The effect of cycling using active passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe Multiple Sclerosis.

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Abstract

Background: Exercise is an important treatment strategy for people with Multiple Sclerosis (MS). However, exercise options are limited for those with higher levels of disability, as is the evidence to support the benefits. Lower limb active passive trainers (APTs) are used for people with higher levels of disability but there is little evidence on their efficacy. The aim of this thesis was to investigate the effects of lower limb APTs on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe MS.

Included studies: The first study included was a systematic review of the effects of cycling using lower limb APTs on spasticity, cardiovascular fitness, function and quality of life in people with neurological conditions. The second was an intervention study to explore the effects of a four-week programme of lower limb APT cycling on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe MS. The final study was to determine if a single session of APT cycling reduced spasticity, measured using neurophysiology (Hoffmans reflex/H-reflex), in people with moderate to severe MS.

Main findings: The systematic review identified that APT interventions may improve walking endurance (6MWT performance, $p<0.001$) but not walking speed ($p=0.31$), however this meta-analysis only included a small number of stroke studies. The effects in other conditions and on other outcomes was unclear, as was whether electrically stimulated cycling was more beneficial than APT cycling alone. The intervention study found APT cycling to be safe and feasible in people with moderate to severe MS. Improvements were noted in the majority of outcome measures, although no significant group differences were found. The APT group also showed significant improvements in their average speed, power output and distance cycled (all $p<0.001$). It was felt some of the outcome measures used lacked sensitivity, especially for spasticity. The H-reflex study found that a single session of APT cycling did not change spasticity measured using H-reflex, clinical scales or patient reported measures. The H-reflex was found to be a feasible and safe outcome measure, however it appeared to be easily influenced by other factors and was time consuming to complete.

Conclusion: This thesis highlighted that APT cycling is a safe and feasible intervention in people with moderate to severe MS, however measuring the effects of the intervention especially in relation to spasticity remain challenging. In addition, the dose, intensity and frequency required to improve symptoms, function and quality of life remains unclear. Further research is merited regarding the benefits of APT interventions and outcomes used in people with higher disability levels associated with MS.

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Author's declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Alison Barclay

Publications and presentations produced from this thesis

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Abbreviations

ADLs – Activities of daily living
APT – Active passive trainer
AS – Ashworth scale
BWSTT – Body weight supported treadmill training
CIS - Clinically isolated syndrome
CNS – Central nervous system
CO – Cardiac output
CO_2 – Carbon dioxide
CPET – Cardiopulmonary exercise test
CPM – Continuous passive motion
CSP – Chartered Society of Physiotherapy
CNS – Central Nervous System
CVD – Cardiovascular disease
DMTs – Disease modifying treatments
EDSS – Expanded disability status scale
EMG – Electromyography
EMOC – Extrapolated maximal oxygen consumption
ES – Electrical stimulation
ESAC – Electrically stimulated assisted cycling
EUSPASM – European assembly for spasticity management
FES – Functional electrical stimulation
FIM – Functional independence measure
H-reflex – Hoffmans reflex
H/M ratio – ratio of maximum H reflex to maximum M wave
HR – Heart rate
Hz – Hertz
L -Litre
O_2 - Oxygen
OUES – Oxygen uptake efficiency scale
MAS – Modified Ashworth scale
MD – Mean difference
MRI – Magnetic resonance imaging
MS – Multiple sclerosis
MSSS-88 – Multiple sclerosis spasticity scale
MSQOL-54 – Multiple sclerosis quality of life
NES – NHS Education for Scotland
NHSGGC – NHS Greater Glasgow & Clyde
NICE – National institute for health and clinical excellence
NRU – Neurological rehabilitation unit
O_2 – Oxygen
OT – Occupational therapy
OUES – Oxygen uptake efficiency slope
PA – Physical activity
PD – Parkinson's disease
PDRU – Physically disabled rehabilitation unit
pwMS – People with MS
PPMS – Primary progressive MS
PT - Physiotherapy
QOL – Quality of life
RCP – Royal College of Physicians

RER – Respiratory exchange ratio
RIS – Radiologically isolated syndrome
ROM – Range of movement
RPE – Rated perceived exertion
RPM – Revolutions per minute
RRMS – Relapsing and remitting MS
SLT – Speech and language therapy
SCI – Spinal cord injury
SMD – Standardised mean difference
SPMS – Secondary progressive MS
T25FW – Timed 25-foot walk
TBRST – Total body recumbent stepper training
TUG – Timed up and go
V_e – Minute ventilation
VAT – Ventilatory anaerobic threshold
VCO_2 – Carbon dioxide uptake
VO_2 – Oxygen uptake
VO_{2max} – Maximal oxygen uptake
VO_{2peak} – Oxygen up take at peak exercise
WR – Work rate

Chapter 1 Introduction

Multiple sclerosis (MS) is one of the most common disabling neurological conditions affecting 2.8 million adults worldwide (Walton *et al.*, 2020). It is a chronic, lifelong, progressive disabling disease affecting the central nervous system (CNS) and is characterised by demyelination and neurodegeneration (Correale *et al.*, 2017). Presentation of symptoms is dependent on the area of damage within the CNS, but symptoms are often subtle, starting as fatigue or minor changes within the sensory or visual systems. Progression of disease and disability is characterised by physical manifestation of symptoms such as muscle weakness and spasticity, leading to impaired activity and function (Vidal-Jordana *et al.*, 2017).

Physical activity (PA) is important in helping maintain health and wellbeing. The United Kingdom (UK) Government updated their PA guidelines in 2019 and while they continue to promote a weekly guide regarding dose, frequency and intensity of exercise, they also recognised that any exercise or PA can improve health (Davies *et al.*, 2019). While PA can include normal day to day tasks, occupation and leisure activities, exercise describes an activity that is more specific and structured, which is aimed to improve or maintain physical fitness (Caspersen *et al.*, 1985). Studies have shown that improving health related physical fitness can reduce the risk of mortality by up to 30%, however even small changes in PA levels, which may not influence fitness, can also help (Warburton *et al.*, 2016). Secondary gains include lowering the risk of developing other chronic conditions such as cardiovascular disease, cancer, diabetes, dementia and depression (Alves *et al.*, 2016; Anderson *et al.*, 2019; Davies *et al.*, 2019).

The detrimental effects of physical inactivity are especially seen in people with chronic conditions, such as MS, and leads to de-conditioning, reduced ability to perform daily activities, and a downward spiral of loss of functional capacity (Durstine *et al.*, 2013). Exercise is an important treatment strategy in the management of symptoms of MS. There are many ways people with MS (pwMS) choose to exercise which is driven by personal preference and capability (Motl *et al.*, 2012). However, exercise can be difficult for many pwMS due to their

symptoms, accessibility and transport (Learmonth *et al.*, 2016). In addition, the evidence base to support any benefits of exercise for pwMS with higher levels of disability remains poor (Latimer-Cheung *et al.*, 2013; Edwards and Pilutti, 2017; Kalb *et al.*, 2020) and exercise options are limited for people with moderate to severe MS exercise (Pilutti *et al.*, 2017; Sandroff *et al.*, 2017).

Cycling is an exercise often adopted in people with neurological problems as it improves aerobic endurance, muscle and bone strength, spasticity and function (Peng *et al.*, 2011; Bersch *et al.*, 2015; Giesser, 2015; Edwards and Pilutti, 2017; Shen *et al.*, 2018). Cycling is similar to walking in that they are both cyclical activities, involve reciprocal contraction and relaxation of major muscle groups of the lower limb and share sensori-motor control mechanisms (Barbosa *et al.*, 2015; Bersch *et al.*, 2015; Giesser, 2015; Edwards and Pilutti, 2017). For people with higher levels of disability, however, cycling on a normal bicycle or ergometer can be difficult or impossible, for reasons such as poor balance, weakness and spasticity. Lower limb active passive trainers (APTs) are an alternative to ergometers and allow cycling from a seated or supine position. The speed, resistance and type of exercise (active, active assisted or passive) can be adjusted depending on the person's abilities.

People with MS and higher levels of disability are admitted to the Neurological Rehabilitation Unit (NRU), formerly known as the Physically Disabled Rehabilitation Unit (PDRU), in Glasgow for medical review and intensive rehabilitation. APT's are regularly used as part of a treatment programme during their rehabilitation. The rationale for the current PhD has come from patients who anecdotally report improvements in limb spasticity and 'tightness' after use of an APT. An audit in NRU involving people who used APTs as part of their rehabilitation programme showed that nine out of the ten people surveyed reported to feel better or very much better after using it. Furthermore, some community rehabilitation/exercise settings offer APTs, and many people affected with MS purchase their own APTs to use at home, despite the lack of evidence to support their use.

Currently there is limited evidence regarding the effects of APT cycling on spasticity in pwMS and higher levels of disability, and this PhD aims to further

investigate this. The knowledge produced by this thesis will improve our understanding of the use of APTs and any benefits gained. It will also help inform practice so that health professionals can better advise on appropriate protocols to aid long term self-management of pwMS. Supporting people to manage their conditions may also reduce the reliance on carers or other health services.

1.1 Overall research aims

The overall aim of this thesis was to investigate the effectiveness of lower limb APTs in the management of symptoms associated with moderate to severe MS. The primary symptom of interest is spasticity, with the effects on other areas such as cardiovascular fitness, function and quality of life also of interest. To achieve this the thesis was split into three studies.

The first study explored the existing evidence regarding MS and its symptoms, and then considered exercise interventions for people with higher levels of disability (Chapter 2). An initial literature search regarding APT cycling in pwMS highlighted a lack of evidence and was expanded to include the use of electrical stimulated APT cycling and other neurological conditions. This was developed into a systematic literature review titled 'the effects of cycling using lower limb active passive trainers in people with neurological conditions' (Chapter 3). The aim was to examine the evidence for the use of lower limb APT, with and without neuromuscular stimulation, and to determine their effects in relation to spasticity, cardiovascular fitness, function and quality of life in people with neurological conditions.

The second study in this thesis, funded by the CSP Charitable Trust, aimed to evaluate the feasibility and potential effectiveness of a four-week programme of cycling using lower limb APTs in people with moderate to severe MS who were in-patients (Chapter 4). The primary aim was to determine the effect of lower limb APT interventions on outcomes such as spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe MS. The secondary aim was to test the feasibility of the intervention by establishing if

participants could tolerate a daily cycling programme for 30 minutes, in line with exercise guidelines, and if this resulted in any negative effects.

An area highlighted for future research from the second study was the need to identify a more sensitive measure of spasticity. The third study aimed to identify if neurophysiology (Hoffmans reflex (H-reflex)) was a feasible and more sensitive method of measuring spasticity than clinical scales and patient reported measures, following a single session of APT cycling in people with moderate to severe MS (Chapter 5). Neurophysiology measures were taken alongside clinical and patient reported measures, and feasibility was also considered as it was the first time this had been used in people with higher levels of disability from MS.

1.2 Impact of Covid-19 pandemic

The outbreak of Covid-19 pandemic occurred prior to the start of the H-reflex study (Chapter 5) and resulted in a suspension of research activity, and the studies of the author from April 2020 until August 2021. This delayed the study by a year and continued to impact following recommencement of research activity due to ongoing restrictions. This will be discussed further in Chapter 5.

Chapter 2 Multiple Sclerosis

Multiple Sclerosis (MS) is a neurodegenerative condition that affects the CNS causing damage to the myelin and nerves. It is characterised by focal regions of discolouration of white and grey matter and plaques which mainly occur in the optic nerves, periventricular areas, brain stem, cerebellum and spinal cord (Gajofatto *et al.*, 2015; Grigoriadis *et al.*, 2015; Vidal-Jordana *et al.*, 2017). Symptoms depend on the area of demyelination or plaque formation but will often include visual disturbances such as optic neuritis and diplopia; sensory symptoms including loss of sensation, paraesthesia, proprioception and balance (Vidal-Jordana *et al.*, 2017). Other common early symptoms include fatigue, pain and continence issues (Shah, 2015). As the disease progresses spasticity and motor impairments such as paresis and paralysis become more apparent leading to functional changes. MS affects 100,000 people in the UK and is the most common cause of physical disability in young adults (National Institute for Health and Care Excellence UK, 2022). Scotland has one of the highest incident rates of MS, which is reported to be 8.76/100,000 by the Scottish MS register (Kearns *et al.*, 2019).

Current theory regarding the pathogenesis of MS suggests it is an autoimmune and inflammatory disorder led by T-lymphocytes, B-cells and plasma cells within the CNS (Gajofatto *et al.*, 2015; Grigoriadis *et al.*, 2015; Dargahi *et al.*, 2017). T-cells mediate the inflammatory process and induce an inflammatory cascade, driving disease and tissue injury which culminates in demyelination and plaque formation. The principal target of the inflammatory infiltrate is the myelin sheath and oligodendrocytes, the latter being the cells responsible for myelin production and maintenance. Demyelinated plaques can be repaired and remyelinated presenting as shadow plaques, due to a reduction in myelin density (Lassmann, 2013). However, these shadow plaques are frequently targeted for further attacks, resulting in additional damage. Demyelination is the hallmark of MS with relative axon sparing, however in some cases axonal damage and loss can also occur early in the disease process (Grigoriadis *et al.*, 2015; Lemus *et al.*, 2018). Axonal loss is also associated with brain atrophy, which also correlates with both motor and cognitive decline and leads to the clinical presentation of neurological deficits seen in pwMS (Lassmann, 2013; Grigoriadis

et al., 2015; Lemus *et al.*, 2018). Both motor and somatosensory systems can be affected leading to physical signs and symptoms of MS as previously mentioned.

Diagnosis of MS is made using the McDonald criteria, updated in 2017, which requires lesions to be disseminated in time and space within the CNS, demonstrated on MRI (Thompson *et al.*, 2018). Analysis of cerebrospinal fluid for the presence of oligoclonal bands is also recommended to support a diagnosis, and especially when a diagnosis of clinically isolated syndrome (CIS) has been given (Vidal-Jordana *et al.*, 2017; Thompson *et al.*, 2018).

The clinical course of MS is characterised by periods of relapse then stability, and/or disease progression (Sand, 2015). Studies have shown that relapses play an important role in disability long term. A relapse is defined as newly appearing neurological symptoms without fever or infection that last for longer than 24 hours. In comparison, disease progression is continual worsening of symptoms over at least six months (Kamm *et al.*, 2014). More frequent attacks or relapses in the early stages of the disease, with short intervals between attacks are associated increased likelihood of disability long term (Kalincik *et al.*, 2014; Goodin *et al.*, 2016; Stewart *et al.*, 2017; Vidal-Jordana *et al.*, 2017). Other risk factors associated with this are older age at disease onset, being male, longer disease duration and Secondary Progressive MS (SPMS) (Goodin *et al.*, 2016; Stewart *et al.*, 2017; Vidal-Jordana *et al.*, 2017; National Institute for Health and Care Excellence UK, 2022). Studies have also shown that relapse activity in multiple neurological areas resulting in pyramidal, bladder and bowel, and cerebellar symptoms are more likely to associate with increased disability. In contrast relapses occurring in the sensory or visual systems are associated with greater recovery and less disability (Kalincik *et al.*, 2014; Stewart *et al.*, 2017). A study by Kalincik et al (2014) looked at 14,969 patients and considered over 89,949 episodes to analyse characteristics relating to initial relapse activity. They found that 71.4% of episodes affected only one system and presented with sensory, pyramidal or visual signs; sensory system (36.8%), visual (21.1%), pyramidal (17.7%), brainstem (15.6%), cerebellar (5.3%), bladder and bowel (2.4%), cognitive (1.1%).

Neurological impairment in MS is measured by the Expanded Disability Status Scale (EDSS) which is used by neurologists to classify disability. The EDSS was developed to score neurological signs, physical impairment and the impact of the disease by rating different functional systems to produce a combined score (Kurtzke, 2008). The scale ranges from 0, which indicates normal neurology and no disability, to 10, indicating death by MS. Lower scale values of the EDSS measure impairments based on neurological examination while upper values measure handicap. The minimal clinical important difference (MCID), which represents a meaningful change in function, has been shown to be 1.0 when EDSS is less than 5.5 and 0.5 when the score is between 5.5 and 8.5 (Meyer-Moock *et al.*, 2014). Clinically relevant milestones of the EDSS are reported to be at scores of 4.0, 6.0 and 7.0, when disability increases and independence and quality of life (QOL) worsen. Wynia et al (2012) undertook a longitudinal study over a 5-year period evaluating QOL and disease severity in 245 pwMS. They noted a significant relationship between increased disability and decrease in QOL in participants with EDSS scores of 0 to 4.5. In contrast they reported no such relationship in the more disabled population with EDSS ≥7 to <10.

EDSS is commonly used within research and clinical trials to define the level of disability and has been shown to have good validity and comparability (Meyer-Moock *et al.*, 2014). However, its limitations are the lack of cognitive or upper limb assessment as the focus is predominantly on walking ability. It has also been suggested to have limited inter and intra-rater reliability (Meyer-Moock *et al.*, 2014). Despite this it continues to be widely used in clinical practice.

There are different classifications of MS; primary progressive (PPMS), relapsing and remitting (RRMS) and SPMS (Stewart *et al.*, 2017; Vidal-Jordana *et al.*, 2017). In addition, CIS, the first episode of demyelination and clinical symptoms, and radiologically isolated syndromes (RIS), where patients are without clinical symptoms were added in 2017 (Lublin, 2014; Sand, 2015; Stewart *et al.*, 2017; Vidal-Jordana *et al.*, 2017). Both CIS and RIS present as a single episode of demyelination which may be suggestive of MS, but diagnosis cannot be made due to lack of dissemination in either time or space, in accordance with the McDonald diagnostic criteria (de Angelis *et al.*, 2019).

RRMS accounts for 85% of pwMS and is characterised by relapse or inflammatory activity followed by periods of stability or remission. SPMS is defined by gradual progression after a relapsing course, and the point of transition can be difficult to define. It is characterised by more diffuse demyelination and injury to both white and grey matter resulting in global neurodegeneration and clinical disability (Grigoriadis *et al.*, 2015). PPMS represents 15% of people diagnosed with MS and can present with or without inflammatory activity. It is characterised by gradual, continual neurological deterioration from disease onset (Stewart *et al.*, 2017; Vidal-Jordana *et al.*, 2017).

The cause of MS is unknown but is thought to be linked to various environmental and genetic factors. The most common age of onset is between 20-40 and having a first degree relative with the disease also increases the risk (Kamm *et al.*, 2014; Waubant *et al.*, 2019). Females are twice as likely to be affected than men (Kamm *et al.*, 2014; Vidal-Jordana *et al.*, 2017) although this sex-difference has been found to be slightly higher in Scotland with a ratio of 2.3:1 (Kearns *et al.*, 2019). The incidence of MS worldwide is 2.1 per 100,000 people (Walton *et al.*, 2020) and in Scotland is 8.76 per 100,000 (Kearns *et al.*, 2019). There is also a strong relationship between prevalence of MS and latitude, with MS less common nearer the equator (Waubant *et al.*, 2019; Walton *et al.*, 2020).

