86.25	25.86	55.70	86.48	100.00
Turn 10	100.00	100.00	80.60	77.01	20.33	41.26	94.33	100.00
% on each trigger (mean)	99.49	100.00	95.50	90.78	27.21	72.01	97.70	100.00
% on each trigger (SD)	1.61	0.00	7.76	6.52	13.32	16.18	4.43	0.00

Participant PED 07; percentage activity for each wheel bin, affected quadriceps

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 7	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 9	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (mean)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (SD)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Participant PED 07; percentage activity for each wheel bin, affected hamstrings

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 7	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 9	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (mean)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (SD)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Participant PED 07, percentage activity for each wheel bin, unaffected quadriceps

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	0.00	0.00	95.45	100.00	100.00	100.00	53.25
Turn 2	0.00	0.00	0.00	76.21	100.00	100.00	100.00	18.50
Turn 3	0.00	0.00	0.00	84.76	100.00	100.00	100.00	35.37
Turn 4	0.00	0.00	0.00	71.43	100.00	100.00	100.00	74.38
Turn 5	0.00	0.00	0.00	80.93	100.00	100.00	100.00	26.11
Turn 6	0.00	0.00	0.00	79.58	100.00	100.00	100.00	26.88
Turn 7	0.00	0.00	0.00	86.08	100.00	100.00	100.00	40.74
Turn 8	0.00	0.00	3.24	88.21	100.00	100.00	100.00	53.55
Turn 9	0.00	0.00	0.00	57.75	100.00	100.00	100.00	58.00
Turn 10	0.00	0.00	0.00	73.77	100.00	100.00	100.00	35.48
% on each trigger (mean)	0.00	0.00	0.32	79.42	100.00	100.00	100.00	42.23
% on each trigger (SD)	0.00	0.00	1.03	10.46	0.00	0.00	0.00	17.27

Participant PED07, percentage activity for each wheel bin, unaffected hamstrings

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	100.00	97.60	24.46	0.00	0.00	0.00	0.00	38.46
Turn 2	100.00	100.00	49.74	0.00	24.87	10.82	0.00	47.98
Turn 3	100.00	100.00	53.81	0.00	13.61	6.88	35.18	33.54
Turn 4	100.00	100.00	38.59	0.00	3.31	0.00	0.00	32.50
Turn 5	100.00	100.00	42.62	0.00	0.00	4.47	1.05	52.23
Turn 6	100.00	100.00	25.00	0.00	11.43	16.20	0.00	50.63
Turn 7	100.00	100.00	32.97	0.00	0.00	7.22	1.03	57.41
Turn 8	100.00	100.00	43.78	0.00	29.14	0.00	0.00	57.42
Turn 9	100.00	100.00	22.73	1.60	0.00	7.56	23.37	42.00
Turn 10	100.00	100.00	73.41	0.00	0.60	15.20	0.00	0.00
% on each trigger (mean)	100.00	99.76	40.71	0.16	8.30	6.84	6.06	41.22
% on each trigger (SD)	0.00	0.76	15.76	0.51	11.09	5.96	12.55	17.07

Participant PED 09, percentage activity for each wheel bin, affected quadriceps

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	5.69	0.00	76.72	71.92	90.27	80.37	100.00
Turn 2	100.00	84.27	91.92	100.45	100.00	99.02	100.00	52.47
Turn 3	100.00	74.37	85.77	56.47	40.99	81.58	30.73	50.22
Turn 4	59.83	100.00	0.97	19.08	12.54	8.23	38.07	0.00
Turn 5	0.84	0.84	0.00	19.61	0.00	0.00	3.59	0.00
Turn 6	12.44	0.00	1.83	0.00	0.00	0.00	9.51	12.00
Turn 7	8.12	63.81	20.59	2.53	71.43	0.49	31.27	23.88
Turn 8	88.70	70.92	22.12	25.00	65.64	0.00	78.24	31.43
Turn 9	41.53	53.02	24.08	25.48	96.44	100.00	100.00	100.00
Turn 10	69.88	67.72	90.99	85.13	78.85	81.90	100.00	100.00
% on each trigger (mean)	48.13	52.07	33.83	41.05	53.78	46.15	57.18	47.00
% on each trigger (SD)	40.97	36.60	39.64	35.89	38.03	47.24	38.53	40.67

Participant PED 09, percentage activity for each wheel bin, affected hamstrings

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	67.44	98.58	72.89	60.32	5.42	0.00	0.00	0.00
Turn 2	0.00	62.50	100.00	100.45	33.33	0.49	0.00	5.38
Turn 3	0.00	0.00	78.66	100.00	87.84	35.79	20.00	0.00
Turn 4	0.00	0.00	0.00	58.40	95.47	75.76	52.28	5.21
Turn 5	0.00	0.00	0.00	0.00	72.09	100.00	84.30	51.28
Turn 6	53.11	22.27	46.33	100.00	62.31	93.00	100.00	100.00
Turn 7	100.00	56.19	32.77	45.57	28.57	0.00	94.59	100.00
Turn 8	100.00	100.00	67.31	25.00	54.36	100.00	69.95	94.29
Turn 9	100.00	78.14	53.93	58.17	23.56	0.00	0.00	67.51
Turn 10	47.49	98.43	99.55	83.08	49.52	23.08	0.97	0.00
% on each trigger (mean)	46.80	51.61	55.14	63.10	51.25	42.81	42.21	42.37
% on each trigger (SD)	44.37	42.73	36.00	33.85	28.99	44.56	42.51	44.95

Participant PED 09, percentage activity for each wheel bin, unaffected quadriceps

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	56.98	100.00	100.00	100.00	65.02	23.01	18.69	41.67
Turn 2	55.21	90.32	100.00	100.45	100.00	75.49	26.99	22.42
Turn 3	0.00	17.09	46.25	100.00	100.00	84.21	81.95	7.86
Turn 4	11.35	28.57	14.49	27.10	100.00	100.00	94.42	80.09
Turn 5	25.63	40.08	0.00	8.33	50.78	100.00	100.90	89.74
Turn 6	70.81	16.59	6.42	84.62	27.14	57.98	100.00	100.00
Turn 7	100.00	61.90	10.92	35.02	0.00	0.00	41.31	100.00
Turn 8	100.00	100.00	100.00	31.48	4.10	0.00	10.36	62.86
Turn 9	100.00	100.00	100.00	83.17	17.33	3.72	0.00	22.84
Turn 10	42.86	96.06	100.00	100.00	91.35	32.13	19.42	0.00
% on each trigger (mean)	56.28	65.06	57.81	67.02	55.57	47.65	49.40	52.75
% on each trigger (SD)	36.90	36.33	46.06	36.93	41.26	40.85	40.38	38.61

Participant PED 09, percentage activity for each wheel bin, unaffected hamstrings

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	99.22	100.00	100.00	60.85	40.39	100.00	98.13	100.00
Turn 2	83.33	99.19	95.77	86.61	47.62	67.16	100.00	85.65
Turn 3	92.31	87.94	100.00	100.00	100.00	50.00	29.27	82.10
Turn 4	66.38	0.00	78.26	100.00	100.00	68.83	59.39	42.18
Turn 5	86.13	74.68	71.43	62.75	100.00	100.00	99.10	48.21
Turn 6	71.29	100.44	100.00	100.00	100.00	100.00	100.00	90.22
Turn 7	59.90	79.52	100.00	100.00	100.00	0.99	96.53	100.00
Turn 8	56.96	77.55	48.56	100.00	100.00	100.00	100.00	99.59
Turn 9	100.00	81.40	63.35	66.83	100.00	88.37	100.00	100.00
Turn 10	100.00	100.00	80.18	89.74	89.42	100.00	100.00	100.00
% on each trigger (mean)	81.55	80.07	83.75	86.68	87.74	77.53	88.24	84.79
% on each trigger (SD)	16.81	29.97	18.41	16.77	23.35	32.39	24.23	21.95

Additional original data sets contributing to scatter plots, figures 16 and 17

Participant PED 05; percentage activity for each wheel bin, affected quadriceps

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 7	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 9	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (mean)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (SD)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Participant PED 05; percentage activity for each wheel bin, affected hamstrings

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	0.00	0.00	0.00	15.94	5.99	1.71	0.00
Turn 2	0.00	0.00	3.72	0.00	0.57	4.28	0.00	0.00
Turn 3	0.00	0.00	0.00	6.06	12.50	3.23	2.75	0.00
Turn 4	0.00	0.00	0.00	0.00	0.00	25.90	25.43	0.00
Turn 5	0.00	0.00	0.00	5.45	9.75	43.07	36.89	30.75
Turn 6	0.00	0.00	0.00	6.37	21.71	44.74	67.35	43.49
Turn 7	26.55	28.52	10.45	5.68	40.00	69.33	49.43	45.19
Turn 8	0.00	0.00	0.00	0.00	18.40	76.08	56.93	16.43
Turn 9	0.00	0.00	0.00	0.00	0.00	58.23	65.63	73.93
Turn 10	0.00	0.00	0.00	0.00	0.00	39.56	82.90	43.78
% on each trigger (mean)	2.65	2.85	1.42	2.36	11.89	37.04	38.90	25.36
% on each trigger (SD)	8.39	9.02	3.38	3.05	12.92	26.71	30.34	26.04

Participant PED 06; percentage activity for each wheel bin, affected quadriceps

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 7	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 9	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (mean)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (SD)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Participant PED 06; percentage activity for each wheel bin, affected hamstrings

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 7	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 9	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Turn 10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (mean)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% on each trigger (SD)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Participant PED 13; percentage activity for each wheel bin, affected quadriceps

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	75.16	61.34	11.33	52.33	90.38	92.65	92.19	69.27
Turn 2	94.90	70.00	38.14	65.22	100.00	83.48	53.96	41.19
Turn 3	65.95	66.04	26.19	36.42	84.77	100.00	83.43	98.40
Turn 4	100.00	73.10	40.20	77.55	100.34	100.00	100.00	100.00
Turn 5	100.00	90.98	39.44	98.97	13.18	100.00	100.34	97.31
Turn 6	99.40	92.25	86.14	89.94	99.56	93.98	100.00	100.00
Turn 7	100.00	100.00	98.58	17.43	69.16	100.00	100.00	100.00
Turn 8	74.50	98.31	91.81	34.45	92.47	100.00	100.00	100.00
Turn 9	94.86	98.27	100.00	100.00	100.00	93.22	100.00	100.00
Turn 10	100.00	100.00	93.93	78.01	96.05	100.00	100.00	91.18
% on each trigger (mean)	90.48	85.03	62.58	65.03	84.59	96.33	92.99	89.73
% on each trigger (SD)	13.22	15.56	34.44	28.87	26.90	5.53	14.77	19.54

Participant PED 13; percentage activity for each wheel bin, affected hamstrings

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8
Turn 1	100.00	100.00	0.00	26.94	9.86	0.00	14.32	83.45
Turn 2	100.00	100.00	96.33	85.22	15.64	0.00	21.99	72.28
Turn 3	100.00	99.84	63.69	39.70	21.55	0.00	0.00	82.62
Turn 4	100.00	100.22	50.98	18.03	0.00	0.00	22.70	81.17
Turn 5	100.00	99.82	65.49	54.11	0.00	0.00	24.48	74.25
Turn 6	100.00	100.00	72.61	67.75	37.18	34.21	0.00	6.70
Turn 7	79.28	100.00	100.00	78.57	50.78	11.46	11.46	30.26
Turn 8	74.50	100.00	100.00	86.29	47.60	0.00	0.00	7.42
Turn 9	70.69	100.00	100.00	61.22	17.97	0.00	0.00	0.00
Turn 10	60.16	100.00	97.65	29.91	7.63	0.00	0.00	0.00
% on each trigger (mean)	88.46	99.99	74.68	54.77	20.82	4.57	9.50	43.82
% on each trigger (SD)	15.62	0.11	32.09	25.09	18.50	11.02	10.71	37.91

Appendix IV
Publications

STUDY PROTOCOL

Open Access

Clinical efficacy and prognostic indicators for lower limb pedalling exercise early after stroke: Study protocol for a pilot randomised controlled trial

Nicola J Hancock^{1*}, Lee Shepstone¹, Philip Rowe², Phyo Kyaw Myint¹, Valerie Pomeroy¹

Abstract

Background: It is known that repetitive, skilled, functional movement is beneficial in driving functional reorganisation of the brain early after stroke. This study will investigate a) whether pedalling an upright, static exercise cycle, to provide such beneficial activity, will enhance recovery and b) which stroke survivors might be able to participate in pedalling.