Prevalence has been studied across the continents and reported to be 4.8 per 100,000 in the Western Pacific, 8.6 per 100,000 in Southeast Asia, 8.8 per 100,000 in Africa, 32.9 per 100,00 in Eastern Mediterranean countries, 117.3 per 100,000 in America and 142.9 per 100,000 in Europe (Walton *et al.*, 2020). It is thought that the prevalence of MS is linked to lower sun exposure and vitamin D deficiency, which is also considered to be a risk factor for MS. Studies have shown a correlation between low vitamin D and increased susceptibility of developing MS, however, research regarding the use of vitamin D supplements in MS requires large randomised controlled trials to fully support their use (Sintzel *et al.*, 2018; Waubant *et al.*, 2019; Rodney *et al.*, 2020). Other strong associations for developing MS include exposure to the Epstein Barr Virus (Kamm *et al.*, 2014; Vidal-Jordana *et al.*, 2017; Waubant *et al.*, 2019) and cigarette smoking (Kamm *et al.*, 2014; Gajofatto *et al.*, 2015; Vidal-Jordana *et al.*, 2017),

with smokers also reported to have higher relapse recurrence (Kamm *et al.*, 2014; Gajofatto *et al.*, 2015; Vidal-Jordana *et al.*, 2017; Waubant *et al.*, 2019).

2.1 Treatment of MS

The National Institute for Clinical Excellence (NICE) produced guidelines regarding the management of MS, which were last updated in 2022 (National Institute for Health and Care Excellence UK, 2022). These include evidence-based guidance for the management of modifiable risk factors, treatment approaches for relapse and progression, and symptom management. Treatment is aimed at slowing the impact of the disease and can be considered in two themes. The first aims to reduce the rate of relapses by use of disease modifying therapies (DMTs) and the second on managing symptoms and disability associated with MS.

2.2 Disease Modifying Treatments

Disease modifying treatments (DMTs) are used to reduce the frequency and severity of relapses to slow the course of the disease. There are currently 14 DMT's that are approved for use in the UK with treatment predominantly aimed at RRMS, however more recently two have been licenced for progressive MS. For RRMS these include; Alemtuzumab, Cladribine, Dimethyl fumarate, Diroximel fumarate, Fingolimod, Glatiramer acetate, Interferon beta (1a and 1b), Natalizumab, Ofatumumab, Ozanimod, Ponesimod and Teriflunomide. Currently there is only one DMT available for PPMS, Ocrelizumab, and for SPMS, Siponimod, and are only recommended for use where active inflammation is evident (National Institute for Health and Care Excellence UK, 2022).

The rationale for treating relapses is to treat early, as disease activity in the early, relapsing stages predicts long term disability (Filippi *et al.*, 2018). Comi et al (2017) suggests that 80% of pwMS will develop severe disability which results in a reduction in life expectancy by 10 years. The aim of treatment is to

prevent disease activity and usually starts by using an induction strategy, where the patient will start on a safer, lower risk drug such as Interferon beta or Glatiramer acetate (Comi *et al.*, 2017; Vidal-Jordana *et al.*, 2017). In cases of failure where further relapse activity occurs, treatment is escalated to more aggressive options such as Alemtuzumab, Natalizumab, Fingolimod or Teriflunomide (Gajofatto *et al.*, 2015; Wingerchuk *et al.*, 2016; Comi *et al.*, 2017). Most of these treatments produce anti-inflammatory effects, with some drugs having immunosuppressive properties and others targeting specific cells as monoclonal antibodies (Wingerchuk *et al.*, 2016; Comi *et al.*, 2017).

Many factors can influence the drug prescribed such as patient age, comorbidities, lifestyle, active disease from onset as well as local treatment guidelines (Comi *et al.*, 2017; Vidal-Jordana *et al.*, 2017; Giovannoni, 2018). Each therapy has a different safety to risk profile, with Giovannoni (2018) suggesting that early aggressive treatment should be the adopted approach rather than on evidence of new disease activity. This view was echoed by Cameron et al (2019) who interviewed neurologists prescribing DMTs within the UK. They reported that clinicians prescribe based on drug familiarity, positive experience associated with DMTS, as well as uncertainty over long term effects and risks associated with the drug.

2.3 Symptom Management

There are a wide range of symptoms caused by MS which can be unpredictable and varied (Gustavsen *et al.*, 2021). These include disorders of mood, incontinence, impaired mobility and cognition, fatigue and spasticity (Kalincik *et al.*, 2014; Stewart *et al.*, 2017). Until recently symptom management has been the sole focus of treatment of progressive MS, which aims to minimise disability and loss of function, while maintaining independence and QOL (Wynia *et al.*, 2012; Newsome *et al.*, 2017; Gil-González *et al.*, 2020). Often many symptoms of MS are interlinked and the number and severity closely relate to QOL (Higginson *et al.*, 2006; Langeskov-Christensen *et al.*, 2015; Newsome *et al.*, 2017; Conradsson *et al.*, 2018; Filippi *et al.*, 2018; Gil-González *et al.*, 2020; Gustavsen *et al.*, 2021).

In many chronic conditions mental health is known to be a moderator for poor QOL, which is similar in MS with guidelines suggesting it should be regularly monitored (Haddad, 2009; Newsome *et al.*, 2017; National Institute for Health and Care Excellence UK, 2022). A systematic review studying the prevalence of depression and anxiety in pwMS (n= 87,756) found 31% of participants reported depression and 22% anxiety. There was also evidence that both were more prevalent in people with higher levels of disability, although high heterogeneity within the studies and the availability of data reported limited further analysis (Boeschoten *et al.*, 2017).

Continence issues are also one of the most frequently reported symptoms by pwMS and are linked to increased age and disease severity (Hinds *et al.*, 1990; Shah, 2015; Preziosi *et al.*, 2018). For the bowel this presents as constipation or faecal incontinence, and in the bladder most issues are caused by detrusor overactivity or sphincter dyssynergia, leading to increased urge, frequency, incontinence and nocturia (Shah, 2015; al Dandan *et al.*, 2020). Both can also be exacerbated by poor diet, fluids and immobility. Continence issues can directly and indirectly impact on other symptoms. For example, increased urinary urge and frequency can limit socialisation, and result in fatigue from frequency and nocturia (Boeschoten *et al.*, 2017).

Fatigue is reported to be prevalent in over 70% of pwMS and can be one of the most disabling symptoms of MS (Karatepe *et al.*, 2011; Khan *et al.*, 2014). The precise mechanism of fatigue is unknown but primary fatigue is thought to result from the physiological changes caused by the disease and secondary fatigue because of symptoms such as low mood, sleep disturbance and deconditioning (Ayache *et al.*, 2017; Beckerman *et al.*, 2020). Fatigue impacts on cognition, physical and social function and is closely linked to depression and QOL (Kalb *et al.*, 2018). There has been no sole treatment approach identified to reduce the severity or impact of fatigue, however pacing strategies, exercise to improve deconditioning or central nervous systems stimulants have been found to reduce fatigue in some patients (Ayache *et al.*, 2017; Rooney *et al.*, 2019; National Institute for Health and Care Excellence UK, 2022).

Mobility or gait dysfunction can be prevalent early in the disease process and are also associated with progression and QOL (LaRocca, 2011; Bethoux, 2013). One study reported the prevalence of walking difficulties to be 41%, while 70% felt it was the most challenging aspect of MS (LaRocca, 2011). Gait impairment can result over time from age and disease progression, but also due to symptoms such as muscle weakness and deconditioning, fatigue, balance issues and spasticity.

Spasticity is also considered to be one of the most troublesome symptoms of MS, with studies reporting it to effect 66-85% of pwMS (Oreja-Guevara *et al.*, 2013; Flachenecker *et al.*, 2014; Milinis *et al.*, 2016). In some people spasticity can mask lower limb weakness by creating limb stiffness, aiding mobility and the ability to complete functional transfers. To others it is of no benefit and leads to reduced ability to perform self-care tasks, balance, walk and climb stairs (Bethoux *et al.*, 2016; Milinis *et al.*, 2016; Safarpour *et al.*, 2017; Royal College of Physicians of London *et al.*, 2018). With reduced mobility comes deconditioning and loss of cardiorespiratory fitness (Kileff *et al.*, 2005; Latimer-Cheung *et al.*, 2013; Langeskov-Christensen *et al.*, 2015; Klaren *et al.*, 2016), with all being associated with disease severity. Treatment to minimise these issues involves maintenance of activity, exercise and physical function, and will be covered in more detail in sections 2.4 and 2.5.

2.4 Spasticity and MS

Spasticity was proposed by Lance in 1980 to be a motor disorder characterised by a velocity dependant increase in tonic stretch reflexes with exaggerated tendon jerks resulting from hyper excitability of the stretch reflex, and is one of the components of the upper motor neurone syndrome. In 2005 a European working party, EUSPASM, developed a newer, more encompassing definition. They describe spasticity as being disordered sensory motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles (Pandyan *et al.*, 2005). This newer definition is considered more clinically appropriate as it describes a collection of symptoms rather than the loss of spinal reflex inhibition.

Spasticity develops after CNS damage, as a result of the loss of the inhibitory influence of the brain which leads to over stimulation of the spinal reflexes, involuntary motor unit recruitment and increased muscle activation (Gracies, 2005a, 2005b; Pandyan *et al.*, 2005). In addition, the spinal reflexes become more sensitive and reactive, creating an increase in the speed and force of the response. Spasticity is often referred to as hypertonia, known as increased muscle tone or stiffness, which describes the resistance within the muscle to changes in length. Following CNS damage three mechanisms have been suggested to account for this increased stiffness; passive muscle stiffness, neural mediated stiffness and active muscle stiffness (Foran *et al.*, 2005; Gracies, 2005a, 2005b; Stecco *et al.*, 2014).

Passive muscle stiffness describes the biomechanical changes that occur from muscle atrophy and a change in properties and function of that muscle. These changes occur due to the negative features of CNS damage such as muscle paresis or paralysis (Gracies, 2005a). Over time muscle tissue is lost due to atrophy of these fibres and a reduction in fibre diameter, leading to a loss in muscle volume and cross-sectional area. Contractile tissue is replaced by connective tissue resulting in the muscle becoming less elastic and flexible, and stiffer to move (Gracies, 2005a; Walton, 2011; Stecco *et al*. 2014). Over time connective tissue increases in volume and proliferates, both within the muscle and to surrounding areas. This affects the muscle, tendon and the joint, and can lead to fibrosis and contractures (Foran *et al.*, 2005; Gracies, 2005a; Stecco *et al.*, 2014).

Neural mediated stiffness describes the changes within the reflex arc and is caused by the influence of the muscle spindle on the alpha motor neurons in the spinal cord. An increase in connective tissue, as described above, leads to reduced flexibility and compliance within the muscle, which increases muscle spindle sensitivity to stretch. This stimulates the alpha motor neurons in the spinal cord causing reflex contraction, and is felt to contribute to the stretch sensitive form of muscle overactivity (Stecco *et al.*, 2014). It is also more apparent in muscles held or immobilised in a shortened position (Gracies, 2005a; Stecco *et al.*, 2014).

Active muscle stiffness describes changes in visco-elastic properties of soft tissue and cross-bridge mechanism within the muscle (Pandyan *et al.*, 2005; Lakie *et al.*, 2019). When a muscle is immobilised the concentration of extracellular matrix (ECM) increases (Foran *et al.*, 2005; Stecco *et al.*, 2014). The ECM is important to help maintain muscle tissue and provide structure, and forms the intramuscular connective tissue structure that encloses the myofibrils (endomysium), muscle fascicles (perimysium), and the entire muscle (epimysium) (Foran *et al.*, 2005; Stecco *et al.*, 2014). An increase in ECM in turn decreases the viscosity of the connective tissue and reduces the gliding effect between the layers of muscle tissue, making it stiffer (Foran *et al.*, 2005; Stecco *et al.*, 2014). Alongside these changes, the number of crossbridge attachments within the resting muscle also increase adding to short term stiffness (Lakie *et al.*, 2019). However, this stiffness reduces upon voluntary contraction or passive stretch, with this change in stiffness through movement often referred to as muscle thixotrophy (Vattanasilp *et al.*, 2000; Lakie *et al.*, 2019). Thixotrophy is seen in substances that form weak bonds, which are destroyed by agitation and reform progressively, with muscles being known to show similar behaviours (Lakie et al., 2019).

A muscle that remains in a static or immobilised position over a period of time, is at risk of contracture formation, and it is agreed that a strong relationship exists between presence of spasticity, muscle paresis and contracture formation. All can lead to loss of flexibility, and contribute to balance and mobility deficits (Gracies, 2005a, 2005b; Hoang *et al.*, 2014; Nair *et al.*, 2014; Bethoux *et al.*, 2016; Royal College of Physicians of London *et al.*, 2018).

Previous studies have surveyed the severity and consequences of spasticity in pwMS (Oreja-Guevara *et al.*, 2013; Flachenecker *et al.*, 2014; Bethoux *et al.*, 2016), the impact on day-to-day activities (Flachenecker *et al.*, 2014; Bethoux *et al.*, 2016) and the association with other impairments and QOL (Flachenecker *et al.*, 2014; Milinis *et al.*, 2016). The severity of self-reported spasticity in those surveyed was rated moderate to severe by 35% in the study by Bethoux et al (2016) (n=10,200) and by 40% in the Oreja-Guevara et al (2013) study (n=2,029). While 44% of the participants found this to be moderate in the study by Flachenecker et al (2014) and 29% severe in nature (n=414). It should be

noted that each study used a different measure to rate severity with the global impression of change, a numerical rating scale for spasticity and the performance scales spasticity subscale for MS used.

Relationships between spasticity and other symptoms have been studied, with positive correlations found with worsening mobility (r=0.53), bladder dysfunction (r=0.46), levels of fatigue (r=0.47) and pain (r=0.50) (all p<0.0001) (Bethoux *et al.*, 2016). Patients with spasticity also had significantly more day spasms (67.1%), urinary dysfunction (70.4%) and sleep disturbance (50.9%) (all p<0.001) (Oreja-Guevara *et al.*, 2013). Each study noted a correlation between severity of spasticity, worsening of the disease and reduced QOL (Oreja-Guevara *et al.*, 2013; Flachenecker *et al.*, 2014; Bethoux *et al.*, 2016).

Only one study considered the impact of spasticity on upper limb function (Bethoux *et al.*, 2016), with 7.7% of participants reporting it to be an issue. The main limitations from spasticity were reported to the lower limbs and specifically the impact on activities such as the ability to transfer, mobilise and climb stairs.

2.4.1 Treating spasticity

Interventions to manage spasticity are frequently required, however few pwMS report being satisfied with current treatments (Oreja-Guevara *et al.*, 2013; Flachenecker *et al.*, 2014; Bethoux *et al.*, 2016). Treatment focuses on three areas; management of trigger factors, use of pharmacological agents and a physical management plan (Walton, 2011; Nair *et al.*, 2014; Royal College of Physicians of London *et al.*, 2018; National Institute for Health and Care Excellence UK, 2022).

Spasticity can be aggravated by stimuli from other systems often referred to as trigger factors which include bladder and bowel dysfunction, infection, skin issues and pain (Nair *et al.*, 2014; Royal College of Physicians of London *et al.*, 2018). Identification and treatment of triggers is the first approach taken to manage spasticity, and if issues persist pharmacological agents may be

considered, which act to reduce cortical stimulation or inhibit stretch reflex sensitivity (Nair *et al.*, 2014; Otero-Romero *et al.*, 2016; Royal College of Physicians of London *et al.*, 2018).

Oral antispasmodic agents are often referred to as skeletal muscle relaxants and include Baclofen, Tizanidine, Dantrolene, Gabapentinoids and Benzodiazepines. The NICE guidelines on management of MS (2022) suggest that Baclofen and Gabapentin should be the initial drugs of choice and the other medications considered if no improvement is found. Nabiximols or Sativex, an oral cannabinoid spray, can then be tried in moderate to severe MS when other oral therapies have failed or been intolerable. Access to Sativex, however, can be difficult with approval for use only recently being endorsed by the Scottish Medicines Consortium in 2022. And while these medications can inhibit spasticity, they often cause central side effects of drowsiness and fatigue especially at higher doses, which can limit patient tolerance and compliance (E. Chang *et al.*, 2013; Nair *et al.*, 2014; Otero-Romero *et al.*, 2016).

Other treatments include the use of focal injections with agents such as botulinum toxin and aqueous phenol, injected to target a specific muscle(s) or nerve(s) affected by spasticity. Botulinum toxin is injected into a muscle and works by blocking the release of acetylcholine at the neuromuscular junction resulting in reduced muscle contraction (Otero-Romero *et al.*, 2016; Royal College of Physicians of London *et al.*, 2018). Phenol can be injected to identified motor points within the muscle, or to a nerve where it causes chemical neurolysis (Nair *et al.*, 2014; Otero-Romero *et al.*, 2016). While botulinum toxin is frequently used as treatment for spasticity in pwMS the evidence to support the efficacy is limited and most of this evidence exists in spasticity following stroke. Two reviews considered its use in pwMS (Dressler *et al.*, 2017; Safarpour *et al.*, 2017) and both reported it to be an effective treatment in arm and leg spasticity. Safarpour et al (2017) also suggested it to be effective in the management of overactive bladder.

Lastly a physical management plan is a key treatment strategy in managing spasticity (Walton, 2011; Nair *et al.*, 2014; Royal College of Physicians of London *et al.*, 2018). This focuses on motor training to maintain movement and

function, as well as prevention of secondary complications such as soft tissue shortening and contracture formation (Gracies, 2005a; Dietz *et al.*, 2007). The relationship between spasticity and contracture formation is poorly studied, although it is accepted that spasticity is a contributing factor alongside paresis and immobility (Gracies, 2005b, 2005a). Hoang et al (2014) considered the prevalence of spasticity and muscle weakness in pwMS (n=156), and reported 60% of their participants had a contracture in at least one joint and muscle weakness in at least one group. There is also a strong association between disability levels and contracture (Oreja-Guevara *et al.*, 2013; Kalincik *et al.*, 2014; Bethoux *et al.*, 2016; Milinis *et al.*, 2016; Stewart *et al.*, 2017). Thus, prevention of contracture formation and maintaining muscle strength and function, remain key components of a physical management programme.

Stretching has been shown to be effective in improving and preventing contractures in early animal studies by Williams (1988 & 1990). Williams (1990) determined that when a contracted muscle was stretched at end of range for 30 minutes connective tissue content was normalised, sarcomere number restored and atrophy prevented. The process is thought to occur by creep, which describes the process of progressive deformation and lengthening when a constant load is applied over time to a muscle when at end of range (Sharman *et al.*, 2006).