Methods/Design: Participants (n = 24) will be up to 30 days since stroke onset, with unilateral weakness and unable to walk without assistance. This study will use a modified exercise bicycle fitted with a UniCam crank. All participants will give informed consent, then undergo baseline measurements, and then attempt to pedal. Those able to pedal will be entered into a single-centre, observer-blinded randomised controlled trial (RCT). All participants will receive routine rehabilitation. The experimental group will, in addition, pedal daily for up to ten minutes, for up to ten working days.

Prognostic indicators, measured at baseline, will be: site of stroke lesion, trunk control, ability to ambulate, and severity of lower limb paresis.

The primary outcome for the RCT is ability to voluntarily contract paretic lower limb muscle, measured by the Motricity Index. Secondary outcomes include ability to ambulate and timing of onset and offset of activity in antagonist muscle groups during pedalling, measured by EMG.

Discussion: This protocol is for a trial of a novel therapy intervention. Findings will establish whether there is sufficient evidence of benefit to justify proceeding with further research into clinical efficacy of upright pedalling exercise early after stroke. Information on potential prognostic indicators will suggest which stroke survivors could benefit from the intervention.

Trial Registration: ISRCTN: ISRCTN45392701

Background

Therapy early after stroke

In the first few weeks after stroke, the brain is 'primed' for neurological recovery in response to rehabilitation training [1]. Indeed, Cramer [2] describes a 'golden period' for initiating restorative therapies, starting in the first days after onset and continuing for several weeks. However, animal studies on early therapy are equivocal. Kozlowski et al [3] demonstrated an increase in lesion size following early training and proposed a 'use-it-but-don't-overuse-it'

strategy in this period. In contrast, Biernaskie et al [4] found that rats given enriched rehabilitation training from day five after an induced lesion demonstrated a marked improvement in recovery, whilst those given similar training beginning at day 30 improved no more than controls.

Whilst animal studies provide insights into brain changes underlying recovery, caution must be observed in generalising to human populations. Nonetheless, clinical studies do support early rehabilitation intervention to improve outcomes [5,6]. It is also possible that, if rehabilitation onset is delayed, patients might establish compensatory behaviours that could impact negatively on recovery of useful functional activity [7,8]. Additionally, National Clinical Guidelines for Stroke in the

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United Kingdom advise that people with acute stroke should be mobilised as early as possible [9]. However, the optimal dose and type of physical therapy required to drive useful functional reorganisation in early stroke survivors with different clinical characteristics remains unknown.

Repetitive, functional training early after stroke

In the first days to weeks after onset, stroke survivors can present particular therapeutic challenges. Leg weakness is often substantial and the ability to contract paretic muscle sufficiently to be able to take part in functional, relevant activity, such as walking training, can be severely compromised. There are interventions which can be used to improve ambulatory capacity early after stroke-including treadmill training with and without partial body weight support, and walking facilitated 'hands-on' by therapists-but these are often time-consuming and likely to require extensive physical assistance from one or more members of a therapy team. The effort required from both patient and therapist(s) is often too great to enable more than a few repetitions of activity. This dose might be too low for effect.

Although the number of repetitions of an activity needed to facilitate human brain reorganisation has not been established, animal model studies suggest that 300-400 repetitions in a 30 minute session might be needed [10]. Repetition of motor activity has been demonstrated to produce changes in cortical representation maps [10,11], and may be an important consideration in rehabilitation programmes.

Repetition of motor activity alone, however, is not a sufficient driver to induce functional reorganisation of cortical networks. Motor skill acquisition, or motor learning, has been demonstrated to play a central role, in both animal [12] and human [13,14] studies. It has also been suggested that there may be benefit from goal-directed functional activity associated with normal afferent stimulation [15]. The salience of a task is an important consideration in rehabilitation programmes [7]. Indeed, current clinical guidelines suggest that functional, task specific activity is a key component of rehabilitation after stroke; gait re-training to improve independence in walking is such a functional activity and a principle goal for many patients [9]. Such evidence might suggest that optimal rehabilitation programmes should involve task specific activity and increasing levels of motor skill [16].

Therapists are therefore challenged to find strategies that enable repetitive, relevant and skilled activity in early stroke survivors. However, it remains unknown a) which specific physical therapies might drive brain reorganisation and motor recovery and b) which patients might respond best to which therapies.

Cycling as a potential therapeutic activity early after stroke

Cycling is a functional activity that has potential to benefit patients when used as an adjunct to therapy after stroke [17]. It requires that agonist and antagonist muscles are contracted reciprocally and in a similar pattern to that required for walking [18]. Therefore, it is a repetitive muscle activity that may be beneficial in retraining gait [19]. Indeed, pedalling may facilitate phasic, co-ordinated muscle activity even in patients with severe hemiparesis [20]. Whilst familiar to many stroke survivors, reciprocal pedalling is likely to require re-acquisition of motor skill following the onset of hemiparesis.

Clinically, there is therefore potential to use static cycling for repetitive, co-ordinated exercise training as part of stroke rehabilitation programmes aiming to address deficits in motor function. However, the evidence in support of cycling interventions is preliminary. The early findings from our ongoing systematic review are that, whilst research into aerobic capacity after stroke has often incorporated a cycling paradigm [21-23], few trials have specifically evaluated the effects of cycling exercise on motor function early after stroke. There are some indications that cycling activity may have a positive effect on strength, reciprocal activation of antagonistic muscle groups and balance in stroke survivors in the sub-acute and chronic stages but cautious interpretation of these results is required for a number of reasons: sample sizes were relatively small ($n = 24$ [24]; $n = 17$ [20]; $n = 8$ [25]), exact time since stroke onset was not specified [24] and findings related to a single session which was not repeated over time [20].

In addition, much of this work has used a recumbent position with a standard leg cycle ergometer for cycling exercise [20,22,24,25]. Although suitable for cardiovascular training, this position does not replicate the upright posture needed for walking. We propose that cycling to provide functional training of the lower limbs early after stroke is best provided in an upright posture, in order to maximise potential for activity in major lower limb muscle groups, in a posture similar to walking. Indeed, muscle activation patterns during pedalling are not fixed and are modified according to body position [26,27] and heightened levels of activity in quadriceps and hamstrings have been demonstrated in more upright pedalling postures [26].

We have therefore adapted a standard exercise bike a) to provide trunk support in an upright pedalling posture and b) to maximise opportunities for patients with severe lower limb weakness to pedal, with use of the UniCam crank (UniCam Inc, Emerson, New Jersey, USA; see *instrumentation*). This crank enables a reduced circumference of the pedalling circle on the paretic side, where position 2 (P2) is the smallest circle and position

9 (P9) the largest (i.e normal pedalling). A preliminary study (unpublished, 2004/05, Wandsworth UK, Local Research Ethics Committee 03.0102) has demonstrated that stroke survivors can: a) pedal the modified exercise cycle for up to ten minutes with no adverse effects, and b) tolerate the different positions of the right and left pedals. Participants were included in this observational study if they were at least 14 days after stroke onset, able to sit without support for one minute, able to follow a one-stage command, previously independently mobile but now unable to mobilise and having no other limiting disease process or pathology.

Potential prognostic indicators for therapeutic interventions

Therapists use a wide range of clinical interventions in their repertoire but there is little research evidence to guide clinical decisions on which patients are likely to respond to which therapies. Possible influential factors include the location and size of brain lesion [28,29], degree of motor weakness; and ability to control the trunk to sit independently [30,31]. It is unknown whether these factors are prognostic for obtaining benefit from pedalling exercise early after stroke.

Aims

The driver for this proposed research is the hypothesis that UniCam crank-assisted upright pedalling (UP), used as an adjunct to conventional physical therapy, enhances recovery of lower limb motor function in stroke survivors with substantial paresis early after stroke. However, before this hypothesis can be tested in a phase III trial, it is important to establish whether there is sufficient evidence of benefit (clinical efficacy) to justify proceeding to subsequent larger trials and which stroke survivors are most likely to be able to participate in UP (prognostic indicators). Therefore, the aims for the current early phase clinical research study are:

1. Clinical Efficacy

To determine whether there is sufficient evidence for UP, balancing efficacy and potential adverse events (pain and fatigue), to justify proceeding to subsequent larger clinical trials; as assessed by:

- a) ability to voluntarily contract paretic muscle;
- b) production of reciprocal activation of antagonistic muscle groups during pedalling, similar to walking;
- c) timing of onset and offset of activity in antagonist muscle groups during pedalling, similar to walking;
- d) ability to walk independently.

2. Prognostic Indicators

To determine whether site of stroke lesion, trunk control ability, severity of lower limb paresis and/or ambulatory ability predicts ability to use UP within 30 days of stroke onset.

Methods

Design, setting and randomisation

The proposed study will be a single centre, early phase randomised controlled trial with observer blinding, preceded by an observational component. This design is illustrated in figure 1.

Study procedure

All participants will undergo baseline measurement set 1 (prognostic indicators). They will then be assessed for their ability to perform UP. Potential participants will be taken to the treatment area and shown the cycling equipment. If content to proceed, a hoist will be used to seat them on the bike safely. They will be asked to pedal slowly for one minute to familiarise themselves with the equipment. They will then be asked to pedal for one further minute and a visual observation of whether they can pedal or not will be made.

Those unable to pedal and who are 31 days or more after stroke onset will be excluded from the randomised part of this trial. Those unable to pedal and who are 30 days or less after stroke onset will be offered further pedalling assessments approximately every three days. The rationale for further pedalling assessments is that, during the first 30 days after stroke, people may experience fear of movement or emotional distress and therefore may need more than one experience of pedalling within a therapeutic environment. Without repeated opportunities for pedalling assessment some participants may be excluded unfairly from the opportunity to participate in UP.

Those participants able to pedal for one minute and who are 30 days or less after stroke onset, will then undertake baseline measures set 2 (clinical efficacy). Participants will then be allocated randomly to either routine conventional physical therapy (CPT; control group) or to CPT plus UP (experimental group). Randomisation order will be generated before the trial begins by an independent statistician, in blocks of four. Group allocation will be concealed in sequentially numbered opaque sealed envelopes held by an independent administrator, who is not involved in the study and will have no contact with study participants. The next highest number envelope will be opened by the independent administrator in response to a telephone request from the research therapist. After opening, envelopes will be stored securely with the participants' study data. Randomisation will be concealed from the independent outcome

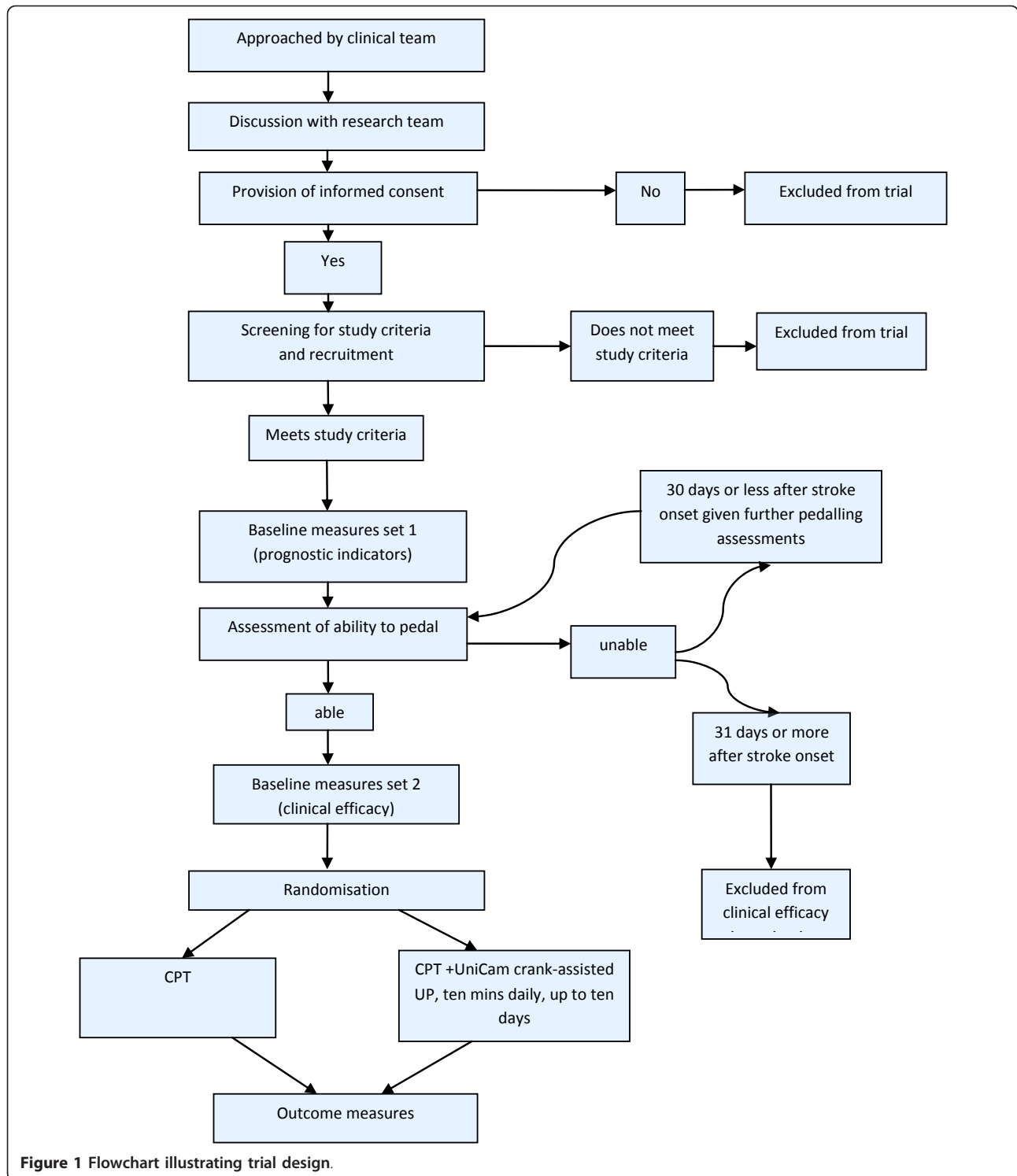


Figure 1 Flowchart illustrating trial design.

assessor and participants will be asked not to discuss group allocation with the outcome assessor.

Participants will receive their allocation intervention for up to ten minutes a day, for up to ten working days or discharge from acute stroke care, whichever occurs first. On

completion of the intervention phase, participants will undertake clinical efficacy outcome measures. Every attempt will be made to undertake outcome measures even if participants withdraw or are discharged before the intervention phase is completed (intention to treat principle).

Blinding

Blinding of research therapists in a therapy intervention study is not always feasible and patients are clearly aware that they are undergoing therapeutic interventions. Consequently, for this exploration of pedalling exercise, blinding of therapists and participants is not possible. However, the independent assessor of clinical outcome measures will be a trained therapist blinded to group allocation.

Ethical considerations

Patients with communication deficit (particularly aphasia) are frequently excluded from stroke rehabilitation research, despite having potential for motor benefit. In clinical practice, however, stroke survivors with aphasia are included in motor rehabilitation. This protocol ensures that, providing patients can follow a single-stage command, they can participate. Thus the results of this trial will be applicable to clinical practice. In addition, the protocol addresses a frequent complaint from stroke survivors with aphasia; namely that they are not given opportunities to be involved in research.

However, in clinical practice as well as research, it is important to distinguish between language and cognitive communication impairment and close liaison with the clinical team, in particular the Speech and Language Therapy members, is essential. Before approaching a potential participant, the researcher will therefore discuss decision making capacity of individuals with the clinical team. If, as a result of their assessment, the clinical team's conclusion is that communication impairment is too great to allow an individual to give informed consent, then the researcher will not approach the potential participant. If the clinical team's conclusion is that informed consent is possible, albeit with the use of enhanced communication strategies, then the researcher will approach the potential participant.

Enhanced communication strategies will be used in this trial. These include the use of diagrams, charting information, repetition in a variety of ways and checking for understanding. In addition, information sheets and informed consent forms present information in a textual and pictorial form.

All potential participants will be given at least 24 hours (1 working day) to consider the information and ask questions. They will be encouraged to consult with others, outside of the research team, before making their decision.

All data will be encrypted and then stored on an laptop computer by the researcher before leaving the stroke unit. Data will be transferred onto a secure hard drive in the research laboratory. No names will be used in any recorded material except for the initial screening document. Participants will be anonymised with the use of study ID numbers.

The research study has received the **approval of the Essex 1Research Ethics Committee, UK (09/H0301/52)**.

Participant inclusion criteria and recruitment process

Participants will be recruited from an acute stroke unit and, if necessary due to pressure on stroke beds, medical wards; in a University Hospital Trust. Consultant and therapy teams have agreed to support this trial.

Stroke survivors will initially be approached by a clinical team member responsible for their care, to check that they agree to speak to a researcher. If they agree, then a researcher will provide potential participants with verbal and written printed information about the trial. A video of the procedure for getting on and off the exercise cycle will also be available if patients wish to view it. A minimum of twenty four hours (1 working day) later, informed, signed consent will be sought. Those providing written informed consent will be participants in this trial. All potential participants will then be screened to check that they meet the study criteria, which are;

- adults aged 18+
- three to thirty days following a unilateral stroke resulting in unilateral muscle weakness with or without sensory deficit;
- fit to participate as assessed by a consultant-led medical team with resting oxygen saturations 95% or above, resting heart rate 90 beats per minute or less and systolic blood pressure of 100-160 mmHg
- score 0, 1 or 2 on the Functional Ambulation Categories [32]. Clinically, this means unable to walk; or need the help of two or more people; or require firm continuous or intermittent support of one person assisting with weight and balance;
- be able to sit unsupported for 30-seconds on the edge of a bed with feet on the floor.
- have sat out of bed in a chair or wheelchair at least once for a continual period of 15-minutes i.e. have appropriate sitting tolerance to participate in this cycling intervention;
- be able to follow a one-stage command i.e. sufficient communication, orientation and memory to participate in this cycling intervention;
- be independently mobile with or without an aid prior to the index stroke;
- have no co-existing pathology contributing to observed impairment in the paretic lower limb e.g. osteoarthritis with associated knee deformity.

Sample Size

This early phase trial is the first to use this equipment and with this participant group. Consequently there are no data to inform a power calculation. Sample size will therefore be based on practical considerations, using

estimates of the number of participants we could expect to recruit within a 12 month time period. Using data from our previous trials of rehabilitation early after stroke [e.g [33]], we estimate a recruitment rate of two participants per month. Therefore, the sample size has been set at 24 participants.

Intervention and Instrumentation

All participants will receive routine conventional physical therapy (CPT) as deemed appropriate by the clinical team. To enable replication of CPT we will record its content and dose (minutes of therapy) with a standardised schedule [34].

Control intervention

Participants allocated to the control group will receive CPT only as described above.

Experimental Intervention

Participants allocated to the experimental group will receive UP in addition to CPT. All experimental participants will be asked to pedal at 50 revolutions per minute (50 rpm) at a comfortable resistance whilst maintaining a heart rate of 85% or below their age-predicted maximum (i.e. less than $220 - \text{age} \times 0.85$ beats per minute). If patients cannot achieve 50 rpm, the research therapist will be guided by their response in setting the maximum rpm. The mean rpm achieved will be recorded for each participant for each intervention session. It is anticipated that few patients this early after stroke will immediately manage ten minutes of pedalling, so the number of minutes pedalled, up to ten minutes, will be recorded.

Each intervention session will also involve recording: the pedal crank setting; the degree of reciprocal activation of antagonistic muscle groups (see measurement battery); the timing of onset and offset of activity in antagonistic muscle groups (see measurement battery); and the distance pedalled (m). This description of each intervention session will allow replication of the intervention and information on how to progress the intervention over time in subsequent clinical trials.

Instrumentation

Maintaining sitting balance early after stroke often requires substantial concentration and physical effort which may limit production of selective movement in the paretic lower limb. We have therefore adapted a standard exercise bike so that postural support for the trunk is provided if needed (figure 2).

We have also incorporated a UniCam crank, an adjustment that can be applied to any commercially available exercise bike and which enables movement of the axis of the crank towards the centre of rotation of the bike pedal. This thereby reduces the circumference of the pedalling circle and reduces the required range of movement at the knee and hip, allowing patients who

may have substantial lower limb weakness and/or limitations in the range of joint movement to still pedal.

EMG data will be collected using the *Datalink* system (Biometrics, UK). Muscle activity in quadriceps and hamstring muscles for each leg will be recorded using SX 230 (Biometrics, UK) preamplifiers. The preamplifiers connect to 4 analogue channels of the *Datalink* subject unit, which is connected to the base unit. Information from the base unit is collected on a lap top computer running the *Datalink* software system. Continuous EMG data will thus be recorded during pedalling.

The bicycle wheel is demarcated every 45 degrees using reflective tape. As the participant pedals, an LED sensor placed at a fixed point on the bicycle frame, is triggered as each of the eight markers passes (figure 3). This trigger creates a drop in voltage, creating a spike in the software. The spikes are recorded synchronously, via a digital channel on the *Datalink* subject unit, with the EMG data. This system allows for muscle activity to be related to the position of the pedal during the 360 degree turn.

Measurement battery

Baseline measures will be made before randomisation and outcome measures after the intervention phase has been completed (figure 1). Baseline measures consist of two sets: prognostic indicators and clinical efficacy. Outcome measures will consist of clinical efficacy measures only.

The *participant characteristics* to be recorded for all potential participants and participants will be: gender, age (years), type and site of the stroke lesion (liaison with medical team from scanning/clinical findings) and time since stroke onset at entry to the trial and at each set of study measures (days).

Clinical efficacy measures

As the primary aim of this pedalling intervention is to enhance ability to voluntarily contract paretic muscle, the primary measure enables assessment of impairment level change. The Motricity Index [35] is a simple measure that can be used easily in the clinical setting to assess the severity of motor impairment. It is also a significant predictor of ambulatory outcomes after stroke [30,36]. Hence it is a highly clinically relevant measure, as it provides a direct assessment of motor function that is correlated with eventual mobility outcomes.

To detect changes in muscle activity underlying participants' observed performance, EMG data will be employed. Therapists in the clinical setting frequently observe and record alterations in, for example, muscle strength and walking ability, but cannot accurately measure the biological changes in muscle activity that might contribute to changes in functional performance. In recording, processing and analysing at this level, the proposed trial will be



Figure 2 The modified exercise cycle.