There is, however, little evidence to support the use of stretching in humans, even though it is common practise in clinical settings. A Cochrane review by Harvey et al (2017) considered stretch for the treatment and prevention of contractures in both neurological and non-neurological populations. The review included 49 studies and 2,135 participants but concluded that stretch did not affect short or long-term outcomes in neurological conditions. They did report that many of the included studies showed bias due to lack of blinding and concealment during randomisation. In addition, the stretch dosage used was highly variable, and ranged from five minutes to 24 hours per day, with many not achieving the 30-minute length shown to be effective by Williams (1990). Nor was it clear if the stretch applied during studies was at end of range (Williams, 1990).

Stretching of muscle can occur during active exercise or passively with help from another person or equipment. Splints are often used clinically to apply a prolonged stretch in the upper limbs (at the elbow, wrist and fingers) and in the lower limbs (hip, knee and ankle). Standing frames can also be used to help stretch the trunk and the lower limb flexor muscles through supported weightbearing ,and has been recommended for use in pwMS with higher levels of disability (Kalb *et al.*, 2020).

In some specialist settings continuous passive motion machines (CPMs) and APTs are used to assist in upper and lower limb movements. A CPM passively moves a limb slowly and continuous from flexion to extension, the speed, time and range of movement being pre-programmed. They are frequently used post operatively in orthopaedic and surgical settings, however research has also reported positive effects in reducing lower limb spasticity in children with cerebral palsy (Cheng *et al.*, 2012), complete spinal cord injury (Y. J. Chang *et al.*, 2013) and mixed neurological conditions (Noble *et al.*, 2019).

An APT however, can work in passive, active assisted or active function. They can be utilised as a means of exercise and will be described in more detail in section 2.8.1, with the evidence base for APT use explored in Chapter 3.

2.5 Exercise, PA and MS

PA is defined as any body movement produced by skeletal muscle that requires energy expenditure (WHO, 2020). As mentioned in Chapter 1, it can be categorised into PA and exercise. PA includes occupational, household or leisure, while exercise is structured, planned and repetitive with the goal of improving or maintaining physical fitness (Dalgas *et al.*, 2019; Kalb *et al.*, 2020; WHO, 2020). Both have been reported to improve health in pwMS (Dalgas *et al.*, 2019; Kalb *et al.*, 2020).

It has been suggested that exercise should be prescribed as a form of medicine in the early stages of MS due to the benefits it brings (Dalgas *et al.*, 2019). The NICE guidelines for MS (2022) also strongly promote exercise as a treatment in

MS. They recommend anyone with MS should participate in regular programmes of exercise which include moderate, progressive, resistance and aerobic training, but make no comment as to the level of intensity, duration or method of exercise. Many forms of exercise have been shown to have positive effects in pwMS (Edwards and Pilutti, 2017; Halabchi *et al.*, 2017; Motl, Sandroff, *et al.*, 2017; Pilutti *et al.*, 2017; Sandroff *et al.*, 2017) and the choice of exercise is often made by patient ability, preference and accessibility (Motl, Sandroff, *et al.*, 2017; Barnard *et al.*, 2020).

Guidelines regarding exercise and PA for pwMS are dated, focus solely on exercise and only consider people with mild to moderate MS (Petajan *et al.*, 1996; Dalgas *et al.*, 2008; Latimer-Cheung *et al.*, 2013). They proposed that people with mild MS should undertake 30 to 60 minutes of moderate intensity aerobic training and complete resistance training, 2 to 3 times per week, and at moderate intensity (Latimer-Cheung *et al.*, 2013). However, pwMS have been shown to struggle with adherence to these recommendations (Barnard *et al.*, 2020) and although not evidence based an 'anything is better than nothing' approach is often adopted by health professionals.

A group of experts brought together by the MS Society were asked to review the current body of evidence and create a consensus on optimal exercise and lifestyle PA for pwMS with all levels of disability (Kalb *et al.*, 2020). They used the EDSS to help categorise levels of disability which they termed mild impairment (EDSS 0-4.5), increasing mobility impairments (EDSS 5.0-6.5) and non-ambulant/reduced ability to perform ADLs (EDSS 7.0-9.0). Guidance on dose, intensity and duration for each category were given in relation to aerobic, resistance, stretching, balance and co-ordination exercises. They also advocated the use of adaptive equipment such as recumbent style bikes, three-wheel bikes and neuromuscular stimulation for the more disabled group (Kalb *et al.*, 2020). While this was the first comprehensive guidance that included all levels of disability associated with MS, they did concede some of this was based on clinician experience rather than published evidence. This was more so for the higher levels of disability, and further research involving this group is recommended.

2.6 The benefits of exercise for people with MS

Exercise has always been considered an essential component in managing MS. However, pwMS are known to be less active and engage in less exercise and PA than the healthy population regardless of their symptoms (Barnard *et al.*, 2020). As well as promoting health and independence, exercise is also known to lower the risk of developing other co-morbidities and help manage symptoms associated with the disease. For example, the incidence and prevalence of cardiac, cerebrovascular and peripheral vascular disease is known to be higher in pwMS (Marrie *et al.*, 2010). Common co-morbidities also include diabetes, hyperlipidemia, hypertension, arthritis, irritable bowel syndrome, chronic lung disease, osteoporosis and increased fracture risk (Bazelier *et al.*, 2012; Marrie *et al.*, 2013; Gupta *et al.*, 2014; Kępczyńska *et al.*, 2016).

There is also growing evidence to suggest exercise can provide neuroprotection. Studies have shown that higher PA and physical fitness levels during childhood and adolescence reduce the risk of developing MS in the future (Cortese *et al.*, 2018; Wesnes *et al.*, 2018). The mechanism by which this occurs is not fully understood but is thought to be due to a reduction in circulating inflammatory agents and permeability of the blood brain barrier (Negaresh *et al.*, 2019). In addition, programmes of progressive exercise over 8-12 weeks have resulted in increased production of neurotrophic factors and serum contactin-1 and 2 in RRMS (Banitalebi *et al.*, 2020; Bilek *et al.*, 2022). These proteins are responsible for survival and growth of nerve cells, axonal function and neural regeneration suggesting exercise can also provide disease modifying effects. Studies have also reported an increase in brain derived neurotrophic factor in pwMS following exercise, which also aids neuroregeneration and neuroprotection (Shobeiri *et al.*, 2022). A meta-analysis within this review considered the optimum type and duration of intervention and found no significant difference between aerobic or resistance training, or in interventions of less than or more than 12 weeks. However, these studies only involved people with mild disability (EDSS <4.0) and less is known about the effects in people with higher disability levels.

Exercise is most commonly studied in relation to its effects on physical function and symptoms associated with MS. Evidence exists to support the positive effects on muscle function (Platta *et al.*, 2016; Jørgensen *et al.*, 2017), walking (Snook *et al.*, 2009; Pearson *et al.*, 2015), aerobic fitness (Langeskov-Christensen *et al.*, 2015; Platta *et al.*, 2016), depression (Dalgas *et al.*, 2015; Herring *et al.*, 2017) and QOL in pwMS (Alphonsus *et al.*, 2019; Dauwan *et al.*, 2021). The effects on other symptoms such as fatigue, cognition and spasticity are less conclusive and are often hindered by their design, with the primary focus measuring physical function rather than the symptom itself (Klaren *et al.*, 2016; Etoom *et al.*, 2018; Rooney *et al.*, 2019; Ergul *et al.*, 2020; Razazian *et al.*, 2020; Moss-Morris *et al.*, 2021).

While exercise has been reported to be effective for some symptoms of MS the optimum type or dose has yet to be identified. In addition, the studies primarily involve pwMS with lower levels of disability and so cannot be generalised across all levels of MS. Higher quality research is needed to fully establish the effects of exercise interventions on all the common symptoms of MS and also consider the impact on QOL. And lastly, research aimed to include people with moderate to severe levels of disability is a priority.

2.7 Exercise for people with moderate to severe disability

Many barriers exist to participation in exercise interventions. Increased disability and symptoms often impact as well as environmental and psychosocial factors. Barriers to exercise have been identified as motivation, social support and access to appropriate facilities as well as symptoms such as fatigue (Moffat *et al.*, 2019; Barnard *et al.*, 2020).

As previously stated, studies involving exercise interventions for people with moderate to severe MS are limited and frequently acknowledged as priority in future research. Edwards et al (2017) and Pilutti et al (2017) undertook separate reviews to consider the evidence for exercise in people with higher levels of disability (EDSS levels of ≥6.0). Interventions were grouped into

conventional or adapted exercise, with conventional exercise involving resistance or aerobic training by rowing, arm or leg ergometers. While adapted exercise involved body weight supported treadmill training (BWSTT), total body recumbent stepper training (TBRST) and electrical stimulated assisted cycling (ESAC).

The two reviews reported the results for both types of exercise to be mixed but promising. Studies involving conventional exercise and BWSTT found significant improvements in leg extensor strength, walking endurance, balance and fatigue. While ESAC interventions led to significant improvements in muscle oxygen consumption, thigh circumference and acute changes in spasticity. However, neither intervention resulted in improved aerobic fitness (Edwards and Pilutti, 2017; Pilutti *et al.*, 2017). Both reviews acknowledged the limitations of the studies involved as they used small samples, a wide variety of outcome measures and differing exercise protocols, thus limiting their comparability. In addition, no intervention was found to be more effective than any other, with the optimum type and dose to manage fitness, function and symptoms yet to be established.

Finding a safe way to achieve exercise recommendations especially vigorous exercise, can be challenging for pwMS due to reduced mobility and fear of falling (Barnard *et al.*, 2020). Static cycling is one method often used as a safer means of exercise for people with balance or mobility issues (Barbosa *et al.*, 2015; Shen *et al.*, 2018). Cycling is performed from a seated position, does not require the participant to be mobile or have good balance and avoids the possibility of trips and falls. It also shares the same movement pattern as walking as it involves reciprocal flexion and extension of the legs (Raasch *et al.*, 1999).

Cycling has been shown to be an effective rehabilitation tool in many neurological conditions. Evidence shows cycling can improve physical function after stroke (Barbosa *et al.*, 2015; Shen *et al.*, 2018; Shariat *et al.*, 2019), improve symptoms of bradykinesia, tremor, motor dysfunction and cognition in Parkinson's disease (PD) (Ridgel *et al.*, 2011, 2012; Laupheimer *et al.*, 2013) and improve muscle mass, strength and spasticity in Spinal Cord Injury (SCI) (Kuhn *et*

al., 2014; Yasąr *et al.*, 2015; Phadke *et al.*, 2019). Lastly, in pwMS it has been shown to improve physical function, aerobic fitness and spasticity (Szecsi *et al.*, 2009; Çakt *et al.*, 2010; Briken *et al.*, 2014; Hochsprung *et al.*, 2020).

2.8 The benefits of cycling in pwMS

While cycling is a safe way for people with mobility issues to exercise, it is also beneficial in many ways as it challenges the cardiorespiratory system and metabolic functions of the whole body (Oja *et al.*, 2011). It is an intervention often adopted by studies to deliver vigorous, intensive exercise and measure fitness. Studies indicate the positive effects of leg cycling as a form of conventional exercise training in pwMS with an EDSS of less than 6.5 (Petajan *et al.*, 1996; Ponichtera-Mulcare *et al.*, 1997; Mostert *et al.*, 2002; Kileff *et al.*, 2005; Rampello *et al.*, 2007; Çakt *et al.*, 2010). These studies involved cycling interventions which differed in intensity, frequency and duration. Their interventions used ergometers with participants cycling for 30-40 minutes, 2-4 times a week and between 4-24 weeks in length. They also included a wide variety of outcome measures, with the most common considering the effects on aerobic fitness, gait and QOL.

Following these interventions significant improvements were reported to measures relating to aerobic fitness (Petajan *et al.*, 1996; Ponichtera-Mulcare *et al.*, 1997; Rampello *et al.*, 2007), walking endurance (Kileff *et al.*, 2005; Rampello *et al.*, 2007; Çakt *et al.*, 2010), walking speed (Rampello *et al.*, 2007; Çakt *et al.*, 2010), leg strength (Petajan *et al.*, 1996), balance (Çakt *et al.*, 2010) and QOL (Petajan *et al.*, 1996; Mostert *et al.*, 2002; Rampello *et al.*, 2007; Çakt *et al.*, 2010).

While positive, the results should be interpreted with caution as questions around the quality and design of the studies exist. For example, while five of the studies stated their focus was to consider the effect of cycling on aerobic fitness, only three directly measured it using appropriate outcome measures (Petajan *et al.*, 1996; Ponichtera-Mulcare *et al.*, 1997; Rampello *et al.*, 2007). The other studies chose measures that focused on the effects on physical

function instead (Mostert *et al.*, 2002; Kileff *et al.*, 2005). These results also cannot be generalised as they only included participants with lower levels of disability (EDSS scores <6.5), all of whom were physically able to cycle. Less is known regarding the effects or benefits from cycling training in participants with EDSS of ≥6.5, where assistance to cycle will be required, an area this PhD aims to address.

2.8.1 Methods of lower limb cycling

There are many static exercise bicycles for lower limb cycling available from upright ergometers, recumbent bicycles to APTs. Upright ergometers require patients to be able to stand and step up on to them to cycle, whilst maintaining seated balance. Recumbent bicycles provide more support at the hips and back, but still require the ability to stand and transfer. Both styles of bike also require the participant to have good leg strength and be able to maintain foot contact with the pedal whilst completing a revolution independently. There are two phases to a cycling revolution, the power phase when the pedal is pushed from a 12 o'clock to 6 o'clock position, and the recovery phase which brings the pedal back up to the 12 o'clock position (Ambrosini, Parati, *et al.*, 2020). Muscles activated during cycling include the gluteals, quadriceps, hamstrings and plantarflexors, with the extensors more active in the power phase and flexors more so in the recovery phase.

Many pwMS with EDSS levels of ≥6.0 are unable to use upright or recumbent ergometers or complete a revolution of cycling without assistance. Assistance can be delivered in two ways, an APT which is a machine that assists the revolution of the pedals or by electrical stimulation of muscles required in the phases of cycling. The latter is often referred to as electrical stimulated assisted cycling (ESAC) or functional electrical stimulated (FES) assisted cycling.

APTs are on a moveable frame, allowing cycling from a fixed seated position or normal chair (Figure 2.1). They can assist the participant to cycle by way of a motorised unit and offer more support at the calf and foot than other cycle ergometers. The frame is adjustable in height, has footplates with velcro to

attach around the feet to keep the foot in contact with the pedal, and comes with or without calf supports. APTs also feature a display panel which is approximately 1.5 metres in front at eye level which provides feedback on the user's speed, distance cycled both actively and passively, power output and symmetry of cycling (Figure 2.2). Some APTs also use gamification to help to improve symmetry, speed or simply visual distraction by cycling virtual along a virtual road.

Figure 2.1 Lower limb MOTOmed APT

Figure 2.2 MOTOmed APT screen

The speed, resistance and type of cycling (active, active assisted or passive) can be adjusted depending on the ability of the person. For example, if the person has no active movement in their legs the APT will rotate the pedals at a minimum speed of 10 revolutions per minute (rpm) and complete the cycling in a

passive setting. However, if the person can assist the revolution of the pedals the rpm count increases and the APT allows the user to actively cycle. If for any reason they are unable to continue to cycle, for reasons like fatigue or a spasm, then the APT reverts to passive setting and moves their legs at 10rpm. APTs are an alternative to ergometers as they can be used by people with all levels of disability, which is especially important in MS.

APTs can also be used in combination with neuromuscular stimulation, referred to earlier as ESAC or FES assisted cycling, with the stimulation assisting the cycling motion. FES involves using electrical current to activate muscles through the stimulation of intact peripheral motor nerve and is used in neurological conditions associated with an upper motor neuron lesion and muscle weakness (Martin *et al.*, 2012).

FES assisted cycling involves stimulating specific muscles that are activated during the power or recovery stage of a revolution (Pilutti *et al.*, 2019). The muscles stimulated depend on the neurological impairment, however, commonly include the gluteal, quadriceps, hamstrings and plantarflexor muscles (gastrocnemius and soleus). Square electrodes are placed over the nerve that supplies the muscle(s) or motor end plates of the individual muscles. Stimulators come in two, four, eight and twelve channels with the stimulation parameters used for most trials being a pulse width of 200–300 μsec, a frequency of 20–50Hz and a cycling cadence of 10–50rpm (Pilutti *et al.*, 2019). The intensity of the stimulation is increased to provide visible or palpable muscle contraction but remains below the participant's pain threshold. If sensation is partially or fully preserved FES can be painful, which can limit its use. However, it has been reported to be a safe and well tolerated in pwMS (Pilutti *et al.*, 2019).

Much of the evidence on FES assisted cycling is derived from people with a SCI. In this population it is used to reduce the effects of immobility by improving muscle health (muscle volume, circumference and ratio of fibre types), circulation, bone density and cardiovascular and metabolic health (Peng *et al.*, 2011; Martin *et al.*, 2012; van der Scheer *et al.*, 2021). However, it is also often used to reduce spasms and spasticity (Martin *et al.*, 2012; van der Scheer *et al.*,

2021). A systematic review by van der Scheer et al (2021) considered the evidence regarding the use of FES assisted cycling in SCI (n=92) but reported mixed results. Many studies reported significant improvements to outcomes relating to muscle health (n=30), power output (n=34) and aerobic fitness (n=20), cardiovascular and metabolic health (n=16) and bone health (n=11). However, the quality of the studies was reported to be poor limiting the strength of these findings. It is also an intervention frequently used within specialist rehabilitation units and within SCI as a component of activity based restorative therapy (Martin *et al.*, 2012; Bersch *et al.*, 2015).

Less is known about the benefits of FES in other neurological conditions as research is more limited. Two systematic reviews have been undertaken on the use of FES assisted cycling in people with stroke (Shariat *et al.*, 2019; Ambrosini *et al.*, 2020) and two involving pwMS (Pilutti *et al.*, 2019; Scally *et al.*, 2020). The review by Ambrosini et al (2020) considered the evidence of FES assisted cycling on outcomes relating to walking ability, muscle strength, spasticity, balance and ADL's. While Shariat et al (2019) compared the effects of cycling with or without FES on outcomes relating to walking and balance. A meta-analysis by Ambrosini et al (2020) reported a small but significant effect on walking distance (n=6) (SMD 0.40, p=0.04) and sitting balance (n=3) (MD 7.2, p=0.02), and a non-significant improvement (n=5) to leg strength (SMD 0.23, p=0.11). While Shariat et al (2019) could only consider balance in a meta-analysis of FES assisted cycling, due to limited data reported, and found this to have improved (n=2, SMD 1.48; p< 0.001). They also undertook a meta-analysis of cycling alone and found small but positive effects on walking endurance (n=5) (SMD 0.41, p<0.007), walking speed (n=6) (SMD 0.30, p<0.02) and balance (n=5) (SMD 0.32, p<0.01). And while positive, three studies within the analysis of cycling alone used a combined intervention which also involved treadmill, strength and balance training. This may have contributed to these positive results.