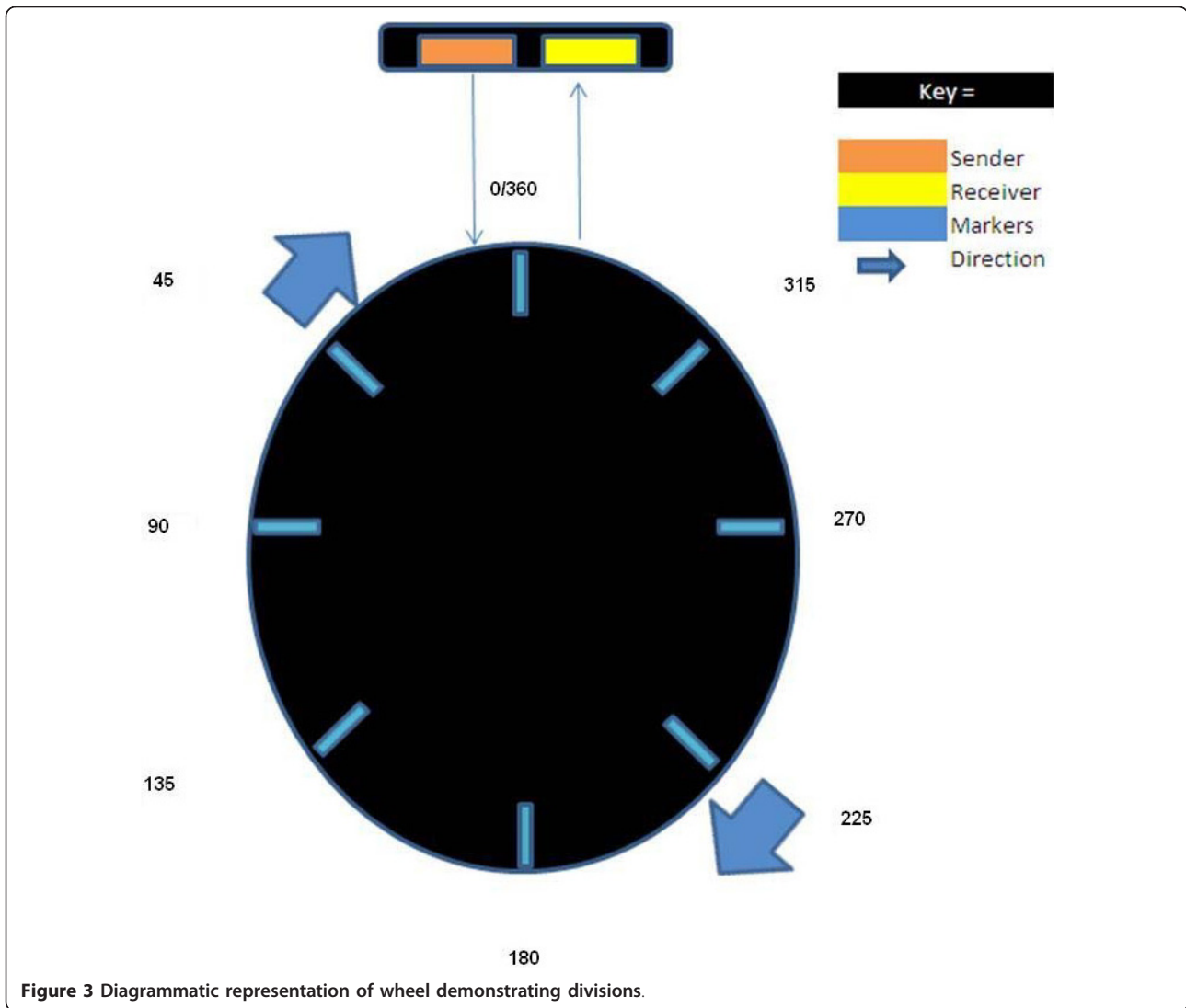
able to evaluate biological change alongside frequently used clinical measures of recovery. This change in motor activity will be able to be detected earlier than if using clinical measures of movement performance alone.

Regaining mobility is a key goal for stroke survivors and independent mobility enables independence in other activities of daily living [9,30]. It is possible that, as pedalling exercise uses similar motor control patterns to those required for walking, UP after stroke might have a positive effect on ambulatory function. A measure of walking ability has therefore been included in this study. The Functional Ambulatory Categories (FAC) [32] has demonstrated

sensitivity in stroke survivors who cannot walk at the beginning of their rehabilitation period, applicable to participants in this trial, who are not mobile at inclusion. This measurement of ambulatory function provides an assessment of an activity level change that is highly relevant after stroke and completes a spectrum of measures for this trial from body structure through function to activity.

Primary outcome 1. Ability to voluntarily contract paretic muscle

This will be measured by the Motricity Index (MI) lower limb section [35]. The MI is a widely used measure and



has established validity and reliability for use after stroke [37]. It is an ordinal weighted scale with six measurement levels within each of three categories for the lower limb. The three categories are: ankle dorsiflexion, knee extension, and hip flexion. For each movement, a score of 0, 9, 14, 19, 25, or 33 is given, where 0 is no movement, 19 is full range movement against gravity not against resistance and 33 is normal power.

Secondary outcomes 2. Ability to walk independently

As measured by the Functional Ambulation Categories (FAC) [32]. This scale is designed to give detail on physical support needed by patients for walking, so has clinical relevance, and is easy to use. It has established validity and reliability for use after stroke [38]. It is an ordinal scale, patients scoring from 0-5, where 0 indicates a patient who is not able to walk or needs help of 2 therapists, and 5

indicates a patient who is independent in ambulation even on stairs.

3. Onset and offset of EMG activity of antagonistic muscle groups during pedalling

EMG activity will be recorded in quadriceps and hamstring muscles for each leg. Before getting on the bike, participants will have a small (37 mm × 18 mm) pre-amplifier applied to the front and back of their thigh on both sides, following skin preparation to minimise signal interference. Electrode position is known to be a vital factor in achieving accurate EMG information [39]. For this study, a single researcher will place the electrodes for each participant and for every session, using published guidelines [40]. When the participants are positioned comfortably on the bike, the leads from the

pre-amplifiers will be connected as described in *instrumentation*.

Resting EMG activity will be recorded as a voltage at 1,000 Hz whilst the participant's foot is resting firmly on a box so that the leg is still and supported with the knee in 5-15 degrees of flexion, for 30 seconds. This will be undertaken for each leg. EMG data (voltage) will be collected continuously during pedalling for a minimum of 30 seconds at approximately 50 rpm.

Baseline EMG values will be calculated from the rectified, processed signal as the mean \pm 3 SD (standard deviations) during the 30 seconds baseline data collection period. Onset of activity in each of the four muscle groups will be defined as the time point during the 360 degree turn at which EMG voltage exceeds the mean baseline value plus 3SD for 20 consecutive data points (20 ms). Offset of activity in each of the four muscle groups will be defined as the time point during the 360 degree turn at which EMG voltage falls below the mean baseline value minus 3SD for 20 consecutive data points (20 ms). The time point for onset and offset of muscle activity in each of the four muscle groups will also be recorded as a function of the position of the pedal during the 360 degree turn.

4. Reciprocal activation of antagonistic muscle groups (muscle activity) during pedalling

Rectified EMG data for each antagonistic muscle group will be analysed using Spearman's correlation coefficient. An r value of 1.0 indicates perfect positive correlation and therefore complete co-contraction, no reciprocal activation, of an antagonistic muscle pair. An r value of 0 indicates no correlation and therefore no relationship between EMG activity of an antagonistic muscle pair. An r value of -1.0 indicates a perfect negative correlation and therefore complete reciprocal activation of antagonistic muscle groups.

Prognostic indicator measures

5. Site of stroke lesion

The location and size of stroke lesion have been demonstrated to be a prognostic factor for functional outcomes after stroke [28,29]. It is possible, therefore, that this clinical factor might be linked to the ability to take part in rehabilitation interventions. Brain lesion location will therefore be recorded from the clinical scan.

6. Degree of muscle weakness as measured by the Motricity Index (see clinical efficacy measures)

7. Ambulatory Capacity as measured by the Functional Ambulatory Categories (see clinical efficacy measures)

The FAC has been found to have good predictive validity for community ambulation after stroke (FAC \geq 4 predicts community ambulation at six months with 100% sensitivity and 78% specificity) [38]. It is proposed that pedalling exercise might have a positive effect on walking and thus postulated that the ability to walk might influence the ability to pedal and respond to pedalling intervention.

8. Ability to control the trunk

As measured by the Trunk Control Test [37]. This is a short, simple measure of motor loss developed for use after stroke. Patients are asked to do four movements-rolling to their weak side, rolling to their strong side, sitting up from lying down and balancing in a sitting position. Each movement is scored according to ability, either 0, 12 or 25, leading to a total score out of 100. Validity and reliability (comparison with Rivermead Motor Assessment at six, twelve and eighteen weeks post-stroke-Spearman's rho, $r = 0.70, 0.72$ and 0.79 respectively; interrater reliability, Spearman's rho, $r = 0.76, p < 0.001$) have been established [37].

Balance (trunk) control is highly specific to ambulatory control, and makes a crucial contribution to the ability to perform activities of daily living [41]. The Trunk Control Test has been found to be a predictor of functional outcomes after stroke, including significant correlation with: discharge Functional Independence Measure (Pearson's $r = 0.738$) and gait velocity (Pearson's $r = 0.654$) [31]; and discharge walking ability (Spearman's rho = 0.71) [36]. It is possible, therefore, that trunk control early after stroke might influence the ability to perform rehabilitation activities and thus will be assessed as a potential prognostic indicator for pedalling exercise after stroke.

Adverse events

There is a small risk that for some people, UP might lead to an "overuse" syndrome, as expressed through an increase in pain or fatigue. We will monitor for this by checking for participant reports of lower limb pain, either verbal or behavioural. Intervention will cease and an adverse event recorded if a participant demonstrates a decrease of 2 or more minutes in ability to pedal on 2 consecutive treatment days, or a 25% reduction in mean rpm on 2 consecutive treatment days.

Statistical Analysis

The aim of the analysis is not to definitively demonstrate efficacy in this early phase trial. Rather the data will be used to inform a decision on whether or not to undertake subsequent studies of UP. Assuming a normal distribution, independent t-tests will be used to compare groups between trial arms for follow-up measures, together with

95% confidence intervals to inform preliminary conclusions on clinical benefit. Within-group analysis will be assessed using paired t-tests. If a normal distribution cannot be assumed, analogous non-parametric methods will be used.

Associations between potential prognostic indicators and the ability to pedal will be examined using Fishers Exact test.

Trial management

A Trial Management Group (TMG) will provide overall supervision and ensure good conduct of the trial (i.e. adherence to the Declaration of Helsinki). The TMG will meet every three months during the course of this trial. In accordance with the MRC code of good practice in clinical trials and the CONSORT guidelines, we will document all decisions regarding eligibility for entry, consent giving, inclusion, exclusion and attrition. Members of the TMG will be: the researcher (NH) and members of the research team (VP, LS, PR, PKM). Every six months during data collection, the TMG will include an invited independent patients' advocate from the clinical stroke service.

Discussion

This protocol describes an original, two-stage early phase trial, in which a group of early stroke survivors will first be evaluated for their ability to pedal a modified upright exercise cycle. Those who can pedal the cycle will then be participants in an early phase randomised controlled trial of daily pedalling intervention, for up to ten subsequent working days of their in-patient hospital stay.

Findings from neuroimaging studies suggest that rehabilitation programs incorporate repetition, motor skill acquisition and functional activity in order to optimally drive useful cortical plasticity [e.g. [10-14]]. It has been suggested that early rehabilitation intervention might exploit a crucial period in which the brain is primed to begin repair, in the first few days after stroke onset [1,2]. Therapists are therefore challenged to find rehabilitation strategies incorporating these underlying principles. Cycling provides a paradigm through which such activity might be achieved even in early stroke participants with severe weakness. For this trial, a prototype upright exercise cycle has been developed to enable such patients to experience bilateral pedalling motion. The locomotor strategies employed during cycling are akin to those used in ambulation [18] and our exercise cycle also incorporates adaptations to allow stroke survivors with considerable weakness to attempt to pedal in an upright posture, similar to walking.

Whilst evidence exists correlating clinical aspects of stroke to functional outcomes [e.g. [28-30]], prognostic

information on what factors might influence the ability to take part in specific rehabilitation activities has yet to be established. This information has the potential to inform the design of future research and provide indicators to clinicians about which patients might best take part in which activities. The current trial will record four potential prognostic indicators-site of lesion, trunk control, paretic leg motor function and walking ability-before participants attempt to use the equipment; links to the ability to pedal the pedalling activity will be analysed and contribute to clinical conclusions and inform future research. For this novel aspect of the study, selection of potential indicators was based on those factors previously demonstrated to correlate to functional outcomes after stroke.

Some exploratory studies have investigated the potential clinical efficacy of pedalling exercise after stroke [20,24,25] but the early findings of our systematic review (in progress) suggest that no trial has evaluated upright pedalling in a group of stroke survivors within one month of stroke onset. The potential challenges that early stroke survivors might face in taking part in this activity, such as safely sitting in an upright posture and taking part in repetitive exercise, have been addressed: firstly by using a modified exercise cycle, and secondly, by ensuring that physiological parameters and evidence of fatigue are monitored and recorded by the research team.

It is possible that our results might indicate none of the prognostic indicators are linked to the ability to pedal, and/or clinical efficacy of the intervention is not demonstrated. If this is the case, the risk of wasting valuable research resources on larger-scale trials, using the current indicators and measures, is minimised. However, interpretation of findings, whether negative or positive, will reflect the small sample size and early phase nature of this work.

A further novel aspect is that this study of pedalling exercise incorporates biological level measures, alongside more frequently used clinical, functional measures. EMG data from quadriceps and hamstrings will be recorded at baseline and outcome as well as at each pedalling session, providing evidence of any change at a biological level that might contribute to, and underpin, possible changes in functional measures. Using sessional EMG recordings will also allow analysis of whether pedalling is being achieved by the unaffected leg propelling the crank i.e with the use of compensatory strategies, or whether there are changes in recordable activity in the affected leg suggestive of recovery.

The control group will undergo conventional therapy only, and this will be quantified on a standardised treatment schedule, allowing for comparisons of amount and type of therapy across trial arms. Concern has been expressed that reporting of research into complex interventions often lacks sufficient detail on comparators

[42]. The use of careful recording of conventional therapy in this trial will go some way towards addressing these concerns and might provide important information for potential dose-matching in later phase work.

This trial is being carried out in an acute stroke unit, and uses portable EMG equipment so that all trial measures can be taken on site. This enables participants to take part in an active rehabilitation setting and hence exploration of the feasibility of the use of the modified bicycle in a busy therapeutic environment; and ensures close collaboration between clinical and research teams for the duration of data collection.

In summary, the proposed novel, early phase research will increase knowledge of prognostic indicators for, and clinical efficacy of, upright pedalling exercise early after stroke. It will provide essential information for the design of subsequent trials.

Abbreviations

UP: UniCam crank-assisted upright pedalling; RCT: Randomised Controlled Trial; CPT: Conventional Physical Therapy; FAC: Functional Ambulatory Categories; MI: Motricity Index; TMG: Trial Management Group

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Authors' contributions

NH, LS, and VP participated in the study design. PKM provided medical clinical collaboration at the site and contributed to study design. PR provided bioengineering design support. NH drafted the manuscript and is the lead researcher at the site. VP and PKM contributed to the final draft of the manuscript, and it was approved by all authors. NH is undertaking this work as part of a PhD at the University of East Anglia, UK.

Competing interests

The authors declare that they have no competing interests.

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Effects of lower limb reciprocal pedalling exercise on motor function after stroke: a systematic review of randomized and nonrandomized studies

Nicola J. Hancock^{1*}, Lee Shepstone¹, Will Winterbotham² and Valerie Pomeroy¹

This review systematically synthesized current evidence on the effects of lower limb reciprocal pedalling exercise on motor function poststroke. Detailed analysis of single studies in the review revealed multiple instances of heterogeneity including outcome measures; therefore we decided to avoid undertaking a single, potentially misleading meta-analysis. We found that despite beneficial (although nondefinitive) effects on balance, functional independence, and muscle strength, it is not possible to make clinical recommendations that support or refute the use of reciprocal pedalling exercise to enhance recovery of motor function after stroke. Our findings provide proof-of-concept for pedalling interventions and provide a foundation for subsequent research, suggesting a need for further standardized, controlled clinical trials of clearly described pedalling interventions for stroke survivors and with subsequent transparent reported findings.

Key words: cycling, pedalling, rehabilitation, stroke, systematic review, therapy

Background

Poststroke, it is possible to drive beneficial functional reorganization of the brain with behavioural training (1,2). Repetition of motor activity can produce changes in brain representation maps (3,4). Motor skill acquisition, or motor learning, may drive these changes (4–6). The findings suggest

rehabilitation programmes incorporate these underlying principles and hence involve:

- increasing levels of motor skill
- goal-directed activity (7), and
- tasks that are meaningful for participants in rehabilitation programmes (8).

It remains unclear which specific therapeutic modalities are best used to provide the repetitive, skilled activity necessary to drive brain changes that might lead to improvements in functional activities, like gait.

Regaining walking independence is a principle objective for many patients (9); interventions contributing to this functional outcome are therefore important in a goal-directed rehabilitation programme. Poststroke, patients often have substantial leg weakness and are unable to contract paretic muscle sufficiently to take part in functional, relevant activity, like walking training.

Both patient and therapist effort is often too great to enable more than a few repetitions of activity; and this dose might be too low for effect. The number of repetitions of an activity needed to facilitate brain reorganization has not been established in human studies, although animal model studies suggest that 300–400 repetitions in a 30-min session might be required (10). Therapists are challenged to find strategies that enable repetitive reciprocal activity in those with lower limb weakness poststroke.

Pedalling is a repetitive, functional activity that has been proposed to have potential benefit to patients when used as an adjunct to therapy after stroke (11). While familiar to many stroke survivors, reciprocal pedalling is likely to require reacquisition of motor skill following the onset of haemiparesis. It requires that agonist and antagonist lower limb muscles are contracted reciprocally and in a similar repeating pattern to that required for walking (12). Evidence from an exploratory observational study suggests that pedalling may facilitate phasic, coordinated muscle activity even in patients with severe haemiparesis (13).

Pedalling might enhance motor recovery after stroke but to the best of our knowledge, the current available evidence has not been collated nor analysed. This paper presents a systematic review carried out to synthesize existing knowledge of the

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effects of pedalling exercise after stroke. The aim of the review was to establish whether there is currently sufficiently robust research evidence to justify using lower limb pedalling exercise to enhance motor recovery after stroke.

Methods

The design of this review followed recommendations of the Cochrane Collaboration (14). The review protocol was not published prior to this report. The review was carried out by the lead author (N. H.) and an independent reviewer (W. W.).

Search strategy

The following databases were searched electronically: COCHRANE: Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; Central Register of Controlled Trials; Cochrane Methodology Register; Cochrane Stroke Group; MEDLINE; EMBASE; CINAHL; AMED; PEDro; PsycINFO. The search was developed in close liaison with a medical librarian and terms were adapted according to the specific requirements of each database (Box 1).

The search period was conducted to cover induction of the databases to March 2010. Reference lists included in the full text papers retrieved were hand searched for any extra possible relevant records, as were our own private databases of

Box 1 Example search strategy for electronic databases: ovidMEDLINE, EMBASE, AMED, psycINFO

1. exp Cerebrovascular Disorders/
2. exp Stroke/
3. (cerebral or cerebellar or brainstem or vertebro-basilar or brain).mp.
4. (infarct* or ischemia or thrombo* or embol*).mp.
5. 4 and 3
6. (cerebral or brain or subarachnoid or intracerebral or intracranial or cerebellar).mp.
7. (haemorrhage or hematoma or bleed*).mp.
8. 6 and 7
9. (hemipleg* or hemipar*).m_titl.
10. 8 or 1 or 9 or 2 or 5
11. limit 10 to (English language and humans and 'all adult (19 plus years)')
12. (bicycl* or bike or pedal* or ergomet* or cycle or cycling or cyclical).mp.
13. (cycle* adj menstrea*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14. 12 not 13
15. limit 14 to (English language and humans and 'all adult (19 plus years)')
16. 11 and 15

references was undertaken. Contact was made with key authors in the field. These were identified as those publishing three or more papers in the area of study following the initial title scan.

Criteria for inclusion of studies

Types of study

The initial scoping exercise revealed a limited number of randomized controlled trials (RCTs) of the intervention, which is not uncommon for rehabilitation interventions (15). Stringently restricting design may have led to the exclusion of studies of interest. Consequently, the review was not confined to RCTs and all study designs were included.

Types of participants

Adults, over 18 years, at any time poststroke.

Types of interventions

There were no methodological restrictions on dose, frequency, intensity, or duration of intervention. The following interventions were included:

- reciprocal pedalling exercise designed to enhance motor recovery in paretic lower limb
- reciprocal lower limb pedalling exercise as part of an aerobic exercise programme; outcomes include evaluation of effect on motor function
- reciprocal lower limb pedalling exercise in any body position, and
- reciprocal lower limb pedalling exercise as a one-off intervention or series of interventions over time.

The following interventions were excluded:

- pedalling exercise where used solely to achieve a maximal exercise stress test for the evaluation of aerobic capacity
- pedalling exercise where used as an adjunct to other therapeutic interventions, e.g. with functional electrical stimulation; or as part of a combined therapeutic exercise programme, and
- pedalling used for movement analysis/modelling, i.e. pedalling not used for the investigation of efficacy.

Types of outcome measures

All outcomes of motor function after stroke used in the included studies (excluding upper limb outcomes). 'Motor function' here encompasses a spectrum from the physiological functioning of body systems and structure, through to the execution of specific tasks by an individual. Outcomes included:

- timing of onset and offset of muscle activity
- reciprocity of muscle activity
- muscle strength, and
- balance and walking, and stair-climbing ability.

Examples of measures included: electromyography, the Motricity Index, the Functional Ambulatory Categories, timed walking, and stepping tests and measures of functional independence.

Study selection

To ensure consistency of reviewers' selection of studies, we randomly selected 50 titles from the total pool, using a computerized random number system. These titles were sent to the second reviewer for identification of potential studies. A preliminary meeting was then held, where agreement of response was evaluated and any disagreements discussed to finalize criteria for study selection.

The two reviewers then worked independently to identify eligible studies, using the criteria for inclusion of studies. The reviewers considered each reference independently via a title scan, categorizing as 'definitely relevant', 'possibly relevant' or 'definitely irrelevant'. This process was repeated for abstracts and full papers. Disagreements were resolved in one-one discussion. Any persistent disagreements were referred to a third party and were resolved by discussion and re-referral to the original paper. This process eventually resulted in all full papers being categorized as 'definitely relevant' or 'definitely irrelevant'.

Assessment of potential risk of bias

The potential risk of bias within all included studies was assessed by using the Cochrane Collaboration tool (14). This is normally only used for RCTs but we also chose to use the same tool for risk assessment of potential bias within the nonrandomized studies. While it was not developed with such studies in mind, the general structure is suggested as useful where studies are heterogeneous and no quantitative synthesis is planned (14). The use of this tool for the nonrandomized studies allowed for heterogeneity to be clearly demonstrated.