Also, of note three studies within the review by Shariat et al (2019) compared the effects of FES assisted cycling to cycling alone (Lo *et al.*, 2012; Lee *et al.*, 2013; Bauer *et al.*, 2015). These studies reported significant improvements in walking ability, balance and spasticity following both interventions, with larger

gains made by the FES assisted cycling group (Lo *et al.*, 2012; Lee *et al.*, 2013; Bauer *et al.*, 2015). However, no further analysis or comment on this finding was made by the author.

The two systematic reviews involving pwMS included the same articles (n=8) (Pilutti *et al.*, 2019; Scally *et al.*, 2020), with an additional study included by Scally et al (2020). They did though, consider slightly different aspects (Pilutti *et al.*, 2019; Scally *et al.*, 2020). Scally et al (2020) looked at the effects of FES cycling on cardiovascular, musculoskeletal and functional outcomes in pwMS with mobility impairment. While Pilutti et al (2019) provided a summary of the overall evidence for FES cycling as an exercise modality, considering the effects, prescription, safety and tolerability. Both identified positive trends following FES assisted cycling to physiological fitness, walking ability, acute spasticity, fatigue and pain. However, they were unable to draw any definite conclusions due to the low quality of the evidence available and small samples used. Both highlighted the need for higher quality research involving RCTs and larger samples to fully establish the benefits of FES assisted cycling in pwMS.

Overall, the use and benefits of FES assisted cycling remains inconclusive. While a larger evidence base exists in SCI compared to stroke and MS, the quality of the studies included was poor. Small sample sizes and a large variety of outcome measures used also limits further analysis and so no definite conclusions can be made. FES assisted cycling is only available in specialist rehabilitation centres due to the complexity of equipment and cost implications, and as a result limits its use for clinicians and patients at home. Establishing the benefits and use of FES assisted cycling has been highlighted as an area for further research and will be explored in more detail within a systematic review in Chapter 3.

2.9 The effects of cycling on lower limb spasticity in pwMS

The anti-spasticity effect of leg cycling in pwMS is an area of interest and one that has been studied over the years (Motl *et al.*, 2006, 2007; Sosnoff *et al.*,

2009). Both studies by Motl et al (2006 & 2007) considered the acute effects of a single session of cycling, while Sosnoff et al (2009) reviewed the effects after a month-long intervention.

Motl et al (2006) considered the effects of a single session of unloaded cycling on leg spasticity in pwMS with mild disability (EDSS ≤4.5) (n=27). They measured spasticity using the Modified Ashworth Scale (MAS), a clinical rating scale used to grade hypertonia, and Hoffmans reflex (H-reflex). The H-reflex is a neurophysiological measure and reflects the excitability of the alpha motor neuron pool within the reflex arc in the spinal cord, known to be exaggerated in patients with spasticity (Palmieri *et al.*, 2004; Voerman *et al.*, 2005). The H-reflex can be measured in relation to latency, reflex amplitude or as a ratio of maximal stimulation using the M and H wave, referred to as the H_{max}/M_{max} ratio or H/M ratio (Palmieri *et al.*, 2004; Voerman *et al.*, 2005). The H-reflex will be covered in more detail in Chapter 5 of this thesis, as part of a third study.

Participants of the Motl et al (2006) study completed 20 minutes of unloaded cycling and a control session of 20 minutes of sitting, with the H-reflex and MAS assessed before and up to 60 minutes after. They found the H/M ratio to be significantly reduced 10 minutes (d=-0.38), 30 minutes (d=-0.48) and 60 minutes (d=-0.54) after unloaded leg cycling. As was the MAS, which also significantly reduced after 10 minutes (d=-0.53), 30 minutes (d=-0.43) and 60 minutes (d=-0.37). There was no significant change in either measure after the control condition. And while this study included a small sample of people with low levels of disability, the results suggest that unloaded cycling may have short term anti-spastic effects on lower limb muscles. In 2007, Motl et al completed a follow up study involving pwMS taking anti-spasticity medication (n=6). Like the 2006 study, this study showed that spasticity was significantly reduced for up to 60 minutes after unloaded cycling supporting the conclusions of the 2006 study.

These results, however, differed to the Sosnoff et al (2009) study which reported no change in spasticity following a cycling intervention. This study involved an intervention group (n=12) where participants cycled for 30 minutes, three times a week and for a month using an ergometer, and a control group (n=10) who had no intervention/usual care over that time. They again used the H-reflex, MAS

and a patient reported outcome measure, the MS Spasticity Scale 88 (MSSS-88), to measure spasticity. The only changes found was a reduction in perceived spasticity from MSSS-88 scores after the one month cycling intervention (d=-0.25) which persisted up to a month after the intervention had finished. However, they measured spasticity a day after completion of the intervention rather that immediately following which may account for the difference in results.

Other studies have considered the effects of leg cycling on spasticity in pwMS using APTs (Edwards *et al.*, 2018; Barclay *et al.*, 2019; Backus *et al.*, 2020; Hochsprung *et al.*, 2020). These studies will be considered alongside others involving other neurological conditions as part of a systematic review, detailed in Chapter 3.

2.10 Aerobic fitness and exercise testing in pwMS

While cycling, using ergometers, has been shown to improve aerobic fitness in people with mild MS (Petajan *et al.*, 1996; Ponichtera-Mulcare *et al.*, 1997; Rampello *et al.*, 2007), little is known if these benefits extend to people with moderate to severe disabilities who use APTs.

Aerobic fitness, cardiorespiratory fitness and aerobic capacity are terms often used interchangeably in research, and reflect the combined efficiency of the lungs, heart, vascular system and muscles in the transport and use of oxygen (Nazzari *et al.*, 2016). Aerobic fitness can be improved by increasing physical activity or by exercise, with the intensity considered to be an important determinant of the physiological response to training (Garber *et al.*, 2011). However, it is also accepted that even low intensity exercise or physical activity can improve aerobic fitness (Nazzari *et al.*, 2016; Myers *et al.*, 2021).

Aerobic fitness is evaluated using cardiopulmonary exercise tests (CPETs), which assess a person's aerobic capacity and physiological response. They involve the measurement of oxygen uptake (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER), heart rate (HR) and work rate (WR) during an

exercise test (Albouaini *et al.*, 2007; Chambers *et al.*, 2019). The most frequently used CPET is VO_{2max} which describes the maximal amount of oxygen (O_2) utilised in the body during intense exercise (Albouaini *et al.*, 2007; van den Akker *et al.*, 2015). A VO_{2max} test is usually completed on either a treadmill or exercise bike, where participants are exposed to increased intensity of exercise stopped by volitional exhaustion or when symptoms are displayed that make it unsafe to carry on (Albouaini *et al.*, 2007). These include exhaustion, muscle fatigue, extreme dyspnoea or light headedness (Albouaini *et al.*, 2007).

Testing aerobic fitness in pwMS can be challenging due to existing physical impairments and the ability to work at a level required during maximal exercise testing (Klaren *et al.*, 2016). Langeskov-Christensen et al (2014) considered the validity and reliability of testing VO_{2max} in pwMS as part of a systematic review. Only two studies had considered this and while both found it to be a valid and reliable test, both involved participants with low levels of disability and the ability to complete it (EDSS <4.0) (M. Heine *et al.*, 2014; Langeskov-Christensen *et al.*, 2015). The study by Heine et al (2014) also included participants with moderate levels of disability (n=9, mean EDSS 5.7 ± 0.5) who were noted to be unable to reach the required intensity to complete the test. Submaximal exercise tests were suggested for use in this group instead.

Submaximal exercise tests are used to predict maximal oxygen consumption and to determine aerobic fitness in those with physical limitations or when maximal exercise testing is unsafe. Measurement of HR and VO_2 at two or more workloads are analysed and data used to calculate different measures. These include the ventilatory anaerobic threshold (VAT), extrapolated maximal oxygen consumption (EMOC), the slope of the regression line between minute ventilation (V_E) and carbon dioxide (CO_2) production (V_E/VCO_2 slope) and the oxygen uptake efficiency slope (OUES). However, some of these measures have been shown to have major limitations or be an invalid measure of cardiorespiratory fitness/VO_{2max}. For example, studies have shown the VAT to be unidentifiable in some individuals (Pichon *et al.*, 2002; Davies *et al.*, 2006). The V_E/VCO_2 slope has also been shown to correlate weakly to VO_{2max} and the usefulness of the EMOC has yet to be proven in comparison to other measures (Akkerman *et al.*, 2010). The OUES however, has been shown to significantly

correlate to VO_{2max} in a healthy population (Baba *et al.*, 1996; Pichon *et al.*, 2002) and in pwMS (M. Heine *et al.*, 2014; Edwards, Klaren, *et al.*, 2017).

2.10.1 Oxygen Uptake Efficiency Slope

The OUES was conceived by Baba et al (1996) and describes the relationship between VO_2 uptake (ml/min) and V_E (l/min) during incremental submaximal exercise. A regression slope of VO_2 (the y axis) relative to V_E (the x axis) is produced, with the gradient of the line indicating how effectively O_2 is extracted into the body indicating cardiorespiratory fitness (Akkerman *et al.*, 2010; Baba *et al.*, 1996). The OUES can be calculated from submaximal exercise testing and is unlike other exercise tests which are influenced by length of testing, motivation and symptoms limiting the test. It has also been shown to be independent of intra and inter-rater variability (van Laethem *et al.*, 2005).

2.10.2 The evidence regarding the OUES

The validity and reliability of the OUES has been studied in healthy participants as well as in people with chronic health conditions.

Baba et al (1996) was the first to consider validity in both healthy participants (n=36) as well as people with cardiac disease (n=108), reporting a significant positive correlation between VO_{2max} and the OUES ($r=0.941$, $p<0.01$). Other studies have also reported strong correlation between the OUES and VO_{2max} (Baba *et al.*, 1999; Pichon *et al.*, 2002) as well as to VO_{2peak} (Hollenberg *et al.*, 2000; Buys *et al.*, 2015). The study by Pichon et al (2002) used a young healthy population (n=50, $r=0.792$, $p<0.001$) whereas Baba et al (1999) used adults with heart failure (n=50, r-=0.78, $p<0.01$). It should be noted though that the results from Baba et al (1999) were only based on the 18 participants who were able to fulfil maximal exercise conditions. Buys et al (2015) and Hollenberg et al (2000) compared the validity of the OUES to VO_{2peak} and both included healthy adults. Buys et al (2015) used younger adults with a mean age of 38.6 years (n=1411,

r^2=0.884, p<0.001) and Hollenberg et al (2000) older adults (n=429), and separated their results to report the results in women (r=0.83) and men (r=0.88).

The reproducibility and reliability of the OUES has also been considered (R. Baba *et al.*, 1999; Van Laethem *et al.*, 2009; De Groot *et al.*, 2011; Phypers *et al.*, 2011). Two did so in healthy adults (R. Baba *et al.*, 1999; Van Laethem *et al.*, 2009), one using participants with spina bifida (De Groot et al., 2011) and the other in pre surgical patients (Phypers *et al.*, 2011). Van Laethem et al (2009) reported the intra-test reliability of the OUES to be excellent for both OUES (ICC 0.93) and VO_{2peak} (ICC 0.95) (both p<0.05). Whereas De Groot et al (2011) reported the reliability of the OUES to be good (ICC 0.80) and VO_{2peak} to be excellent (ICC 0.97) (both p<0.05).

Baba et al (1999) reported the reproducibility of the OUES taken a week apart and found the mean difference to be within 20%, in comparison to VO_{2peak} which was within 16%. These values were similar to the study by Van Laethem et al (2009) who reported the mean difference of the OUES to be within 18.7%, and VO_{2peak} to be within 17.3%. They also reported the $OUES_{90}$ to be within 21% and $OUES_{70}$ within 27%, with data analysed from 90% and 70% of the exercise time. As a result, both studies felt the OUES to be highly reproducible, which was stronger when calculating from longer levels of exercise. However, both did use health participants and small samples (n=18 and 19) so may not be generalisable.

While the evidence suggests the OUES to be valid, reliable and reproducible in healthy and in cardiorespiratory pathologies, limited evidence exists in other conditions.

2.10.3 Use of OEUS in MS

Three studies have considered the validity of the OUES in pwMS (M. Heine *et al.*, 2014; Edwards, Klaren, *et al.*, 2017; Valet *et al.*, 2020).

The study by Valet et al (2020) involved participants with mild MS (n=39, median EDSS 2.5) and considered the validity of OUES, RER, peak WR and physical

working capacity at 75% of maximal HR ($PWC_{75\%}$), to $V0_{2peak}$. They reported excellent correlation between the VO_{2peak} and OUES (r=0.88, p<0.001), RER (r=0.73, p<0.01) and peak WR (ICC 0.75, p<0.001). However, no correlation was found when using the $PWC_{75\%}$ (p=0.12).

In comparison Heine et al (2014) studied people with low to moderate levels of disability of MS. They classified low levels as an EDSS of ≤2.0 (n=25), mild disability as 2.5-4.0 (n=22) and moderate as ≥4.5 (n=9). They reported the OUES to correlate with VO_{2peak} (r=0.857, p<0.01), WR_{max} (r=0.514, p<0.01) and RER (r=-0.274, p<0.05). Submaximal OUES values were also calculated from participants who reached a heart rate within 90% of their age predicted maximal HR (n=27). Significant correlation was found between $OUES_{50}$ and $OUES_{100}$ in these participants (r=0.928, p<0.01), and Bland Altman analysis showed a mean difference of -1.8, indicating an important level of agreement between both.

The study by Edwards et al (2017) was the only one to include those with severe disability. Their participants included those with mild disability (EDSS of 1.0-3.5, n=20), moderate disability (EDSS 4.0-5.5, n=22) and severe disability (EDSS 6.0-6.5, n=20). They also reported significant correlation between the OUES and VO_{2peak} (r=0.66, p<0.001), WR_{peak} (r=0.78, p<0.001) and VAT (r=0.71, p<0.001) in pwMS. Like Heine et al (2014) they considered submaximal OUES in participants who achieved 90% of age-predicted maximum HR (n=21). They found the $OUES_{100}$ to significantly correlate with $OUES_{50}$ (r=0.89, p<0.001) and $OUES_{75}$ (r=0.97, p<0.001) in those participants. Bland Altman analysis, used to consider the level of agreement between OUES values, showed the difference between $OUES_{100}$ and $OUES_{50}$ to be 176.6 (SD 272.3) and $OUES_{100}$ and $OUES_{75}$ to be 90.18 (SD 157.2) which were considered acceptable. In addition, the coefficient of variation (COV) for the $OUES_{100}$, $OUES_{50}$, and $OUES_{75}$ was 29.5%, 24.2% and 26.3%, respectively, and suggested these results support the use of submaximal OUES in participants who are unable to attain peak effort.

Overall, the OUES has been shown to be a valid, reproducible submaximal exercise test in various chronic conditions. Although the evidence for use in pwMS is limited, the studies that exist show it to also be valid for use. Further

research in pwMS is merited involving people with higher levels of disability and considering the reliability and reproducibility of the OUES.

The following chapter will present a systematic review of the literature regarding the effect of APTs in neurological conditions, with and without FES.

Chapter 3 Systematic review: The effects of cycling using lower limb APTs in people with neurological conditions

This chapter was published by the International Journal of Therapy and Rehabilitation (Barclay et al. (2022) The effects of cycling using lower limb active passive trainers in people with neurological conditions: a systematic review. International Journal of Therapy and rehabilitation. [Online] 29 (6), 1–21). An update to this original review is also included at the end of this chapter.

3.1 Introduction

Physical inactivity is a leading contributor to global mortality (WHO, 2020), and participation in PA reduces the risk of premature death and development of chronic illness by 20-30% (Warburton *et al.*, 2016). Evidence suggests even minor increases in activity or fitness levels can reduce the risk of developing chronic disease and mortality, in both healthy populations and those with chronic conditions (Warburton *et al.*, 2016). Other potential benefits include improved functional capacity, social interaction and QOL (Anderson *et al.*, 2019).

Exercise is a fundamental treatment strategy for people with neurological conditions (WHO, 2020). Guidelines by the WHO (2020) recommend all adults living with a physical disability should undertake regular exercise aiming to improve aerobic fitness, strength and balance and thus help improve their health, function and QOL (WHO, 2020). However, exercise can be especially difficult for those with severe or progressive conditions such as neurological conditions, due to symptoms, accessibility and transport (Sharon-David *et al.*, 2021).

Cycling is an exercise often adopted by people with neurological conditions as it can be a relatively safe and feasible option and has been shown to improve aerobic endurance, muscle and bone strength, spasticity and function (Raasch *et al.*, 1999; Yang *et al.*, 2014; Barbosa *et al.*, 2015). Cycling is similar to walking

in that they are both cyclical activities, involve reciprocal contraction and relaxation of major muscle groups of the lower limbs and share sensori-motor control mechanisms (Raasch *et al.*, 1999; Yang *et al.*, 2014; Barbosa *et al.*, 2015). But many people with neurological conditions are not able to cycle on a standard bicycle, due to physical limitations.

Lower limb APTs allow cycling from a seated or supine position. The speed, resistance and type of exercise (active, active assisted or passive) can be adjusted depending on the user's level of ability which means they can be used by people with high levels of disability. Users receive visual feedback on their speed, distance cycled, power output and symmetry of cycling which can increase motivation, facilitate motor learning/control and improve rehabilitation outcomes (Raasch *et al.*, 1999; Yang *et al.*, 2014; Barbosa *et al.*, 2015). APTs can be used alone, but are often used in combination with neuromuscular stimulation, usually delivered through Functional Electrical Stimulation (FES). FES can assist with the cycling motion by stimulation of key muscle groups, and therefore is more often used in conditions with lower limb paralysis or lack of muscle innervation. APTs are commonly used clinically with anecdotal reports of benefits, however there is a paucity of evidence of benefits in those with neurological conditions particularly those with higher levels of disability.

The aim of this systematic literature review is to examine the evidence for lower limb APTs, with and without neuromuscular stimulation, and to determine their effects in relation to common issues such as spasticity, cardiovascular fitness, function and quality of life in people with neurological conditions.

3.2 Methods

An electronic literature search was initially complete from inception until June 2021. The following five databases were searched without date restrictions and in populations aged 18 and over: CINAHL, Medline, Embase, Epistemonikos and Google. The search strategy included key terms and words relating to neurological conditions, lower limb cycling, active passive trainers and electrical stimulation (Appendix 1). Articles were eligible to be included if they: 1) were

randomised controlled trials; 2) the population was people with neurological conditions such as MS, stroke, brain injury, spinal cord injury and Parkinson's; 3) the intervention included exercise on a lower limb APT, with or without FES; 4) included at least one outcome related to spasticity, cardiovascular fitness, physical function and quality of life. Articles were excluded if they were not in English, were abstracts or conference proceedings.