Each study was individually evaluated according to the criteria by the lead author, in consultation with the review team.

Data extraction and management

Data were extracted on key aspects of each study, including design, participants, type, dose and duration of intervention, equipment, and setting.

Measures of treatment effect

Cohen's effect sizes were calculated for continuous outcomes in the randomized controlled studies to assess the magnitude of effects. Differences in the direction of measures were corrected, for example multiplication by -1 for those scales where an increase in the measure indicates worsening motor function.

Data synthesis and interpretation

Though effect sizes have been stated where calculable, meta-analysis was not indicated because of heterogeneity across

domains including design, participants, methods, and outcomes. Statistically combining such clinically diverse studies would be meaningless, thus a narrative synthesis was considered most appropriate. Qualitative data synthesis was enabled by tabulation, with motor function outcomes classified according to the *International Classification of Functioning* (16). Interpretation was informed by the assessment of potential biases alongside examination of effect sizes where relevant.

Results

The literature search identified 1628 records from the electronic database searches. Contacts with lead authors produced 23 records and four were identified via the hand search. After removal of duplicates, 1345 records progressed to filtering. Via title screening, 90 records were considered potentially relevant for abstract review, at which stage 52 were eliminated and 38 progressed to detailed filtering by full text review. Twelve papers were finally selected for inclusion in this review (Fig. 1).

Design

The design of the included studies was heterogeneous (Table 1). Five of the 12 were randomized controlled, or randomized clinical, trials (19–21,24,25). One used a prospective matched control design (27). Three studies used a 'before-and-after' design with a single group of participants (13,22,23). Two of these used the same cohort of participants: the earlier paper evaluated and reported pedal reaction force components following bicycle training (22), the second paper evaluated and reported functional outcomes after the pedalling intervention (23). Seki *et al.* (2009) (26) was considered a 'before-and-after' study for the purposes of this review, as the only relevant extractable data were from the single group of stroke survivors in their report.

Two papers presented either case reports or single case studies (11,18).

Participants

The participant details are presented in Table 1. Altogether there were 351 participants included in the 12 studies (range 1–92). Of these, data were extractable on 288 (range 1–90). No study used more than 92 participants, and four used less than 10 (Table 1). The mean age of participants in the 12 studies ranged from 55 (13,18) to 69 (26) years. Time since stroke onset at admission to studies ranged from six-days (27) to a mean of 57 months (21). There was a trend in using participants later after stroke onset – only two studies used participants less than three-months from onset (11,27). Two other studies stated that participants were excluded if they were admitted to the rehabilitation unit where the research took place later than 30 days from stroke onset, but did not clarify at when they were admitted to the research study (19,20).

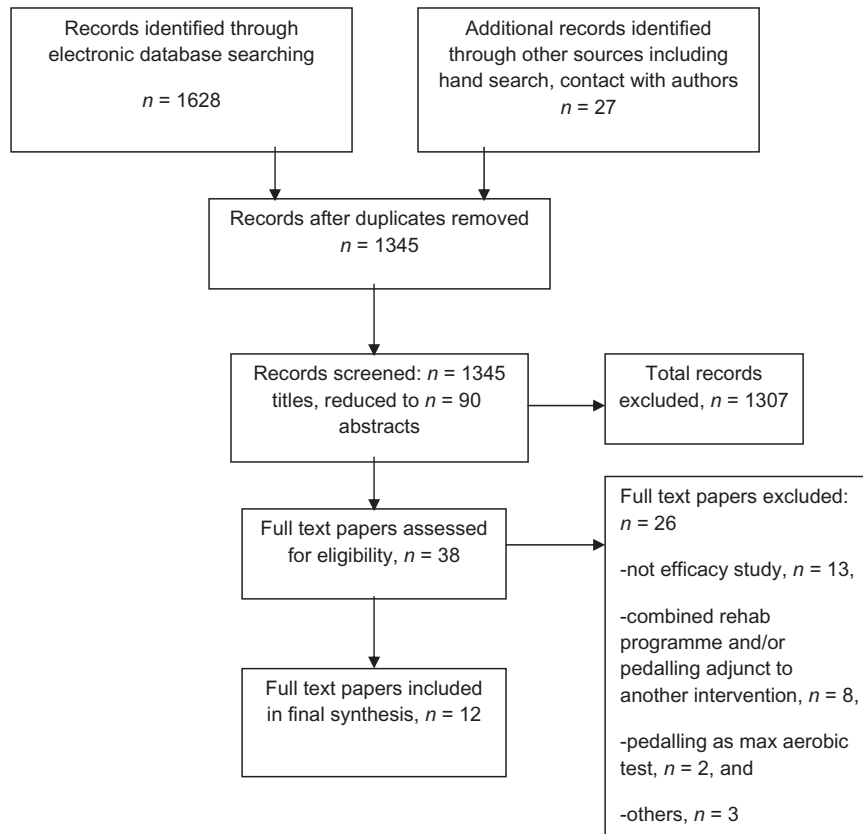


Fig. 1 Flow diagram of results of systematic review search strategy.

Primary purpose, intervention, dose, and equipment

The primary purpose of the included studies was either: (1) to investigate the effects of pedalling exercise on motor function after stroke (11,13,20,22,23,26); and (2) to investigate the effects of aerobic programmes, where pedalling exercise was used as the primary tool (18,19,21,24,25,27) (Table 2).

Although all interventions involved reciprocal pedalling exercise of the lower limbs, there was heterogeneity across numerous domains, including dose and duration of pedalling exercise and variety of cycling equipment (Table 2). The interventions were achieved in different ways, including, for example, pedalling on a standard static exercise bike (18), pedalling an adapted wheelchair (26), and pedalling a limb-loaded cycling device (11). Detailed information about equipment was given in only two studies (11,26).

Dose of pedalling activity varied from a single session of pedalling for eight wheel turns (26), to 30 mins of pedalling three times per week for 10 to 12 weeks (21,24).

Control interventions

The control interventions in the five RCTs were:

- routine therapy only (19,20)

- sham exercise carried out for the same time per session as the intervention (21)
- passive exercise regime carried out for the same time per session as the intervention (24), and
- home-based program of stretching exercises at the same weekly frequency as the pedalling intervention group, with telephone contact by a physical therapist once each week (25).

Outcome measures and effect sizes: summary of findings

The 12 included papers evaluated effects using a range of outcome measures and time intervals for measurement points. Outcomes were classified according to the *International Classification of Functioning* (16) (Tables 3–7). Because of the heterogeneity observed between studies, meta-analysis was not indicated. However, where appropriate data were available, Cohen's effect sizes (defined as the difference in means divided by the pooled within group standard deviation) were calculated to enable presentation of the magnitude of any effects. An approximate 95% confidence interval for this effect size was calculated based on the method described by Reiser and Guttman (28).

Table 1 Participant characteristics

Study	Study design	Side stroke lesion (n)		Type of stroke (n)		Haemorrhage	Time since stroke onset (mean (SD) where given) unless stated)	Age (mean years (SD) unless stated)
		N	Left	Right	Ischaemia/infarct			
Brown <i>et al.</i> (11)	Case series	2	1	1	1, I not stated	–	10 days; 7.5 weeks	77 years, 68 years
Fujiwara <i>et al.</i> (17)	Before-and-after	17	9	8	5	12	158.8 (57.9) days	55.1 (10.9)
Holt <i>et al.</i> (18)	Single case study	1	1	0	0	1	18 months	55
Katz-Leurer <i>et al.</i> (19)	RCT	92	Not stated	Not stated	80	12	Not specifically stated but excluded those admitted to study rehabilitation unit >30 days since acute hospitalization	63 (11)
Katz-Leurer <i>et al.</i> (20)	RCT	24	14	10	24	0	Not specifically stated but excluded those admitted to study rehabilitation unit >30 days since acute hospitalization	63 (9)
Lee <i>et al.</i> (21)	RCT	52*	21	27	33	9	57 (54) months	63.2 (9)
Perell <i>et al.</i> (22,23)	Before-and-after	8	6	2	Not stated	Not stated	Two-years (median)	64.5 (median)
Potempa <i>et al.</i> (24)	RCT	42	19	23	Not stated	Not stated	>Six-months	Range 21–77 years
Quaney <i>et al.</i> (25)	RCT	38	Not stated	Not stated	Not stated	Not stated	4.9 ± 3.3 years	Control group 58.96 (14.7); Ex group 64.10 (12.3)
Seki <i>et al.</i> (26)	Before-and-after	10	5	5	6	4	68.7 days	69 (range 55–81)
Tang <i>et al.</i> (27)	Matched controls	57†	11	12	17	5 (1 unknown)	17.8 days (range 6–62)	64.7 (range 19–90)

*Four participants discontinued after baseline, data stated in paper only for 48 participants.

†Complete participant characteristic data only stated for 23 participants originally allocated to the exercise group. RCT, randomized controlled trial.

Table 2 Primary purpose of study, intervention, dose, and equipment used

Study	Primary purpose of pedalling exercise (MF: motor function; AE: aerobic exercise)	Dose/duration of pedalling exercise	Type of exercise equipment used
Brown <i>et al.</i> (11)	MF: Feasibility of limb-loaded cycling as exercise intervention for stroke	10 sets of 20 repetitions in each session. Patient 1 – 13 sessions completed; Patient 2 – five sessions of hybrid programme developed as unable to complete initial programme.	Limb-loaded cycling device
Fujiwara <i>et al.</i> (17)	MF: Assessment of effects of pedalling exercise on lower limb muscle activity	Single session, pedalling for five-minutes	Servo-dynamically controlled ergometer with trunk support
Holt <i>et al.</i> (18)	AE: Effects of an aerobic programme on participant's functional mobility	Eight-weeks of two and three sessions per week on alternate weeks, 20 sessions total. Twelve-minutes pedalling incrementally increased by two-minutes on alternate sessions to maximum of 30 mins	Static bicycle
Katz-Leurer <i>et al.</i> (19)	AE: Effects of early aerobic training on independence and activity at six-months	Part 1: 10 sessions over two-weeks, two-minutes per session increasing within tolerance to 20 mins per session Part 2: Nine sessions over three-weeks, 30 mins per session	Leg cycle ergometer
Katz-Leurer <i>et al.</i> (20)	MF: Effects of early cycling training on balance	Five sessions per week for three-weeks, individualized programme	Leg cycle ergometer
Lee <i>et al.</i> (21)	AE: Effects of aerobic cycling programme on walking ability	30 sessions over 10 to 12 weeks, each session 30 mins of cycling with resistance adjusted to achieve a target heart rate. After each session, underwent 'sham' leg resistance training.	Semi-recumbent motorized isokinetic cycle ergometer
Perell <i>et al.</i> (22,23)	MF: evaluation of pedal reaction forces following bicycle training	Three sessions per week for four-weeks, each session consisted of 12 one-minute cycling trials with one-minute rests in between.	Recumbent bicycle with adapted pedals to allow for force measurements
Potempa <i>et al.</i> (24)	AE: evaluation of response of stroke patients to aerobic training	3 sessions per week for 10 weeks, 30 mins per session. For first 4 weeks, training load gradually increased, for final 6 weeks, highest training load maintained for each participant	Adapted cycle ergometer
Quaney <i>et al.</i> (25)	AE: Effect of aerobic cycling programme on executive function and mobility	3 sessions per week for 8 weeks, progressing aerobic intensity from week 2	Stationary bicycle
Seki <i>et al.</i> (26)	MF: Assessment of effects of pedalling exercise on lower limb muscle activity	Single session, pedalling for 8 wheel revolutions	Cycling wheelchair
Tang <i>et al.</i> (27)	AE: feasibility of adding aerobic cycle ergometry to standard rehabilitation early after stroke	3 sessions per week, up to 30 mins a session, individualize programme for each participant	Semi-recumbent cycle ergometer