After removing duplicate articles, the titles and abstracts of all the articles were screened against the inclusion criteria by one reviewer (AB). Studies that did not meet the inclusion criteria were removed and where this was not clear the full text was read. Two reviewers (AB, LP) screened the full texts of the remaining articles for eligibility and reference lists of these articles were also checked for relevant studies.

3.2.1 Assessment of evidence quality

The quality of the included articles was assessed using the Downs and Black checklist, a 32-point scale that was developed for use with randomised and non-randomised controlled trials (Downs *et al.*, 1998). The final question on the checklist was adjusted so that a score of 1 was given if a power calculation for sample size was used in the study and 0 if it was not. Each article was independently assessed using the checklist by two reviewers (AB, LP) and scores compared. Any disagreements in score were discussed and a consensus agreed. No study was excluded based on the quality assessment results. This study applied the classification used by O'Connor et al (2015) who rated a study as excellent if it scored 24-28, good 19-23, fair 14-18 and poor if less than 14.

3.2.2 Data analysis

Data were firstly analysed using a narrative synthesis approach, and studies grouped into FES assisted APT cycling or APT cycling. Participant demographics, intervention protocols and outcomes were extracted and summarised. The

results were reported in relation to the exercise intervention received and significance relating to the outcomes of interest: spasticity, cardiovascular fitness, function and QOL. In addition, a meta-analysis was performed using Revman software (version 5.4) to establish the effect of APT on walking speed and endurance. It was not possible to include other outcomes of interest in this analysis due to the variety of outcome measures used, the availability of data and the consistency of how the data was reported. The weighted mean difference between the intervention and control groups was used in the meta-analysis to determine intervention effect. This was calculated using the mean difference and standard deviation (SD) in post intervention scores compared to baseline for both the intervention and control groups reported in each study. If the SD was not reported in the original article this missing data were calculated using the following formula outlined in the Cochrane Handbook (Higgins *et al.*, 2021): [$SD_{diff} = \sqrt{SD_{baseline}^2 + SD_{post}^2 - (2 \times Corr \times SD_{baseline} \times SD_{post})}$]. For this formula the SD_{diff} refers to the SD of the difference, the SD baseline refers to the SD of the baseline score, and the SD_{post} refers to the SD of the post intervention score. Due to the availability of data, the correlation coefficient for this formula was calculated using the values reported in Yang et al (2014). If any article did not report the mean difference and SD for the intervention and control groups or did not provide sufficient data for the result to be calculated, they were excluded from the meta-analysis. Meta-analyses were calculated for walking speed and endurance using a random effects model due to methodological and statistical heterogeneity (calculated using the I^2 and Chi-squared tests). For all tests a significance level of $p < 0.05$ was used.

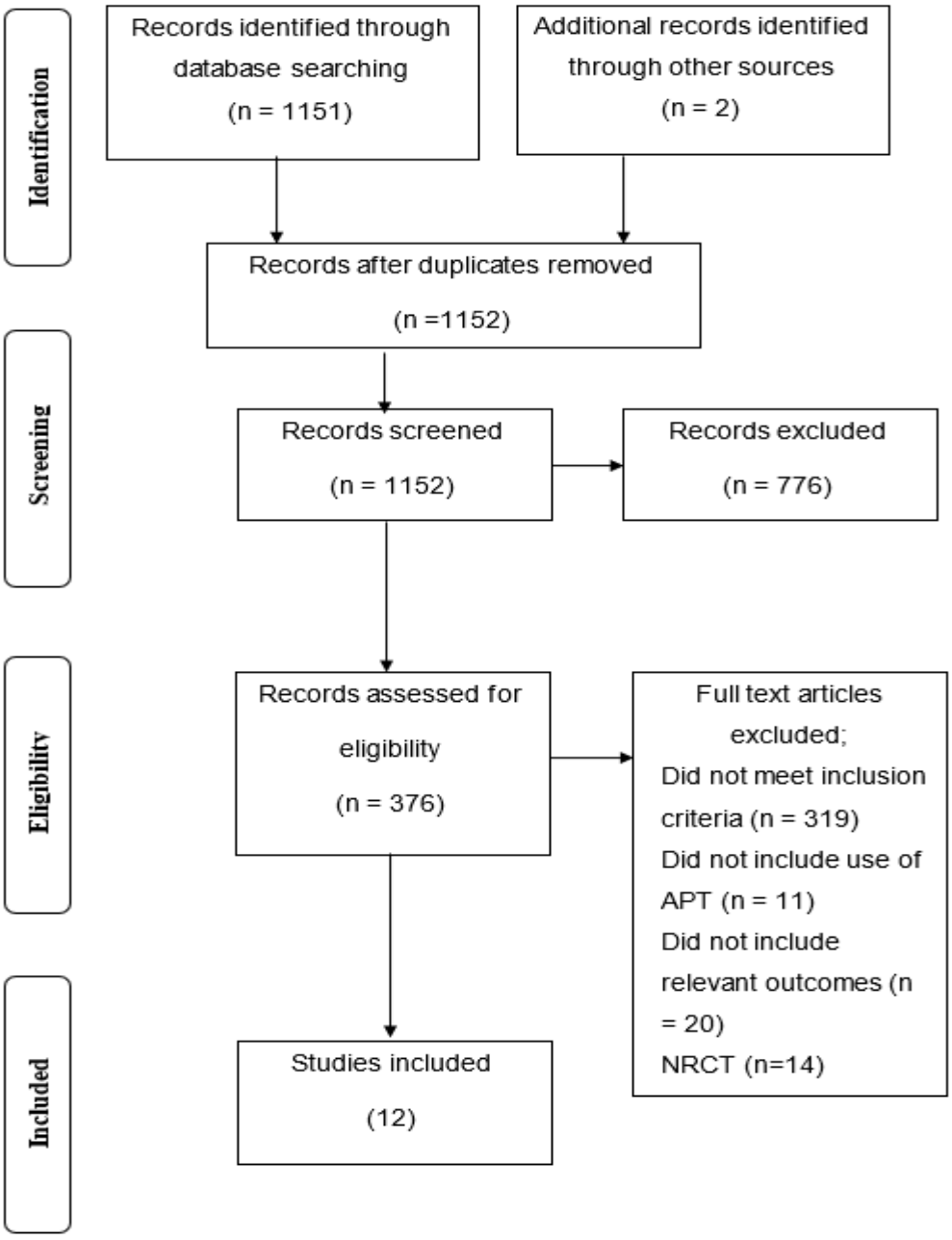
3.3 Results

3.3.1 Search results

The initial search resulted in 1151 articles, with two additional articles found from searching relevant reference lists (Figure 3.1). One duplicate article was removed, thus the titles and abstracts of 1152 articles were screened by one author for relevance. From this, 776 articles were excluded as they did not use APTs or did not include any of the specified outcomes. Three hundred and

seventy-six articles were then identified and following full text review, 12 were included in the review (Table 3.1).

Figure 3.1 Literature search strategy



3.3.2 Participant characteristics

From the 12 RCT's included within this systematic review, six studies used FES assisted APT cycling interventions (Ralston *et al.*, 2013; Bauer *et al.*, 2015; Edwards *et al.*, 2018; Backus *et al.*, 2020; Ambrosini, Peri, *et al.*, 2020; Shariat *et al.*, 2021) and six used APT cycling alone (Kamps *et al.*, 2005; Rayegani *et al.*, 2011; Laupheimer *et al.*, 2013; Yang *et al.*, 2014; Barclay *et al.*, 2019; Hochsprung *et al.*, 2020).

The sample sizes in the studies ranged from 8 to 68 and included a total of 423: 219 males, 160 females and 44 people where gender was not specified. The mean age of the participants was 55 (range 25 to 73). One study involved participants with Parkinson's (n=44) (Laupheimer *et al.*, 2013), two involved spinal cord injuries (n=78) (Rayegani *et al.*, 2011; Ralston *et al.*, 2013), four with MS (n=105) (Edwards *et al.*, 2018; Barclay *et al.*, 2019; Backus *et al.*, 2020; Hochsprung *et al.*, 2020) and five with stroke (n=196) (Kamps *et al.*, 2005; Yang *et al.*, 2014; Bauer *et al.*, 2015; Ambrosini, Peri, *et al.*, 2020; Shariat *et al.*, 2021).

Three studies involved participants within six months of diagnosis (Ralston *et al.*, 2013; Bauer *et al.*, 2015; Ambrosini, Peri, *et al.*, 2020) and seven who were six months or longer from diagnosis (Kamps *et al.*, 2005; Rayegani *et al.*, 2011; Laupheimer *et al.*, 2013; Yang *et al.*, 2014; Edwards *et al.*, 2018; Barclay *et al.*, 2019; Shariat *et al.*, 2021). Two studies did not comment on the time since diagnosis/injury (Backus *et al.*, 2020; Hochsprung *et al.*, 2020). Collectively the participants involved in these studies had differing disability levels. Eight included those who could walk with or without assistance (n=309) (Kamps *et al.*, 2005; Laupheimer *et al.*, 2013; Yang *et al.*, 2014; Bauer *et al.*, 2015; Edwards *et al.*, 2018; Hochsprung *et al.*, 2020; Shariat *et al.*, 2021), while four studies included those who were unable to walk and used wheelchairs (n=114) (Rayegani *et al.*, 2011; Ralston *et al.*, 2013; Barclay *et al.*, 2019; Backus *et al.*, 2020).

Table 3.1 Studies using APT cycling in neurological populations

Reference and study design	Participants' demographics	Intervention and control or comparator	Outcomes	Results
Kamps et al 2005 Cyclic movement training of the lower limb in stroke rehabilitation Randomised controlled trial, two parallel groups	Recruited from outpatient rehabilitation centres in Germany 40 recruited, 31 completed the study (intervention (n=16) control (n=15)) Intervention group: 11 women 5 men Mean age: 63.1±8.1 years Mean time since stroke: 12±9.5 months All infarcts: 9 left hemiplegia, 7 right hemiplegia Control group: 11 women 4 men Mean age: 65.8±10.7 years Mean time since stroke: 15.4±12.1 months	Two sessions per day, minimum 10 minutes' cycling for 4 months, with a 2-3 minute warm up and cool down period Participants aimed to cycle at 50-70rpm each time and were encouraged to increase time and resistance. Participants called every 14 days check on progress Comparator; conventional physiotherapy and exercise	Outcome measures assessed at start and end 2MWT, 6MWT, Tinetti test, BBS, TUG, 10MWT (comfortable and fast pace) were measures used Cycling data also recorded	Significant improvements in 2MWT (p=0.015) & 6MWT (p=0.003), comfortable gait speed (p=0.024) and TUG (p=0.016) in the intervention group No significant difference in Tinetti (p=0.313), BBS (p=0.1) and maximum gait speed (p=0.188) in either group Significant improvements in distance cycled (p=0.027) and power on MOTOmed APT (p=0.009)

	All infarcts: 7 left hemiplegia, 8 right hemiplegia			
Laupheimer et al 2011 Forced exercise: effects of MOTOmed therapy on typical motor dysfunction in Parkinson's Randomised controlled trial, two parallel groups	Recruitment from outpatient support groups in Germany 47 participants, 44 completed the study (intervention (n=21) and control (n=23)) No record of gender Mean age: 68.5±6.8 years Disease duration: 9.2±6.7 years Hoehn & Yahr stage: 2.69±0.68	40 minutes, five times a week, for 10 weeks Cycling procedure consisted of 5 minute warm up, gradually increasing to maximum of 90rpm. Cycle at 90rpm (or as close as able) for 30 minutes, followed by 5-minute cool down, gradually reducing speed Comparator: standard therapy only	Outcome measures assessed at start, end of week 5 and end Timed motor test battery, spiral test, Parkinson's Disease Questionnaire-8 were measures used	Significant improvement in walking time and walking steps ($p<0.001$) in the intervention group Significant changes in pronation and supination ($p=0.03$) of both arms, dressing ($p=0.09$) and depression ($p=0.06$) in the intervention group
Rayegani et al 2011 The effect of electrical passive cycling on spasticity in war veterans with spinal cord injury Randomised controlled trial, two parallel groups	Recruited people with SCI from outpatient clinics in Tehran Recruited 74 over 2 years; 64 completed study (intervention group (n=35), control (n=29)) 61 men, 3 women, Mean age: 43 years, SCI: 11 cervical; 22 upper thoracic; 29	20 minutes' cycling, three times a day for 2 months Comparator: physical therapy for 2 months (included stretching and strength exercises)	Outcome measures assessed at start and end MAS, range of movement at the hip, knee and ankle were measures used Neurophysiology; Hoffman's reflex also recorded	Significant increase in passive range of movement at hip ($p<0.03$), dorsiflexion ($p<0.001$) and plantarflexion ($p<0.001$) Significant reduction in H_{max}/M_{max} ($p<0.001$) and F/M ratio ($p<0.03$) Mean MAS reduced in intervention group ($p=0.003$)

	lower thoracic; 2 lumbar; 1 ASIA B; 63 ASIA A; SCI 15-20 years before			Control group demonstrated no significant change in mean MAS, or passive range of movement No carry over reported at the end of the study or 12 months after
Ralston et al 2013 Functional electrical stimulation cycling has no clear effect on urine output, lower limb swelling, and spasticity in people with spinal injury: a randomised cross-over trial Randomised controlled trial, cross over design	Recruited from two inpatient rehabilitation units in Sydney 14 recruited 11 men, 3 women Median age: 25 (range 22-32) Time since injury: 118 days (range 64-135) Type of injury: 13 ASIA A; 1 ASIA B; 8 cervical and 6 thoracic injuries	30-45 minutes' FES cycling, 4 times a week for 2 weeks Stimulation to quadriceps, hamstrings and gluteal muscles Comparator: no FES cycling for 2 weeks Patients also received standard care which consisted of typical physiotherapy and occupational therapy	Outcome measures assessed at start, end of week 2 and end of week 4 Urine output (ml/hr), lower limb circumference, Ashworth Scale, PRISM, PGIC were measures used	There were no clear effects of FES cycling on urine output, swelling, and spasticity even though all point estimates of treatment effects favoured FES cycling and participants perceived therapeutic effects The mean group differences for lower limb swelling, spasticity and PRISM were -0.1cm, -1.9 points and -5 points respectively. No values reported regarding significance
Yang et al 2014 Effect of biofeedback cycling training on functional recovery and walking ability of lower extremity in patients with stroke	Recruited from stroke rehabilitation clinic in Taiwan 30 recruited: group 1 (n=15); group 2 (n=15) Group 1: 9 men, 6 women	Group 1: 4 weeks of daily cycling intervention followed by 4 weeks of conventional rehab only (1 hr physiotherapy and 1 hr occupational therapy) Cycling procedure: 30 minutes in two sessions.	Lower limb subscale of Fugyl meyer assessment, 6MWT, 10MWT and MAS taken at start of trial and at end of week 4 and 8 Cycling data also recorded	Significant improvements in outcomes in the cycling period compared to the non-cycling period in Fugyl meyer ($p=<0.05$), 6MWT ($p=<0.001$), 10MWT ($p=<0.001$) and MAS ($p=<0.001$)

Randomised controlled trial, cross over design	Type of stroke: left hemiplegia 4; right hemiplegia 11 Mean age: 53.9±10.5 years Mean time since stroke: 11.1±8 months Barthel Index 17.4±2.2 Group 2: 13 men, 2 women Type of stroke: left hemiplegia 7; right hemiplegia 8 Mean age: 54.5±8 years Mean time since stroke: 11.1±9.7 months Barthel Index 16.5±3.8	15 minutes cycling forwards, 15 minutes cycling backwards Comparator: group 2 (n=15) did the converse, with 4 weeks of conventional therapy and 4 weeks of cycling		There was no carryover seen at 8 weeks Symmetry between legs was maintained at 76.5%-81.1% in active pedalling Performance improved from 19.9W to 32.7W and resistance increased from 6.5kg to 9.6kg after 4-week period
Bauer et al 2015 FES-assisted active cycling – therapeutic effects in people with hemiparesis from 7 days to 6 months after stroke: A randomised controlled pilot study Randomised controlled trial, two parallel groups	Recruited from inpatient neurological rehabilitation unit in Salzburg 40 recruited; 21 to intervention, 19 to control. 37 completed the study (intervention n=19, control n=18). 21 were followed up (Intervention n=9, control n=12)	20 minutes, three times a week, for 1 month (12 sessions) 1 minute warm up of active cycling, with 19 minutes of FES-assisted cycling FES stimulation to quadriceps and hamstring muscles	Outcome measures assessed at start, end and 2 weeks after the study completion FAC and POMA, MI, MAS and 10MWT were assessed	Both groups improved significantly over time Significant improvements for the FES group for POMA (p=<0.0004), FAC (p=0.001) and MI (p=0.005) Significant improvements for the control group for POMA (p=0.003) and MI (p=0.004), which were not maintained at follow up

	Intervention group: 12 men, 7 women Mean age: 59±14 years Infarct: n=15; Bleed: n=4 Time since stroke: 62±43 days Right hemiplegia: n=4 Left hemiplegia: n=14 Control group: 9 men, 9 women Mean age: 64±11 years Infarct: n=10; Bleed n=8 Time since stroke: 42±45 days Right hemiplegia: n=10 Left hemiplegia: n=8	Comparator: 20 minutes, three times a week, for 1 month (12 sessions) 1 minute warm up, 19 minutes active cycling		At follow up the control group walked significantly faster than FES group (p=0.049) No significant change MAS score between groups for knee flexors (p=0.988) and extensors (p=0.258) There was no significant difference in 10MWT between groups (p=0.649)
Edwards et al 2018 Pilot randomised controlled trial of functional electrical stimulation cycling exercise in people with multiple sclerosis with mobility disability Randomised controlled trial, two parallel groups	People with MS, recruited via local media announcements in Ottawa 11 recruited: intervention (n=6), control (n=5). Eight completed the study: intervention (n=4), control (n=4) 7 women, 1 man	Three times weekly cycling with for 6 months following protocol that included: 5 minute warm up and cool down of passive cycling. Start with 10-minute sessions of cycling at 50rpm for first month, increased by 10 minutes per month until managing 30 minutes, and continued to 6 months	Outcome measures assessed at start and end T25FW, TUG, MSWS-12, 2MWT, cardio-respiratory fitness – VO_{2peak} and WR_{peak}, muscle strength: dynamometer was used	No significant levels reported only effect sizes FES group showed small improvements in T25FW (d=0.40), TUG (d=-0.30), 2MWT (d=0.20) and VO_{2peak} (d=0.34) Moderate decrease in MSWS-12 (d=-0.68) Moderate improvement in WR_{peak} (d=0.65), knee extensor

	Mean age: 52.9±7.9 years EDSS: 6.3±0.5 Type of MS: RRMS (n=4), progressive MS (n=4) Disease duration: 21.5±6.6 years	FES stimulation to quadriceps, hamstrings and gluteal muscles stimulated at intensity to produce 50 rpm Comparator: three times weekly passive cycling, for 6 months following same protocol as intervention		strength (d=0.56), leg bone mineral density (d=0.57) Large correlation between changes in T25FW and VO_{2peak}/WR_{peak} (p=0.62-0.69) Moderate correlation between changes in T25FW and knee extensor strength (p=0.31)
Barclay et al 2019 The effect of cycling using active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe Multiple Sclerosis (MS); a feasibility study Randomised controlled trial, two parallel groups	Recruited MS participants from inpatient neurological rehabilitation unit in Glasgow 24 recruited, 15 to Intervention, 9 to control Intervention group: 6 men, 9 women Mean age: 54.9±2.6 years Type of MS: PPMS (n=3), SPMS (n=10), RRMS (n=2) Mean EDSS: 7.2±0.2 Control group: 6 women, 3 men	30 minutes, five times a week, for 1 month (20 sessions) No comparator Both groups received physiotherapy, occupational therapy, speech and language therapy and psychology as part of standard care	Outcome measures assessed at start and end MAS, MSSS-88, OUES, FIM, T25FW & MSQOL-54 were used Cycling data also recorded	Both intervention and control groups showed improvements in average scores for each outcome measure, but no significant differences between groups were found (MSSS-88 p=0.363, OUES p=0.838, FIM p=0.290, T25FW p=0.302 & MSQOL-54: MH p=0.631, PH p=0.838) Significant improvements in cycling data for the intervention group with average increase in speed, distance and power output (p<0.01 in all) Significant improvement in average distance cycled (p=0.032), speed (p=0.026) and power output (p=0.006)

	Mean age: 53.6±2.7 years Type of MS: PPMS (n=2), SPMS (n=6), RRMS (n=1) Mean EDSS 7.3±0.2			
Ambrosini et al 2020 A multimodal training with visual biofeedback in subacute stroke survivors: a randomised controlled trial Randomised controlled trial, two parallel groups	Recruited from inpatient rehabilitation unit in Italy 68 recruited: intervention (n=34) and control group (n=34). 52 completed the study, both groups (n=26). At 6 month follow up each group (n=16) Intervention group: 21 men, 13 women Mean age: 73.7±11.7 years Mean time since stroke: 13.9± 5.0 days Right hemiplegia: n=21 Left hemiplegia: n=13 Ischaemic: n=28 Haemorrhagic: n=4 Haematoma: n=1	20 minutes of biofeedback FES cycling and 70 minutes of usual care, five times a week, for 15 sessions Followed by 20 minutes of biofeedback balance training and 70 minutes of usual care, five times a week, for 15 sessions Quadriceps, Hamstring, Lateral gastrocnemius and tibialis anterior were stimulated bilaterally Comparator: 30 sessions of usual care, lasting 90 minutes	Outcome measures assessed at start, after 15 sessions, end of intervention and at 6 month follow up Gait speed, spatio-temporal gait parameters, 6MWT, FIM, MI, trunk control test, BBS, falls efficacy scale were used	Both groups significantly improved over time in all outcome measures ($p<0.001$), which was maintained at follow up A significant effect on gait speed was report at the end of the intervention for both groups ($p=0.048$). Those more severely affected at the start showed more significant improvements ($p=0.008$) A trend in favour of the intervention group was noted for all outcome measures, however this was not significant

	Control group: 17 men, 17 women Mean age: 72.9±12.8 years Mean time since stroke: 18.0±14.3 days Right hemiplegia: n=15 Left hemiplegia: n=19 Ischaemic: n=26 Haemorrhagic: n=5 3 Haematoma: n=3			
Backus et al 2020 Effects of functional electrical stimulation cycling on fatigue and quality of life in people with multiple sclerosis who are non-ambulatory Randomised controlled trial, two parallel groups	Recruited from outpatient MS clinic and services in Atlanta 21 recruited: intervention group (n=12), control group (n=9). 12 completed (n=6 in both groups) 7 women, 5 men Mean age: 55.4±10.3 years (range 39-70) Type of MS: RRMS: n=3, SPMS: n=4, not specified: n=5 EDSS median: 7.2 EDSS 7.0: n=6, EDSS 7.5: n=3, EDSS 8.0: n=1, EDSS 8.5: n=2	FES cycling 30 minutes, three times a week, 12 weeks Gluteus maximus, hamstrings and quadriceps stimulated Aim to cycle at 35-50rpm Comparator: 12 weeks of normal activities	Outcome measures assessed at different points in the study Adverse effects were recorded daily. The other measures were assessed within a week of starting the study and completing the study Safety/adverse effects assessed MAS, muscle strength, MFIS-5, FSMC, medical outcomes pain effects scale, PHQ-9, MSQOL-54 and exercise self-efficacy scale were used	Six adverse effects: 5 in the intervention, 1 in the control group P values not reported, only effect size Minimal change in VAS for fatigue, pain or spasticity following cycling Minimal change in MAS or muscle strength scores Large effect from the intervention on MSQOL-54 subscores for physical health (d=0.85) and health perception (d=1.12), health distress (d=1.22) and physical health composite (d=1.48), with the intervention group

				improving and control group declining Large effects on physical composite of the PHQ-9 (d=0.76) for intervention Moderate effect between groups on MFIS-5 (d=0.60), PHQ-9 (d=0.67) and participants report of self-efficacy (d=0.46) No meaningful difference on FSMC (d=0.29) and pain effects scale (d=0.10)
Hochsprung et al 2020 Effect of visual biofeedback cycling training on gait in patients with multiple sclerosis Randomised controlled trial, two parallel groups	Recruited from multiple sclerosis unit in Seville, Spain 61 recruited: intervention group (n=30) and control group (n=31) Intervention group: 20 women, 10 men Type of MS: PPMS: n=6, RRMS: n=11, SPMS: n=13 Control group; 16 women, 15 men	30 minutes, once a week, for 3 months Working at 75% of the maximal resistance using co-ordination programme Also received a home exercise programme to complete Comparator: home exercise programme only	Outcome measures assessed at start, 1 month and end of intervention Spatio-temporal gait analysis using GaitRite system, including stride length, walking speed and cadence, was used	The intervention group showed significant improvements in spatio-temporal gait parameters within the first month ($p<0.014$) and at the end of the intervention ($p<0.002$). Stride length after a month ($p<0.01$) and at the end of intervention ($p<0.002$) The control group showed significant improvements to stride length by the end of the intervention ($p<0.04$) only

	Type of MS: PPMS: n=8, RRMS: n=16, SPMS: n=7			No significant changes to walking speed or cadence were reported in either group
Shariat et al 2021 Effect of cycling and functional electrical stimulation with linear and interval patterns of timing on gait parameters in patients after stroke: a randomised clinical trial Randomised controlled trial, two parallel groups	Recruited from three rehabilitation units in Tehran 36 recruited; 6 dropped out, 30 completed (linear group n=14, interval=16) 17 men, 13 women Left hemiplegia: n=16 Right hemiplegia: n=14 Stroke onset between 6-12 months: n=9 Stroke onset between 12-18 months: n=21	28 minutes, three times a week, for 4 weeks Each group completed 8 minutes of active cycling and 20 minutes of active cycling with FES stimulation Stimulation to biceps femoris and peroneal muscles Linear group: 8 minutes of active cycling, 20 minutes of active cycling with FES stimulation Interval: 4 bouts of active cycling with FES stimulation, with a break of 1-2 minutes between each	Outcomes measured at start, 4 weeks and 8 weeks 10MWT, FAC, MMAS, AROM, TUG and SLS were used	10MWT: significant group by time effect shown (p=0.001) FAC: significant group by time effect found (p=0.01) Spasticity: significant group by time effect shown at plantarflexors (p=0.023) and in quadriceps (p=0.005) AROM: significant increase in ankle and knee range of movement in interval group (p<0.001 for both) TUG: no significant group by time effect shown (p=0.238). Interval group improved more than the linear group after 4 weeks SLS: no significant group by time effect shown (p=0.260) Significant results were also maintained at follow up

Abbreviations: RPM - Revolutions per Minute, 2MWT - 2 Minute Walk Test, 6MWT - 6 Minute Walk Test, BBS - Berg Balance Scale, 10MWT - 10 Metre Walk Test, TUG - Timed Up and Go, SCI – Spinal Cord Injury, ASIA – American Spinal Cord Injury Assessment, MAS - Modified Ashworth Scale, H_{max}/M_{max} - Hoffmans reflex, FES – Functional Electrical Stimulation, PRISM - Patient Reported Impact of Spasticity Measure recorded, PGIC – Patients Global Impression of Change, W – Watts, FAC - Functional Ambulation Capacity, POMA - Performance

Orientated Mobility Assessment, MI - Motricity Index, EDSS - Extended Disability Status Scale, MS - Multiple Sclerosis, RRMS - Relapsing and Remitting MS, PPMS - Primary Progressive MS, SPMS - Secondary Progressive MS, T25FW - Timed 25 Foot walk, MSWS-12 - 12 Item MS Walking Scale, VO_{2peak} - Peak Oxygen Uptake, WR_{peak} - Peak Work Rate, MSSS-88- Multiple Sclerosis Spasticity Scale, OUES – Oxygen Uptake Efficiency Slope, FIM – Functional Independence Measure, MSQOL-54- Multiple Sclerosis Quality of Life -54, MH - Mental Health, PH - Physical Health, MMAS – Modified Modified Ashworth Scale, AROM – Active ROM, SLS –Single leg stance, MFIS-5 – Modified Fatigue Impact Scale, FSMC - Fatigue Scale for Motor and Cognitive functions, PHQ-9 - Patient Health Questionnaire 9, MMSE – Mini Mental State Examination.

NB p values are included where stated in the papers

3.3.3 Study characteristics

From the 12 studies included in this review, 10 involved two parallel groups (Kamps *et al.*, 2005; Rayegani *et al.*, 2011; Laupheimer *et al.*, 2013; Bauer *et al.*, 2015; Edwards *et al.*, 2018; Barclay *et al.*, 2019; Backus *et al.*, 2020; Ambrosini, Peri, *et al.*, 2020; Shariat *et al.*, 2021) and two included cross over interventions (Ralston *et al.*, 2013; Yang *et al.*, 2014).

The total quality scores using the Downs and Black checklist ranged from 8-24 out of 28 (Table 3.2). One was deemed to be of excellent quality (Ambrosini, Peri, et al., 2020), six were classed as good (Kamps *et al.*, 2005; Ralston *et al.*, 2013; Bauer *et al.*, 2015; Barclay *et al.*, 2019; Hochsprung *et al.*, 2020; Shariat *et al.*, 2021) and five were fair (Rayegani *et al.*, 2011; Laupheimer *et al.*, 2013; Yang *et al.*, 2014; Edwards *et al.*, 2018; Backus *et al.*, 2020).

Table 3.2 Results of Quality assessment - Downs and Black checklist

Author/ Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total
Shariat et al 2021	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	1	1	**22**
Ambrosini et al 2020	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	**24**
Backus et al 2020	1	1	1	0	1	1	1	1	0	0	0	1	1	0	1	1	1	1	0	1	1	0	1	0	0	1	0	**17**
Hochsprung et al 2020	1	1	1	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1	0	1	1	0	1	0	0	1	0	**19**
Barclay et al 2019	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	0	1	0	**22**
Edwards et al 2018	1	1	1	0	0	1	1	1	1	1	0	0	0	0	1	1	1	0	1	1	0	0	1	0	0	1	0	**15**
Bauer et al 2015	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	1	1	**23**
Yang et al 2014	1	1	1	1	0	1	1	1	1	0	0	0	1	0	1	1	1	1	0	1	0	1	1	0	1	1	0	**18**
Ralston et al 2013	1	1	1	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	0	**22**
Laupheimer et al 2011	1	1	1	1	0	0	0	0	1	1	0	0	1	0	0	1	1	1	0	1	1	0	1	0	0	1	0	**14**
Rayegani et al 2011	1	1	1	1	0	1	1	0	0	1	1	0	1	0	0	1	1	1	0	1	1	1	1	0	0	1	0	**17**
Kamps et al 2005	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1	0	0	1	0	**19**

Both FES assisted cycling and APT cycling interventions differed in length, frequency per week and duration of each cycling session (Table 1). Overall, eight studies reported significant changes in at least one outcome. Three studies used FES assisted cycling interventions (Bauer *et al.*, 2015; Ambrosini, Peri, *et al.*, 2020; Shariat *et al.*, 2021), and five studies used APT cycling interventions (Kamps *et al.*, 2005; Rayegani *et al.*, 2011; Laupheimer *et al.*, 2013; Yang *et al.*, 2014; Hochsprung *et al.*, 2020). Only three studies considered follow up after completion of the intervention to determine the longer-term effects and all used FES assisted cycling (Bauer *et al.*, 2015; Ambrosini, Peri, *et al.*, 2020; Shariat *et al.*, 2021). The length of time between the end of the intervention and follow up assessments ranged from two weeks (Bauer *et al.*, 2015) to six months (Ambrosini, Peri, *et al.*, 2020).

3.3.4 Outcome Measures: Spasticity

Seven studies evaluated the intervention effect in relation to spasticity; four used FES assisted cycling (Ralston *et al.*, 2013; Bauer *et al.*, 2015; Backus *et al.*, 2020; Shariat *et al.*, 2021) and three used APT cycling alone (Rayegani *et al.*, 2011; Yang *et al.*, 2014; Barclay *et al.*, 2019). All the studies measured spasticity using the MAS, or versions of it. One study also used neurophysiology, measuring H_{max}/M_{max} and F/M ratio (Rayegani *et al.*, 2011), and two studies used patient reported measures of spasticity (Ralston *et al.*, 2013; Barclay *et al.*, 2019).

Three studies found spasticity to be significantly reduced following cycling interventions according to the MAS or modified versions of it (Rayegani *et al.*, 2011; Yang *et al.*, 2014; Shariat *et al.*, 2021). Each study reported the mean scores of the MAS although did not clarify how this was calculated, and only one study listed the individual muscle group assessed (Yang *et al.*, 2014), where they only considered the effect on knee extensor spasticity of the affected lower limb. Significant improvements to lower limb spasticity were also reported using the H_{max}/M_{max} ($p<0.001$) and F/M ratios ($p<0.03$) (Rayegani *et al.*, 2011). From these results two interventions used APT cycling alone (Rayegani *et al.*, 2011; Yang *et al.*, 2014) and one used FES assisted cycling (Shariat *et al.*, 2021).

Two studies included a follow up assessment after completion of their intervention to determine the longer-term effects (Bauer *et al.*, 2015; Shariat *et al.*, 2021). Only one study reported a prolonged effect on spasticity when assessed a month after the intervention (Shariat *et al.*, 2021).

3.3.5 Cardiovascular fitness

Two studies considered changes in cardiovascular fitness, one using FES assisted cycling (Edwards *et al.*, 2018) and one using APT cycling alone (Barclay *et al.*, 2019). One study assessed peak oxygen (VO_{2peak}) uptake during an incremental exercise test (Edwards *et al.*, 2018), and the other by mean VO_2 during submaximal exercise test (Barclay *et al.*, 2019). The study by Edwards et al (2018) reported a small intervention effect (d=0.34), however no other statistical results were reported.

3.3.6 Physical Function

Ten studies included measurement of outcomes related to physical function, five using APT cycling alone (Kamps *et al.*, 2005; Laupheimer *et al.*, 2013; Yang *et al.*, 2014; Barclay *et al.*, 2019; Hochsprung *et al.*, 2020) and five using FES assisted cycling (Bauer *et al.*, 2015; Edwards *et al.*, 2018; Backus *et al.*, 2020; Ambrosini, Peri, *et al.*, 2020; Shariat *et al.*, 2021). A variety of outcome measures were used to measure physical function (n=15); walking ability (n=10), general function (n=3) and strength (n=2).

3.3.7 Walking ability

Nine studies used at least one walking outcome which included the 10 metre walk test (10MWT) (Kamps *et al.*, 2005; Yang *et al.*, 2014; Bauer *et al.*, 2015; Shariat *et al.*, 2021), six minute walk test (6MWT) (Kamps *et al.*, 2005; Yang *et al.*, 2014; Ambrosini, Peri, *et al.*, 2020), Timed up and go (TUG) (Kamps *et al.*,

2005; Edwards *et al.*, 2018; Shariat *et al.*, 2021), two minute walk test (2MWT) (Kamps *et al.*, 2005; Edwards *et al.*, 2018), Timed 25 foot walk (T25FW) (Edwards *et al.*, 2018; Barclay *et al.*, 2019), Functional Ambulation Category (FAC) (Bauer *et al.*, 2015; Shariat *et al.*, 2021), gait analysis (including cadence, step and stride length) (Ambrosini, Peri, *et al.*, 2020; Hochsprung *et al.*, 2020), Performance Orientated Mobility Assessment (POMA) (Kamps *et al.*, 2005; Bauer *et al.*, 2015), the 12 item MS Walking Scale (Edwards *et al.*, 2018) and the Timed Motor Test Battery (Laupheimer *et al.*, 2013).

Seven studies reported significant improvements in walking ability following interventions (Kamps *et al.*, 2005; Laupheimer *et al.*, 2013; Yang *et al.*, 2014; Hochsprung *et al.*, 2020) and three using FES assisted cycling (Bauer *et al.*, 2015; Ambrosini, Peri, *et al.*, 2020; Shariat *et al.*, 2021). A further two studies showed improvements in walking ability but not to a significant level (Edwards *et al.*, 2018; Barclay *et al.*, 2019).

3.3.8 Quality Of Life

Three studies considered QOL measures, two using FES assisted cycling (Ralston *et al.*, 2013; Backus *et al.*, 2020) and one using APT cycling alone (Barclay *et al.*, 2019). Two studies used the MSQOL-54 (Barclay *et al.*, 2019; Backus *et al.*, 2020) and one used the patient's global impression of change (PGIC) (Ralston *et al.*, 2013). The study by Barclay et al (2019) reported a significant time effect for both physical health ($p=0.007$) and mental health ($p=0.029$) domains within the MSQOL-54 but no interaction effects for either following APT cycling alone. The study by Backus et al (2020) only reported effect sizes due to a small sample size ($n=12$) but found a large effect on the MSQOL-54 subscores for physical health ($d=0.85$), health perception ($d=1.12$), health distress ($d=1.22$) and physical health composite ($d=1.48$) following their intervention. They also reported large effects on physical composite for the patient health questionnaire ($d=0.76$) and a moderate effect on modified fatigue impact scale ($d=0.60$). Ralston et al (2013) did not report any significant improvements using the PGIC.