Table 3 Summary of findings, randomized controlled trials

Author and date	N	Outcome measurement time points	Outcome measures	Means (SD)		Outcomes categorized according to ICF				Cohen's effect size, where calculable (95% CI)
				Control	Intervention	BS/F	A	P		
Katz-Leurer et al. (19)	92	Immediately postintervention	FIM score	101.4 (16.0)	105.8 (12.5)		X			0.31 (-0.10 to 0.72)
			Walking distance (m)	94.8 (107.6)	122.8 (143.0)		X			0.22 (-0.19 to 0.63)
			Walking speed (m/s)	0.45 (0.1)	0.51 (0.1)		X			0.60 (0.18 to 1.02)
			Stair climbing (no. stairs)	18.1 (14.4)	25.4 (14.1)		X			0.51 (0.10 to 0.93)
			PASS total	23.0 (4.3)	28.7 (3.1)		X			1.50 (0.61 to 2.43)
			PASS static	7.2 (1.8)	9.3 (1.5)		X			1.25 (0.38 to 2.15)
			PASS dynamic	15.8 (2.8)	19.4 (1.7)		X			1.54 (0.64 to 2.47)
			FMA score	19.3 (7.1)	26.3 (5.8)		X			1.07 (0.22 to 1.94)
			FIM total	73.1 (22.8)	77.5 (21.8)		X		X	0.20 (-0.61 to 1.00)
			FIM motor	9.2 (3.0)	13.6 (2.4)		X			1.60 (0.69 to 2.55)
Lee et al. (21)	52	Within 1 week final intervention	PASS total	26.4 (3.8)	31.1 (2.2)		X			1.50 (0.60 to 2.42)
			PASS static	9.0 (1.8)	10.7 (1.7)		X			0.97 (0.11 to 1.83)
			PASS dynamic	17.4 (2.3)	20.3 (0.7)		X			1.78 (0.74 to 2.67)
			FMA score	22.1 (6.8)	29.1 (5.9)		X			1.09 (0.23 to 1.96)
			FIM total	79.2 (21.4)	87.8 (23.5)		X		X	0.39 (0.44 to 1.20)
			FIM motor	12.1 (3.2)	16.1 (2.0)		X			1.47 (0.59 to 2.41)
			Six-minute walk (m)	278.1 (162.1)	261.5 (162.7)		X			-0.10 (-0.87 to 0.70)
			Habitual gait velocity (m/s)	0.78 (0.43)	0.74 (0.41)		X			0.09 (-0.68 to 0.87)
			Fast gait velocity (m/s)	0.93 (0.54)	0.94 (0.55)		X			-0.02 (-0.79 to 0.75)
			Stair climb power (W)	116.5 (67.8)	121.3 (80.9)		X			0.06 (-0.70 to 0.83)
Potempa et al. (24)	42	Immediately postintervention	Max strength affected leg (N)	714.1 (225.9)	768.0 (352.7)			X		0.18 (-0.57 to 0.94)
			Peak power affected leg (W)	269.8 (140.2)	229.1 (140.2)		X			-0.27 (-1.07 to 0.49)
			Endurance affected leg (mean no. reps)	5.1 (3.2)	5.7 (4.0)		X			0.16 (-0.60 to 0.93)
			FMI score	183 (7.9)	173 (10.4)			X		-1.11 (-1.75 to -0.42)
			FMA score	81.42 (36.80)	77.84 (34.85)		X			-0.10 (-0.73 to 0.54)
			Berg Balance score	39.05 (14.27)	41.68 (9.62)		X			0.22 (-0.42 to 0.85)
			Get Up and Go fast speed (s)	29.11 (45.26)	15.26 (14.82)		X			0.46 (-0.23 to 1.06)
			FMA score	80.52 (35.72)	76.39 (33.93)		X			-0.19 (-0.75 to 0.51)
			Berg Balance score	38.79 (14.11)	42.06 (9.87)		X			0.27 (-0.37 to 0.91)
			Get Up and Go fast speed (s)	25.74 (35.84)	16.78 (18.32)		X			0.33 (-0.33 to 0.95)
Quaney et al. (25)	38	Immediately postintervention	Berg Balance score	39.05 (14.27)	41.68 (9.62)		X			0.22 (-0.42 to 0.85)
			Get Up and Go fast speed (s)	29.11 (45.26)	15.26 (14.82)		X			0.46 (-0.23 to 1.06)
Quaney et al. (25)	38	8 weeks postintervention	FMA score	80.52 (35.72)	76.39 (33.93)		X			-0.19 (-0.75 to 0.51)
			Berg Balance score	38.79 (14.11)	42.06 (9.87)		X			0.27 (-0.37 to 0.91)
Quaney et al. (25)	38	8 weeks postintervention	Get Up and Go fast speed (s)	25.74 (35.84)	16.78 (18.32)		X			0.33 (-0.33 to 0.95)

Key: Small, moderate, large positive effect; negative effect. CI, confidence interval.

Table 4 Summary of findings, matched-control study

Author and date	N	Outcome measurement time points	Outcome measures	Means (SE)		Outcomes according to ICF			
				Control	Intervention	BS/F	A	P	
Tang <i>et al.</i> (27)	Total = 57; 36 used in end analysis (18 matched pairs; Gait measures: four in each group unable to undertake as nonambulatory and further four not assessed at discharge because of equipment failure)	Immediately prior to discharge, exact times not stated	Preferred pace gait speed (m/s)	0.82 (0.08)	0.84 (0.08)		X		
			Preferred pace gait symmetry (ratio, n = 20 symmetrical at study entry)	1.15 (0.02)	1.28 (0.07)	X			
			Preferred pace gait symmetry (ratio, n = 11 asymmetrical at study entry)	1.17 (0.02)	1.29 (0.04)	X			
			Fast paced gait speed (m/s)	1.19 (0.1)	1.06 (0.11)		X		
			Fast pace gait symmetry (ratio, n = 20 symmetrical at study entry)	1.11 (0.01)	1.28 (0.07)	X			
			Fast pace gait symmetry (ratio, n = 11 asymmetrical at study entry)	1.14 (0)	1.28 (0.05)	X			
			Six-minute walking test distance (m)	288.4 (38.9)	334.2 (33.1)		X		
			SIS QOL subscale	67.1 (4.6)	72.4 (3.8)			X	
			Findings:	No significant between group differences (at $P < 0.05$). Trends to improvement in gait speed and symmetry across both control and intervention groups.					

Table 5 Summary of findings, before-and-after studies

Author and date	N	Outcome measurement time points	Outcome measures	Findings	Outcomes according to ICF		
					BS	A	P
Fujiwara <i>et al.</i> (17)	17	Immediately after intervention, 30 mins after intervention	Muscle activity during knee extension (integrated EMG quadriceps femoris, medial hamstrings, tibialis anterior, medial gastrocnemius)	Increased activity in quadriceps and tibialis anterior immediately after pedalling and continuing for 30 mins. Medial hamstrings and medial gastrocnemius activities reduced after pedalling and reduction continued for 30 mins	X		
Perell <i>et al.</i> (22)	Total = 8 (4 extractable data)	Two days after intervention completed	Pedal reaction forces (N)	Tangential pedal reaction forces directed more posteriorly after pedalling training authors suggest this has implications for ankle control during pedalling	X		
Perell <i>et al.</i> (23)	8	2 days after intervention completed	Muscle strength (N): knee flexors and extensors	Eccentric muscle strength in knee extensors increased bilaterally; concentric muscle strength in knee extensors increased in involved limb ($P < 0.05$)	X		
Seki <i>et al.</i> (26)	10	Immediately after intervention	50-foot walking speed (m/s) Muscle activity during pedalling (EMG gluteus maximus, rectus femoris, hamstrings, tibialis anterior, soleus)	Nonsignificant trend to improved pace of walking following intervention Significant increases in rectus femoris, tibialis anterior, and soleus muscle activity of affected leg during pedalling in comparison with a baseline isometric contraction		X	X

EMG, electromyography.

Table 6 Summary of findings, single case study

Author and date	N	Outcome measures	Measurement time points with outcomes			Outcomes according to ICF		
			Baseline 1	Baseline 2 (within 19 days of baseline 1)	Posttraining (20 sessions)	BS	A	P
Holt <i>et al.</i> (18)	1	10 m timed walk (s)	36.5	35.0	24.0		X	
		Speed gait during 10 m (ms)	0.27	0.29	0.42		X	
		Steps during 10 m walk	37	40	32		X	
		6-min walking distance	99	107	145		X	
		Speed gait during 6 mins walk (ms)	0.27	0.30	0.40		X	
		Motricity Leg Score	65	65	76	X		
		Ashworth Knee Score	2	2	1	X		
		Ashworth Ankle Score	4	4	2	X		

Findings: Positive progression demonstrated in walking speed, distance and muscle strength according to the Motricity index with no adverse effects on spasticity in the upper or lower limb

Table 7 Summary of findings, case series

Author and date	N	Measurement time points	Outcome measures	Outcomes according to ICF		
				BS	A	P
Brown <i>et al.</i> (11)	2	Varies across 2 participants as pedalling regimes varied according to ability	Dynamic load index (load x reps)	X		
		Three times during 10–13 pedalling sessions	FIM		X	
		Three times during 10–13 pedalling sessions	Ambulatory statuses (description)		X	

Findings: For each participant, measures used to demonstrate progression in ability only. Positive progression in FIM score, walking status and Dynamic Load Index demonstrated for both over the intervention period.

Motor impairment

Measures of motor impairment included muscle strength and activity measures and predominated across the smaller, exploratory studies (e.g. (13,22,23,26)). General trends to benefits in strength and activity were observed across these studies (Tables 4 and 5). One RCT (21) also demonstrated a small positive effect on maximum affected knee muscle strength (effect size (E.S.)=0.18, confidence interval (CI) –0.57 to 0.94) and affected leg endurance (E.S=0.16, CI –0.60 to 0.93) (Table 3).

Functional activity

Measures of activity predominated across the randomized studies. Individual study comparisons found a trend towards beneficial effects on balance immediately after pedalling intervention (Postural Assessment Scale for Stroke (PASS), total, E.S=1.5, CI 0.61 to 2.43; PASS static, E.S=1.25, CI 0.38 to 2.15; PASS dynamic, E.S=1.54, CI 0.64 to 2.47; Berg Balance, E.S=0.22, CI –0.42 to 0.85; Get Up and Go, E.S=0.46, CI

–0.23 to 1.06), and at six- to eight-week follow-up (PASS, total, E.S=1.5, CI 0.60 to 2.42; PASS static, E.S=0.97, CI 0.11 to 1.83; PASS dynamic, E.S=1.78, CI 0.74 to 2.67; Berg Balance, E.S=0.27, CI –0.37 to 0.91; Get Up and Go, E.S=0.33, CI –0.33 to 0.91) (20,25) (Table 3). Two studies demonstrated a moderate positive effect size on functional independence measures (E.S=0.31, CI –0.10 to 0.72; E.S=0.39, CI 0.44 to 1.20) (19,20) (Table 3). The study using matched controls found no significant differences between control and intervention groups on a series of walking measures (27) (Table 4). Any beneficial effects have been interpreted with caution alongside the assessment of potential biases and consideration of sample sizes and confidence intervals.

Assessment of potential bias

The results of the assessment of potential bias are presented in Table 8.

Table 8 Potential risk of biases across studies

Study	Sequence generation		Blinding		Incomplete outcome data		Selective result reporting		Other potential biases	
	Allocation concealment?	Adequate sequence generation?	Blinding participants?	Blinding providers?	Blinding assessors?	Where relevant, incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?		
Katz-Leurer et al. (19)	UNCLEAR	YES	UNABLE	UNABLE	UNCLEAR	YES	NO	YES		
Katz-Leurer et al. (20)	UNCLEAR	YES	UNABLE	UNABLE	UNCLEAR	UNCLEAR	YES	YES		
Lee et al. (21)	YES	YES	UNCLEAR	UNABLE	YES-primary NO-secondary	YES	YES	UNCLEAR		
Potempa et al. (24)	UNCLEAR	UNCLEAR	UNABLE	UNABLE	UNCLEAR	YES	YES	UNCLEAR		
Quaney et al. (25)	UNCLEAR	UNCLEAR	UNABLE	UNABLE	YES	YES	YES	YES		
Tang et al.* (27)	UNCLEAR	UNCLEAR	UNABLE	UNABLE	NO	UNCLEAR	YES	UNCLEAR		
Brown et al.* (11)	NO	NO	UNABLE	UNABLE	NO	N/A	YES	NO		
Fujiwara et al.* (17)	NO	NO	UNABLE	UNABLE	NO	N/A	YES	NO		
Holt et al.* (18)	N/A	N/A	UNABLE	UNABLE	UNCLEAR	N/A	YES	YES		
Seki et al.* (26)	NO	NO	UNABLE	UNABLE	NO	N/A	UNCLEAR	NO		
Perell et al.* (22)	NO	NO	UNABLE	UNABLE	UNCLEAR	N/A	YES	YES		
Perell et al.* (23)	NO	NO	UNABLE	UNABLE	UNCLEAR	N/A	YES	YES		

YES: LOW risk of bias; NO: HIGH risk of bias; UNCLEAR: unclear; UNABLE: not possible, e.g. participant blinding in trial where pedalling was the key intervention. *nonrandomized studies.

In summary, none of the included studies had a low risk of bias for all eight assessed design elements. Only one study had adequate allocation concealment (21) and only three studies demonstrated adequate sequence generation (19–21). Assessors were blinded for all outcomes in only one study (25). Blinding of participants and intervention providers was not used in all 12 studies as it is, of course, difficult, if not impossible, to avoid knowledge of provision of an exercise-based intervention. In general, the assessment of bias would have benefitted throughout from improved clarity of reporting of key elements of studies.

Excluded studies

Of the 38 studies, 26 were excluded at the full text review stage (Table 9) (29–54) Reasons for exclusion included: pedalling used as a paradigm for analysing and evaluating movement after stroke, not designed to enhance motor recovery, pedalling used as an adjunct to another intervention, e.g. functional electrical stimulation pedalling used as part of a combined therapy programme where it was impossible to extract data from the pedalling intervention alone.

Interpretation and discussion

The synthesis indicates that there is some, but limited, support for pedalling exercise benefiting muscle activity, muscle strength, balance, and functional independence after stroke, from early phase studies. However, interstudy heterogeneity, small sample sizes, wide confidence intervals for effect sizes, and the risks of potential biases suggest that this evidence is not sufficiently robust to support or refute the use of reciprocal pedalling exercise to enhance recovery of motor function after stroke. These present findings support the conclusion of a narrative review by Fujiwara and colleagues (17), that while pedalling might have potential to enhance motor function in people with central nervous system disorders, further research is needed before use in clinical practice.

The smaller, exploratory studies included in this review show the feasibility of using pedalling interventions (e.g. (12,23,26)). These studies also found some trends towards benefit from pedalling on measures of motor impairment, including lower limb muscle activity and muscle strength. These findings provide proof-of-concept, but insufficient evidence to support or refute the clinical use of pedalling. Risks of potential biases were high for these studies, often as a direct reflection of study design, though reports of results according to design were generally clear. However, it was this set of studies, plus one small randomized pilot study (20) that specifically aimed to examine the effects of pedalling activity on motor function. All of the larger studies used pedalling as a form of aerobic exercise, though did include some secondary outcomes of motor function, evaluated generally using activity level measures. No large-scale study specifically designed to evaluate the effects of pedalling activity

Table 9 Excluded studies

Author and year	Reason for exclusion at full text review stage
Bowden <i>et al.</i> (29)	Not an efficacy study
Brown & DeBacher (30)	Not an efficacy study
Brown & Kautz (31)	Not an efficacy study
Brown & Kautz (32)	Not an efficacy study
Brown <i>et al.</i> (33)	Not an efficacy study
Chen <i>et al.</i> (34)	Not an efficacy study
Dawes <i>et al.</i> (35)	Not an efficacy study
Ferrante <i>et al.</i> (36)	Pedalling as an adjunct to another intervention (functional electrical stimulation)
Janssen <i>et al.</i> (37)	Pedalling as an adjunct to another intervention Electrical Stimulation (ES), stimulation to elicit muscle contraction given to intervention group and 'sensible' stimulation that could be felt but did not elicit activity given to control group
Katz-Leurer & Shochina (38)	Not an efficacy study, examined pedalling patterns as predictor of activity at six-months: other
Kautz & Brown (39)	Not an efficacy study
Kautz <i>et al.</i> (40)	Unilateral pedalling: other
Kautz <i>et al.</i> (41)	Pedalling as part of a combined exercise programme
Kautz & Patten (42)	Not an efficacy study
Kelly <i>et al.</i> (43)	Not an efficacy study
Lennon <i>et al.</i> (44)	Pedalling as maximum aerobic test and upper limb pedalling involved
Makino <i>et al.</i> (45)	Physiological costs of pedalling activity and not a true efficacy study: other
Marklund & Klassbo (46)	Pedalling as part of combined programme
Perell <i>et al.</i> (47)	Not an efficacy study
Rogers <i>et al.</i> (48)	Not an efficacy study
Rosecrance & Guiliani (49)	Not an efficacy study
Sibley <i>et al.</i> (50)	Pedalling as maximum aerobic test
Sibley <i>et al.</i> (51)	Pedalling as an adjunct within a combined programme
Sullivan <i>et al.</i> (52)	Pedalling as part of a combined programme
Sullivan <i>et al.</i> (53)	Pedalling as part of a combined programme
Szecs <i>et al.</i> (54)	Pedalling as an adjunct to another intervention (functional electrical stimulation)

on motor function after stroke was found in this review process. Hence, evidence from the smaller studies in this review might provide precursors for later phase studies of clinical efficacy, incorporating measures of both impairment and activity.

While meta-analysis was not indicated for the RCTs, single study examination revealed large effect sizes for beneficial effect on balance and functional independence, immediately and six-weeks after a pedalling intervention (20). However, the

large effect sizes should be interpreted with caution as sample size for this pilot study was small, with 10 participants in the intervention arm and 14 in the control, confidence intervals were wide; and a moderate risk of bias was evident. A small beneficial effect on balance was also demonstrated in a study of aerobic pedalling exercise but again, sample sizes were small with 19 in each trial arm, confidence intervals were wide and there was a lack of clarity of reporting on key elements (sequence generation) (25). Despite these positive trends, definitive, generalizable conclusions cannot be drawn about effects of pedalling on balance and functional independence. It is noteworthy that one of the larger studies with the lowest risk of bias demonstrated small but positive effects on lower limb muscle strength and endurance with pedalling intervention in 54- to 72-year olds with chronic stroke, supporting observations in the smaller studies (21).

It is of interest that the mean participant age of 63 years was nonrepresentative of the UK stroke population, where 75% of first strokes occur in those aged 65 and over (55). Older stroke survivors may present different research and rehabilitation challenges to younger survivors. For example, the likelihood of multiple pathologies alongside the stroke may be higher, leading to extraneous reasons why participation in rehabilitation activities and research trials might be limited. Further research into pedalling exercise in an older participant group is indicated to ensure generalizability of findings to the surviving stroke population.

Over half of the included studies recruited participants greater than three-months since stroke onset. It is possible that such patients are easier to recruit to exercise trials, as they tend to be more medically stable and with less fluctuation in their abilities. However, current evidence suggests that early therapeutic intervention might optimize potential for recovery. Clinical studies support the concept that early rehabilitation is important for improving outcomes (56–58). Indeed, Cramer (2008) (59) describes a 'golden period' for initiating restorative therapies, when the brain is galvanized to begin repair, starting in the first days after onset and continuing for several weeks. This review has identified that current research into pedalling as a potential therapeutic intervention has not exploited this important window, and thus results cannot be generalized to early stroke survivors. Opportunities therefore exist for further exploration of the effects of pedalling exercise in stroke survivors early after onset.

Studies included in this review used variable doses of pedalling interventions. Evidence on optimal dose of rehabilitation interventions after stroke remains equivocal (60). Although the number of repetitions of an activity needed to facilitate brain reorganization has not been established in human studies, animal model studies suggest that 300–400 repetitions in a 30-min session might be needed (10). Pedalling exercise has the potential to provide high numbers of repetitions of lower limb flexion and extension in reasonable therapeutic time frames, and there are opportunities for future research to explore optimal, tolerable doses in stroke survivors.

Limitations of the review

It is possible that there was some influence of a publication bias as the search was limited to studies written only in English.

Conclusions

This review has, for the first time, systematically synthesized the current evidence on the effects of lower limb reciprocal pedalling exercise on motor function after stroke. Our detailed analysis of single studies included in the review revealed heterogeneity across multiple domains including outcome measures, and thus we decided to avoid undertaking a single, potentially misleading meta-analysis.

Despite some beneficial, though not definitive, effects on balance, functional independence, and muscle strength, the review has found that it is not possible to make clinical recommendations that support or refute the use of reciprocal pedalling exercise to enhance recovery of motor function after stroke. The findings provide proof-of-concept for pedalling interventions and provide a foundation for subsequent research, suggesting a need for further standardized, controlled clinical trials of clearly described pedalling interventions, across a broad range of stroke survivors and with subsequent transparent reporting of findings.

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Abbreviations

AE	Aerobic Exercise
ANOVA	Analysis of Variance
AVERT	A Very Early Rehabilitation Trial
BDC	Bottom Dead Centre
BS,A,P	Body Structure, Activity, Participation
CES	Cohen's Effect Size
CONSORT	Consolidated Standard of Reporting Trials
CPT	Conventional Physiotherapy
EEG	Electroencephalography
EMG	Electromyography
FAC	Functional Ambulatory Categories
FesTivaLS	Functional Strength Training in the Lower Limb later after stroke (Trial)
FIM	Functional Independence Measures
FMA	Fugl Meyer Assessment
fMRI	Functional Magnetic Resonance Imaging
GP	General Practitioner
Hz	Hertz
ICC	Intra-Class Correlation Coefficient
ICF	International Classification of Functioning
iEMG	Integrated EMG
ISRCTN	International Standard Randomised Controlled Trial Number
J-value	Jaccard's Coefficient
LED	Light Emitting Diode
M1	Primary Motor Cortex
MF	Motor Function
MI	Motricity Index

MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NNUH	Norfolk and Norwich University Hospitals NHS Trust
NRS	Non-Randomised Studies
PhaCO ₂	Partial Pressure of Carbon Dioxide
PASS	Postural Assessment Scale for Stroke
PCA	Principle Components Analysis
PET	Positron Emission Tomography
PRISMA	Preferred reporting of Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
RP	Reciprocal Pedalling
Rpm	Revolutions per minute
RR	Risk Ratio
RS	Randomised Studies
SCS	Single Case Studies
SD	Standard Deviation
S-PeD	Smoothness of Pedalling
SPSS	Statistical Package for the Social Sciences
TCT	Trunk Control Test
TDC	Top Dead Centre
TMS	Transcranial Magnetic Stimulation
UEA	University of East Anglia
UP	Upright Pedalling
U-PeD	Upright Pedalling Device
WHO	World Health Organisation

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