3.3.9 Cycling data

Four studies reported cycling data, three following APT cycling alone (Kamps *et al.*, 2005; Yang *et al.*, 2014; Barclay *et al.*, 2019) and one following FES assisted cycling (Edwards *et al.*, 2018). Significant improvements were reported in average power output (Kamps *et al.*, 2005; Barclay *et al.*, 2019), average cycling distance (Kamps *et al.*, 2005; Barclay *et al.*, 2019) and average speed cycled (Barclay *et al.*, 2019). One study also reported moderate improvements in WR_{peak} (d=0.65) but did not report significance due to low sample size (n=8) (Edwards *et al.*, 2018).

3.3.10 Meta-analysis: walking speed and endurance

To allow further analysis, outcomes that assessed walking ability were grouped in relation to walking speed (10MWT, T25FW and gait analysis n=8) and walking endurance (6MWT) (n=4). Five studies were included in the meta-analysis for walking speed (metres per second) (Kamps *et al.*, 2005; Yang *et al.*, 2014; Barclay *et al.*, 2019; Ambrosini, Peri, *et al.*, 2020; Shariat *et al.*, 2021), and three studies for walking endurance (Kamps *et al.*, 2005; Yang *et al.*, 2014; Ambrosini, Peri, *et al.*, 2020). The analysis of walking speed showed a small, non-significant increase in walking speed (0.05m/s) favouring the intervention group (p=0.31). However, the confidence interval was large, indicating an inconsistent effect (95% CI:-0.04-0.14; I^2=85%) (Figure 3.2). A sensitivity analysis including only studies involving stroke participants was completed (Kamps *et al.*, 2005; Yang *et al.*, 2014; Ambrosini, Peri, *et al.*, 2020; Shariat *et al.*, 2021). A more consistent effect was found (95% CI:0.03-0.16; I^2=68%), with a statistically significant increase in walking speed (0.09m/s) favouring the intervention group (p=0.004). The analysis of walking endurance showed a consistent improvement in 6MWT performance (MD=49.68m; 95% CI=41.56-57.81; I^2=34%) in favour of the intervention group, which was statistically significant (p<0.001). However, a sensitivity analysis was not feasible given the already small number of studies included (Figure 3.3).

Figure 3.2 Results from meta-analysis for the effect of APT on walking speed (m/s)

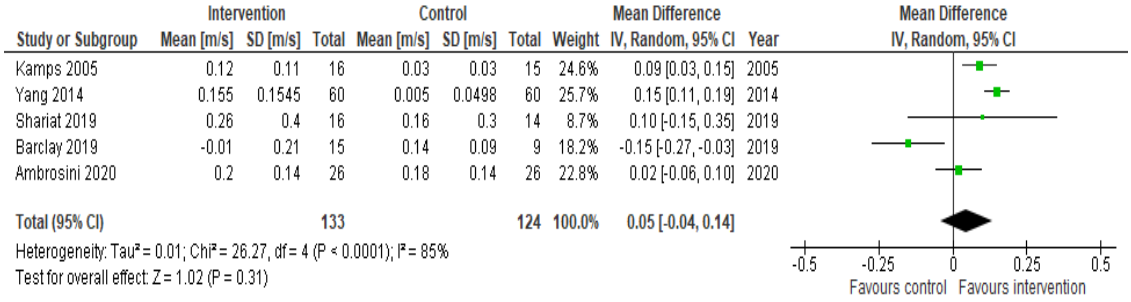
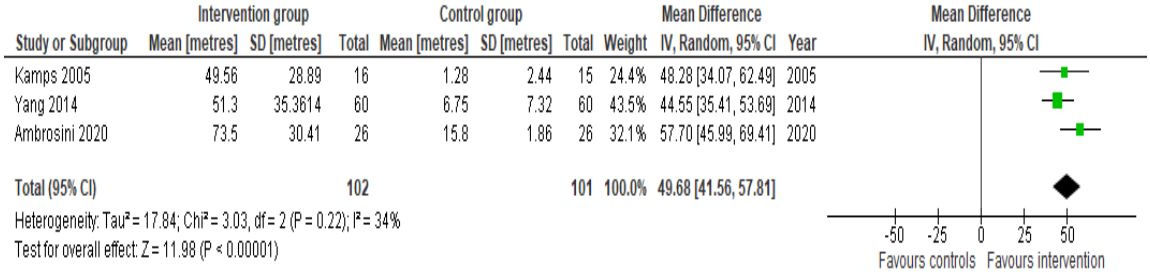


Figure 3.3 Results from meta-analysis for the effect of APT on walking endurance (6MWT)



3.3.11 Muscle strength

Four studies considered muscle strength and all used FES assisted interventions (Bauer *et al.*, 2015; Edwards *et al.*, 2018; Backus *et al.*, 2020; Ambrosini, Peri, *et al.*, 2020). Outcome measures were the leg sub-scale of the Motricity Index (Bauer *et al.*, 2015; Ambrosini, Peri, *et al.*, 2020), isokinetic dynamometry (Edwards *et al* 2018) and manual muscle testing (Backus *et al.*, 2020). Two reported significant improvements in strength following their intervention (Bauer *et al.*, 2015; Ambrosini, Peri, *et al.*, 2020), and one study reported a moderate improvement in knee extensor strength (d=0.56) but did not comment regarding significance (Edwards *et al.*, 2018).

3.3.12 Other outcomes measured

Four studies used other measures that considered the participant's level of disability (Functional Independence Measure (FIM)) (Barclay *et al.*, 2019; Ambrosini, Peri, *et al.*, 2020), balance (Berg Balance Scale (BBS) and trunk control test) (Kamps *et al.*, 2005; Ambrosini, Peri, *et al.*, 2020) and areas specific to Parkinson's (Timed Motor Battery Test and Tremor Spiral Test) (Laupheimer *et al* 2011).

Significant improvements in FIM, BBS and trunk control test were reported by one study (Ambrosini, Peri, *et al.*, 2020), which were maintained at follow up. Laupheimer et al (2011) also reported significant improvements in upper limb forearm movement (p=0.03) and a trend for an improvement in dressing (p=0.09) and depression (p=0.06). There was no change noted to tremor or co-ordination.

3.3.13 Adverse Events

Adverse Events (AEs) were reported in seven studies. Three studies recorded AEs (Ralston *et al.*, 2013; Edwards *et al.*, 2018; Backus *et al.*, 2020), but only one was related to the intervention and was due to skin irritation from the electrodes. Four studies reported no AEs (Yang *et al.*, 2014; Bauer *et al.*, 2015; Barclay *et al.*, 2019; Ambrosini, Peri, *et al.*, 2020) and five made no mention of AEs (Kamps *et al.*, 2005; Rayegani *et al.*, 2011; Laupheimer *et al.*, 2013; Hochsprung *et al.*, 2020; Shariat *et al.*, 2021).

3.4 Discussion

The aim of this chapter was to carry out a systematic review and meta-analysis to investigate the effects of lower limb APTs, with or without FES, on spasticity, cardiovascular fitness, physical function and QOL in people with neurological conditions. This review identified 12 articles that met the specified criteria and these studies included different neurological conditions and participants with differing degrees of disability. Lower limb APT interventions were found to

significantly improve walking endurance in studies involving stroke participants, although this cannot be generalised. Some of the studies included in this review also found improvements in walking speed, however the effect was not consistent across all studies and conditions. In addition, studies used heterogeneous designs, and the prescribed APT intervention differed between studies which made comparisons difficult.

Overall, eight studies reported significant improvements to walking ability, balance, spasticity and strength following interventions, five using APT cycling and three using FES assisted. These studies, however, used a large variety of outcome measures (n=39). The most frequently used measures related to walking speed (n=12), endurance (n=4) and spasticity using the MAS or versions of it (n=7). While few studies considered QOL (n=3) or cardiovascular fitness (n=2).

A meta-analysis was only possible for measures of walking speed (n=5) and endurance (n=3) due to the availability and consistency of data reported, and found a statistically significant improvement from interventions on walking endurance but not speed. However, when data from the stroke studies was considered alone (n=4) a significant benefit was found. These findings are similar to a review by Shariat et al (2019) who considered the effects of cycling and FES assisted cycling in stroke participants. Their meta-analysis also found a significant improvement in walking speed, endurance and balance following cycling interventions (Shariat *et al.*, 2019). Developing or improving walking ability is an important goal for many patients, and a relationship between maintaining mobility and preserving independence and QOL has been demonstrated (Clark, 2015; Mizuta *et al.*, 2020). However, many factors are known to impact walking speed, such as severity of disability, age, confidence, visual issues, deficits in motor control and ankle activity (Clark, 2015; Mizuta *et al.*, 2020). The results suggest APT cycling interventions could be an important adjunct to treatment within rehabilitation settings to help patients maintain or improve their mobility. Further research to establish the effect in other neurological conditions is merited.

Seven studies considered the effect of the interventions on spasticity and three studies found spasticity to be significantly reduced following APT interventions (2 APT alone, 1 APT + FES). However, all these studies used the MAS or versions of it as an outcome measure. While the MAS remains the most clinically used tool for the assessment of spasticity its sensitivity and reliability is questionable (Ansari *et al.*, 2006; Mutlu *et al.*, 2008; Craven *et al.*, 2010; Kaya *et al.*, 2011), and may account for some of the variation in the results across these studies. In addition, data regarding the MAS was not fully or consistently reported by each study precluding further analysis. Other spasticity measures often used within research include biomechanical tools (dynamometry, torque) and neurophysiological measures (electromyography, H-reflex) and have been suggested to be more sensitive than the MAS (Biering-Sørensen *et al.*, 2006; da Luz dos Santos *et al.*, 2017; Balci, 2018). Although they too have limitations with cost, space and training requirements the main barriers to clinical use (da Luz dos Santos *et al.*, 2017; Balci, 2018). It remains unclear regarding the most appropriate measure of spasticity and further research to establish this is needed.

The intensity, frequency and duration of both FES assisted, and APT cycling alone also varied widely between studies. The shortest intervention lasted two weeks (Ralston *et al.*, 2013) and the longest six months (Edwards *et al.*, 2018), with no two studies in this review using the same dose of APT exercise. While five studies involving 118 participants used what may be considered a higher dose (30 minutes cycling, at least 3 times a week and for a month or more), this did not necessarily result in better outcomes as only two studies reported significant improvements (Laupheimer *et al.*, 2013; Yang *et al.*, 2014). In comparison, seven studies involving 305 participants used a lower exercise dose, and six reported significant findings (Kamps *et al.*, 2005; Rayegani *et al.*, 2011; Bauer *et al.*, 2015; Ambrosini, Peri, *et al.*, 2020; Hochsprung *et al.*, 2020; Shariat *et al.*, 2021). Most of these studies included participants with a diagnosis of stroke (n=4), who were able to walk and presented with lower levels of disability, which suggests that pathology and disability levels may influence the outcomes of APT interventions.

Furthermore, cycling data was only recorded in four studies and significant improvements were reported in two (Kamps *et al.*, 2005; Barclay *et al.*, 2019). While APT interventions resulted in improvements in average speed, distance cycled and power output, it remains unclear how these translate into meaningful clinical or functional benefits, given that few studies demonstrated change in functional ability.

Lastly, it is unclear whether FES assisted APT cycling is more effective that APT cycling alone in neurological conditions, as few studies have included comparison. Only one study included in this review did so and reported significant improvements to lower limb strength and walking ability following both interventions in a stroke population (Bauer *et al.*, 2015). They did report significantly larger improvements to walking ability following FES assisted APT cycling, suggesting FES assisted cycling maybe more effective than APT cycling alone. FES assisted cycling is commonly used in conditions with lower limb paralysis or lack of innervation, and much of the evidence on this topic is derived from a spinal cord injured populations (n=1 in this review). In SCI it is considered a key component of activity based restorative therapy, and has been reported to improve metabolic function, muscle strength, spasticity and cardiopulmonary function (Peng *et al.*, 2011; van der Scheer *et al.*, 2021). The study included in this review did not support these findings (Ralston *et al.*, 2013). However, this study only ran for two weeks and primarily aimed to assess the acute effects of FES assisted cycling on urine output and leg swelling rather than muscle bulk and spasticity which were also measured. The effectiveness of FES assisted cycling in neurological conditions other than SCI is less established. Clinically, its use is limited due to the cost, equipment requirements and time that must be taken to set it up (Bersch *et al.*, 2015). This review could not definitively determine whether FES assisted APT cycling is more effective than APT cycling alone across neurological conditions or disability levels, and further research to establish this is merited.

3.4.1 Limitations

There are several limitations to this review. Other studies using APT interventions were identified, however did not use a randomised control trial design so were excluded. The sample size of many of the studies within this review was small and involved different neurological conditions impacting on the ability to generalise. A large number of outcome measures were also used by the studies and few involved follow up review. Data regarding pre and post intervention scores were often not reported which prevented inclusion within a meta-analysis. In addition, the studies used differing study designs, and dose of the APT interventions again limiting the ability to compare results across studies. Lastly, the screening of abstracts and data extraction was completed by a single author, which potentially may have led to bias.

3.4.2 Conclusions

Research is limited regarding lower limb APT cycling, with or without FES, in people with neurological conditions. The results of this review suggest that both APT cycling and FES assisted cycling may have the potential to improve walking endurance, speed and spasticity. However, many of these studies included stroke participants and thus cannot be generalised, and further research in other neurological conditions is merited. In addition, the optimal duration, frequency and dose of APT interventions remains to be established. It remains unclear whether APT cycling alone is more effective than FES assisted cycling, and further research is needed to establish any benefits it may bring to people with neurological conditions. Future studies should use and report outcomes in a consistent, homogeneous manner to allow comparison, and consider the possible benefits in relation to cardiovascular fitness and QOL.

3.5 Future research

This review highlighted several points that merit further investigation. Firstly, the dose and intensity of APT interventions to produce meaningful changes for

participants remain unclear. It also remains unclear whether FES assisted APT cycling is more effective than APT cycling alone across neurological conditions and disability levels. Studies rarely considered both, and future studies should do so to determine this.

Much of the positive evidence exists in stroke populations and in people with lower levels of disability. While the results of this review are suggestive that APT cycling interventions could be helpful in maintaining or improving mobility, it is unclear if this translates to different populations and disability levels.

Future research should also consider consistency when reporting data to allow comparison, and also the outcome measures used. This review highlighted the heterogeneity of study designs and measures used within in them. Spasticity in particular was highlighted as an area of particular need. There are various methods used to measure spasticity which include clinical measures (clinical rating scales and patient reported outcome measures), biomechanical measures (isokinetic dynamometry) and neurophysiological methods (electromyogram, H-reflex). There are strengths and weaknesses for each measure, and no one method has been identified as gold standard in the measurement of spasticity. For example, clinical rating scales and biomechanical measures are used to quantify muscle stiffness, while patient reported measures (PROMs) supplement these tools by providing information on the impact of spasticity on QOL and treatments. Neurophysiological methods however, are direct measures of spasticity, though require specialist equipment and training to use which limits their clinical use. These methods will be discussed in more detail in Chapter 5.

3.6 Review update: articles published since systematic review was conducted

To update the systematic review, a second search was conducted in December 2022 using the same search criteria, databases and eligibility as described in section 3.2. The updated search found an additional 162 articles. Titles and abstracts were screened against the eligibility criteria and 155 were excluded, with the full texts of the remaining seven articles screened. A further four

articles were excluded as they did not use an APT (n=1), were not randomised controlled trials (n=2) or did not consider the outcomes of interest (n=1). One other study was also excluded as it was noted to be a secondary analysis from the study by Edwards et al (2018), included in the original review (Farrell *et al.*, 2022). Two studies met the criteria and were included in this update (Table 3.3).

Table 3.3 Additional APT studies in neurological populations

Reference and study design	Participants' demographics	Intervention and control or comparator	Outcomes	Results
Farkas et al 2021 Energy expenditure, cardiorespiratory fitness and body composition following arm cycling or functional electrical stimulation exercises in Spinal Cord Injury: a 16-week randomised controlled trial Randomised controlled trial, two parallel groups	People with SCI, recruited via word of mouth, posters and SCI clinics in participating institutes (not listed) 13 recruited; arm cycling exercise (ACE) (n=7), FES leg cycling (n=6) 4 women, 9 men Mean age: 40.4±11.9 years Type of injury: Motor complete paraplegia, level T4-10	40 minutes cycling, 5 times a week and for 16 weeks FES leg cycling: 10 minutes passive warm up and cool down at 5rpm, 40 minutes of cycling at 50rpm FES stimulation to bilateral quadriceps, hamstrings and gluteal muscles Comparator: ACE, 10 minute warm up and cool down, 40 minutes exercise at 50rpm Workload progressed throughout both conditions to maintain 75% HR_{max}	Outcome measures assessed at start and end VO_{2peak}, energy expenditure, waist circumference, peak power output and metabolic health were assessed	FES cycling: group showed a reduction in body fat by 5% (p=0.008), fasting insulin (p=0.009) and resting systolic BP (p=0.04) ACE cycling: group showed an increase in relative $V0_{2peak}$ by 22% (p=0.024), energy expenditure by 85% (p=0.002), peak power by 307% (p<0.001), peak work by 19% (p=0.003) and a reduction in total body fat by 6% (p=0.05), triglycerides (p=0.014) and resting systolic BP (p=0.032)
Hu et al 2022 Clinical effects of MOTOmed intelligence exercise training combined with intensive walking training on rehabilitation of	Recruited from 82nd Army Group Military Hospital, China	20 minutes, six times a week and for 8 weeks MOTOmed intelligence training (passive, active	Outcome measures assessed at start and end FAC, 10MWT max speed, lower limb	Both groups showed significant improvements in FAC, 10MWT, lower limb Fugyl meyer, nerve growth factor, neurotrophin-3,

walking, nerve and lower limb functions among patients with hemiplegia after stroke Randomised controlled trial, two parallel groups	52 recruited; intervention (n=26), control (n=26) Intervention group: 16 men, 10 women Mean age: 56.2±10.4 years Average time since stroke: 3.2±1.2 years Control group: 15 men, 11 women Mean age: 57.0±10.2 years Average time since stroke: 3.1±1.2 years	assisted, active cycling) and control conditions Comparator: routine rehabilitation exercises for strength, upper limb, balance, transfer, and walking practice	Fugyl meyer assessment Also had tests on neural function: nerve growth factor, neurotrophin-3, brain derived neurotrophic factor measured Cycling data also recorded	brain derived neurotrophic factor ($p<0.05$) The MOTOmed group had significantly higher improvements in all measures than the control group ($p<0.05$)

Abbreviations: EDSS - Extended Disability Status Scale, VO_{2peak} – Peak Oxygen uptake, HR_{max} – Maximal Heart Rate, FES – Functional Electrical Stimulation, RRMS - Relapsing and Remitting MS, SPMS - Secondary Progressive MS, SCI – Spinal Cord Injury, RPM - Revolutions per Minute, T25FW - Timed 25 Foot walk, 2MWT - 2 Minute Walk Test, 10MWT - 10 Metre Walk Test, TUG - Timed Up and Go, T25FW – Timed 25 Foot Walk, MSWS-12 – MS Walking Scale, ACE – Arm Cycling Exercise, r_s – Spearman's correlation.

From these addition articles, one used an intervention that involved FES assisted cycling in SCI (Farkas *et al.*, 2021) and the other study used APT cycling alone in stroke participants (Hu *et al.*, 2022).

The study by Farkas et al (2021) compared arm cycling (ACE) (n=7) to FES assisted leg cycling (n=6) in SCI. Both groups completed 40 minutes of cycling, five times a week and over a 16-week period. The study found the ACE cycling intervention to be superior to FES assisted leg cycling. Following ACE significant improvements in $V0_{2peak}$ (p=0.024), energy expenditure (p=0.002), body fat (p=0.05), peak power (p=0.003) and metabolic health (triglycerides p=0.014 and resting systolic BP p=0.032) were reported. While FES assisted leg cycling produced significant improvement to body fat (p=0.008) and metabolic health (fasting insulin p=0.009 and resting systolic BP p=0.04).

The second study by Hu et al (2022) considered a lower limb APT cycling intervention in people following stroke. The interventions consisted of 20 minutes of cycling, six times a week and for eight weeks and was compared to a control group who received routine rehabilitation (both n=26). And while both groups had significant improvements to the FAC, 10MWT, Fugyl meyer lower limb assessment and neurotrophic factors (all $p<0.05$), the APT cycling group showed significantly larger improvements than the control ($p<0.05$). Confusingly the study stated that the APT intervention was combined with intensive walking training, however this did not appear to occur or be part of either treatment. The control group was reported to undertake routine exercises which included movement and stretching of the hemiplegic limbs, daily self-care skills, bridging, standing and walking practice. The study reported no detail as to the dose of these exercises, nor did they report any detail regarding walking training, which detracts from their initial aim.

Similar to the findings of the systematic review, the results from these additional studies are somewhat limited by the design, consistency and reporting of data, and the size of samples used. The focus of these studies was on improving function and/or walking performance, with no other outcomes of interest considered. The study by Hu et al (2022) appears to strengthen the theory that APT cycling interventions may be useful in improving walking

performance in people with stroke, however these results are limited by the lack of data reported in their results.

Chapter 4 The effect of cycling using lower limb active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe Multiple Sclerosis (MS); a feasibility study

4.1 Introduction

As identified in the first two chapters of this thesis, exercise is important in the management of MS. This can be more challenging for people with higher levels of disability where assistance or adaptive equipment may be required. The most effective type, frequency and dose of exercise has also yet to be established. APTs are often used within rehabilitation settings and a systematic review completed in Chapter 3 considered the evidence regarding their use. The included studies reported positive effects to outcomes including spasticity, strength, balance, walking ability and function following APT interventions (Kamps *et al.*, 2005; Laupheimer *et al.*, 2013; Yang *et al.*, 2014; Bauer *et al.*, 2015; Hochsprung *et al.*, 2020; Shariat *et al.*, 2021). However, other outcomes such as cardiovascular fitness and quality of life were rarely considered. The review was unable to make any definite conclusions due to limited availability and consistency of data, heterogeneous study designs and differing interventions. It highlighted the need for further RCT's with larger samples of participants.

The primary aim of the study was to determine the effect of lower limb APT interventions on outcomes such as spasticity, cardiovascular fitness, function and QOL in people with moderate to severe MS. Secondary aims were to test the feasibility of the intervention and protocol for a future randomised trial if appropriate. As this was the first study to look at the prolonged effects of APT cycling in people with moderate to severe MS, there were few studies from which to determine the treatment parameters. Adherence and tolerance of the programme, as well as side effects, were also considered. A successful application to the Physiotherapy Research Foundation, which is part of the Chartered Society of Physiotherapy, was made for funding to support the research project.

4.2 Methods

4.2.1 Study design & ethical approval

A randomised, controlled trial was chosen for this four-week study. Ethical approval was granted from the West of Scotland Research Ethics Committee reference 16/WS/0084 (Appendix 2) and research and development approval were obtained through NHS Greater Glasgow and Clyde reference GN15PY148 (Appendix 4). An application to extend the study duration was also sought and approved (Appendix 3).

4.2.2 Recruitment and randomisation

All those admitted to NRU between 1st July 2016 and 31st June 2017 who fulfilled the inclusion and exclusion criteria were invited to take part in the study. Participants were given a participant information sheet (Appendix 5) which was read to them if necessary. Participants were then given a minimum of two days to consider participation, to discuss with relatives if appropriate and ask any questions they may have. Participants who agreed to take part gave written, informed consent (Appendix 6).

The aim of the study was to recruit 30 participants over an eight-month period, based on the previous year's admission rate of pwMS to the rehabilitation unit. Within a similar period from the previous year 40 pwMS has been admitted to NRU therefore recruitment figures were thought to be ambitious but feasible. However, during the study, the rehabilitation unit experienced changes in medical personnel and Consultant shortages resulting in reduced admissions. As a result, the decision was made to extend the study period to a year and reduce the recruitment number to 25 (aiming 15 intervention, 10 control).

Participants were randomly allocated (1:1) to a group by selecting a sealed envelope from the research physiotherapist which contained a piece of paper stating either control or intervention. At the start of the study 30 envelopes were sealed, 15 with a piece of paper stating intervention and 15 stating control. This was later reduced to ensure only 10 participants were in the

control group following the study extension. The envelopes were shuffled each time in front of the participants, and they were asked to select one to determine to which group they were allocated.

4.2.3 Inclusion & exclusion criteria

To enhance external validity the study aimed to be as inclusive as possible and therefore to be eligible to participate the exclusion criteria were kept to a minimum. To be included in the study participants had to

- have a confirmed diagnosis of MS,
- be aged over 18 years,
- have an EDSS of between 6.0 (requires a walking aid-cane, crutch etc-to walk about 100m with or without resting) and 8.5 (essentially restricted to bed much of the day, have some effective use of arms and retains some self-care functions),
- have spasticity in their lower limbs.

Participants were excluded if they

- had significant cognitive impairment such that they could not understand instructions,
- had co-morbidities which would preclude them taking part in exercise such as unstable cardiac or respiratory symptoms, lower limb fractures or lower limb contractures that would prevent cycling,
- had visual impairment such that they could not see the screen on the APT,
- were unable to be seated appropriately in a wheelchair for 30 minutes due to body position or contractures.

4.2.4 Study personnel

The research team consisted of two blind assessors (JG and KS) and the research physiotherapist (AB) all of whom were experienced neurological physiotherapists and had experience of treating pwMS. In addition, a BSc Sport and Exercise Science student (JC) assisted with the transportation of the Douglas bags (inflatable bags used to collect expired air for analysis) after completion of the exercise testing. The two blind assessors were trained by the research physiotherapist on the assessment procedures and practise sessions undertaken to ensure competency. Participants were advised not to inform the assessor to which group they were allocated during the assessments to avoid bias. The assessors also only had access to the assessment paperwork for that session.

4.2.5 Baseline assessment

At baseline, demographic details were recorded for participants in both groups on a participant demographic sheet (Appendix 7) which included details on age, gender, type of MS, time since diagnosis, EDSS, past medical history, medication, mobility status and social circumstances including marital and educational status. Information on smoking and alcohol consumption was also recorded. Medical notes were consulted if the participant was unable to remember details such as type of MS or time since diagnosis. Outcome measures were also recorded as detailed in section 4.6, and each participant's conventional therapy programme was also recorded during the study period. Any changes to medication or relevant medical interventions throughout the study period was also noted in their participant file.

4.2.6 Outcome measures

Outcome measures were taken before and after the four-week study period by one of two research assessors who were blind to the group allocation. For the intervention group this was the day prior to the first exercise session and the day after completing the final session. For the control group this was at the start of

the study period and then four weeks later. If the final day of either group fell on a Friday, then the final assessment was completed the next working day which was a Monday.

The measures assessed were spasticity (Modified Ashworth Scale (MAS) and an MS spasticity scale (MSSS-88)), cardiorespiratory fitness (OUES), function (Functional Independence Measure (FIM) and timed 25-foot walk test (T25FW)) and Quality of life (MSQOL-54), which are illustrated in Appendix 7. Participants were given the questionnaires to complete by the assessor. If the participant was unable to complete the questionnaire or did not understand the questions, then the assessor assisted to fill in the response or explain the question.

4.2.6.1 Feasibility

This was the first study to test the feasibility of a prolonged APT intervention for people with moderate to severe MS. Data were recorded on the number of patients admitted who fulfilled the inclusion criteria during the study period, whether participants agreed to being randomised to the control group, compliance of participants to the intervention, adverse effects, attrition rates and rates of completion of the outcome measures.

4.2.6.2 Spasticity

Spasticity was measured using the MAS and the MSSS-88. The MAS is a clinician-based assessment of spasticity, specifically muscle stiffness whilst the MSSS-88 (described below) is a subjective, patient reported assessment of the impact of spasticity on daily life (Platz *et al.*, 2005; Hobart *et al.*, 2006).

The MAS is a six-point ordinal scale (0-4) which grades the resistance encountered during passive muscle stretching (Bohannon *et al.*, 1987; Pandyan *et al.*, 1999) (see Table 4.1). The amount of resistance felt against the movement represents the tone or spasticity within the muscle.

Table 4.1 MAS

Grade	Description
0	No increase in tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of ROM when the affected group is moved into flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Cited in Bohannon et al 1987, reproduced with permission from Oxford University Press Journals.

The MAS is the most used measure of spasticity within the clinical setting and has been shown to have good inter-rater reliability in patients with central nervous system lesions (Kendall's correlation 0.85, $p<0.001$) (Bohannon *et al.*, 1987). There is however, a lack of standardisation for positioning and performing the movement which impacts on its reliability (Platz *et al.*, 2005).

In this study the patient was assessed while lying flat on a standard hospital bed and the assessor tested the hip extensors, hip flexors, adductors, quadriceps, hamstrings, gastrocnemius, soleus and the ankle invertors in that order on both right and left legs. The assessor evaluated each muscle group by moving the participant's leg two to three times. Any resistance to movement that was felt was then scored according to the MAS (Table 4.1). For example, to assess the hamstring muscle the leg was flexed to 45 degrees at the hip and supported at

the thigh, and the knee was then extended at speed. The MAS for each muscle group was recorded within the data collection pack (Appendix 7).

The MSSS-88 is a self-reported questionnaire that consists of 88 items, split into eight domains. The domains consider the impact of three spasticity specific symptoms, three areas on physical abilities and one on each of emotional health and social functioning (Hobart *et al.*, 2006; Rodic *et al.*, 2016; Freeman *et al.*, 2019). Two studies have considered the validity and reliability of the MSSS-88 (Henze *et al.*, 2014; Rodic *et al.*, 2016) and two considered its correlation to the MAS or versions of it (Henze *et al.*, 2014; Freeman *et al.*, 2019). The internal reliability of the MSSS-88 was found to be excellent with Cronbach's alpha coefficients reported to be 0.92-0.97 by Henze et al (2014) and 0.91-0.96 by Rodic et al (2016). Both studies also reported test-retest reliability, with Rodic et al (2016) finding it to be good (ICC range 0.84-0.91) and Henze et al (2014) moderate to good (ICC range 0.47-0.87). Lastly, it was found to show moderate to strong correlation with the MAS or versions of it with Spearman's correlation of 0.45-0.63 by Henze et al (2014), and 0.41-0.53 by Freeman et al (2019).

4.2.6.3 Cardiovascular fitness

Cardiovascular fitness was measured using the OUES which has previously been validated for submaximal testing of physical fitness in pwMS (Heine *et al.*, 2014; Edwards, Klaren, *et al.*, 2017). Both studies compared the OUES based on the full exercise data ($OUES_{100}$) and at 50% of the test ($OUES_{50}$). Edwards et al (2017) found the $OUES_{100}$ significantly correlated with $OUES_{50}$ ($r=0.89$, $p<0.001$) as did Heine et al (2014) ($r=0.928$, $p<0.001$).

The OUES assessments were led by the research assessor and a BSc sport and exercise student who assisted in setting up the Douglas bags and transportation for analysis. On an occasion he was unavailable, the research physiotherapist assumed his role to prevent any delays in the assessments. Pulmonary gas exchange data for each participant was obtained during a step incremental cycling exercise protocol on the Motomed APT. Each exercise stage lasted two minutes, and Douglas bags were used to collect the expired air throughout the

test. On completion of the test the bags were transported to the University of Glasgow laboratories where the O_2 and CO_2 from each bag was analysed, and the $\dot{V}O_2$ was plotted against the V_E to determine the OUES.

One of two exercise programmes were used via a chip card during testing and the programme selected was based on the participant's ability to move their legs. The programmes were set via computer software and at an 'easy' or 'hard' level. Both programmes included stages taken at rest, passive cycling at 10rpm and at resistance level 0 for two minutes each. The 'easy' test levels then increased from level 0 to level 1 and continued to be increased by 1 level every 2 minutes, until a maximal of level 3 was reached. The 'hard' test increased from level 0 to level 2 and continued to increase by 2 levels each time until a maximal level of 6 was reached. Each participant was given the same instructions during the cycling, being asked to cycle as hard as they could and for as long as they could.

4.2.6.4 Function

Function was assessed using two measures, the FIM and T25FW. The FIM is commonly used within inpatient rehabilitation settings, being designed to measure physical and cognitive disability, and focuses on burden of care (Glenny *et al.*, 2009). The FIM consists of 18 items, 13 motor tasks and 5 cognitive tasks required for daily living. Each task is rated from one, which scores as full assistance, to seven which scores complete independence in the task. Total scores range from 18 to 126 with higher scores indicating higher levels of independence. The FIM has been shown to be reliable and responsive in MS by several studies (Brosseau *et al.*, 1994; Sharrack *et al.*, 1999; van der Putten *et al.*, 1999). Inter-rater reliability was also reported to be good by Brosseau et al (1994) (ICC 0.83) and excellent by Sharrack et al (1999) (ICC 0.99), who also reported similar for intra-rater reliability (ICC 0.94). The responsiveness of the FIM to change was reported to be small by Sharrack et al (1999) (ES 0.46) and Van der Putten et al (1999) (ES 0.30), however this was comparable with other clinical ratings scales used to measure disability.

Walking ability was measured using the T25FW. The T25FW is described as the best characterised measure of walking disability and can be used across a wide variety of walking abilities in MS (Kieseier *et al.*, 2012; Motl, Cohen, *et al.*, 2017). In this test the time taken for the participant to walk along a 25-foot course at their self-selected walking pace, using walking aids as required was recorded. Two metres were added at the start and end of the course for acceleration and deceleration. A two-minute rest was given and then participants were asked to complete the test again, as able, with the average time of the two tests taken. Studies have shown the T25FW to have good test-retest reliability over short and long periods of time in MS (Larson *et al.*, 2013; Learmonth *et al.*, 2013). When testing a week apart Larson et al (2013) reported reliability to be excellent (ICC 0.92) as did Learmonth et al (2013) when tested over a 6-month period (ICC 0.99). It has also been shown that a 20% improvement represents a meaningful change in walking performance in pwMS (Motl, Cohen, *et al.*, 2017).

4.2.6.5 Quality of Life

QOL was measured with the MSQOL-54, a condition specific, multi-dimensional health-related quality of life measure (Vickrey *et al.*, 1995). The measure consists of 54 questions that are split into 12 subscales and two single item scales scored between 0-100, with the average score taken for each subscale. These produce two summary scores; one for physical and one for mental health, with a higher score indicating a better QOL. Again, participants who were unable to complete this on their own were assisted to complete it with the assessor.

The MSQOL-54 has been reported to be valid and reliable for assessing health related QOL in pwMS (Vickrey *et al.*, 1995; Nicholl *et al.*, 2005; Heiskanen *et al.*, 2007; Füvesi *et al.*, 2008). Reliability was reported by Vickrey et al (1995) to range from good to excellent across the subscales (ICC 0.67-0.96), as was the internal reliability with Cronbach's alpha coefficients ranging from 0.75-0.96. Other studies also found the measure to be reliable with Cronbach's alpha

coefficients reported to range from 0.81-0.88 across the subscales by Heiskanen et al (2007) and from 0.79-0.95 by Füvesi et al (2008).

4.2.7 Intervention protocols

Both groups (intervention and control) received four weeks of conventional inpatient rehabilitation (usual care) and in addition the intervention group received four weeks (20 sessions) of cycling on the APT (described in section 4.2.8).

For both intervention and control groups, the conventional care received was fully recorded. This included the frequency, duration and content of each rehabilitation session and for each health care professional group, not just physiotherapy (Appendix 8). Each person admitted to NRU had their needs assessed by Medical and Nursing staff as well as Physiotherapy (PT) and Occupational Therapy (OT). Speech and Language Therapy (SLT) and Psychology were also available dependant on need. Each patient was provided with an individualised weekly therapy timetable with time slots scheduled for each relevant discipline. A weekly programme of Physiotherapy within NRU can include eight gym sessions which each last up to an hour. The content of these sessions is dependent on individual requirements but can include stretching, strengthening, balance, transfer and mobility practise. OT can include dressing practise in the morning, transfer practise, kitchen practise and three group sessions of upper limb therapy lasting for an hour a day.

4.2.8 APT Intervention

The participants were seated on a standard chair or wheelchair in front of a Motomed APT with their feet strapped into the footplates, so that they could comfortably cycle with a maximum of 120-degree knee flexion (see section 2.8.1). Each exercise session began with a two-minute warm up of passive cycling at 10rpm. The rationale for a two-minute warm up was a pragmatic

decision. Adherence and tolerance of the APT intervention was unknown and a short warm up was selected as a result. A one-minute warm up was anecdotally felt to be too short and with no existing evidence to guide this, two-minutes was selected instead. On completion of the warm-up, an alarm sounded to indicate to the participants to begin to actively cycle. The participant was then asked to cycle for 26 minutes at a rate that was described as feeling somewhat hard, and to try and maintain a symmetrical pattern of movement using the feedback on the display. The display screen shows revolutions per minute (rpm), distance cycled (active and passive), resistance level, participation time and time remaining. The screen could be paused and set on any of the displays according to patient preference. At the end of the 26 minutes of active cycling an alarm sounded again to indicate to the patient that they had entered the cool down phase and a two-minute cool down was then completed.

Each participant started the intervention at resistance level one on the Motomed, and a rating of perceived exertion (RPE) score was taken using the Borg scale at the start, midway through and at the end of the active cycling component. RPE is widely used to assess perception of effort and plan intensity of a regime, where 6 represents no exertion at all and 20 maximal effort. An RPE of 12-14 has been shown to reflect moderate intensity exercise, described as feeling somewhat hard, which correlates to improvements in fitness and cardiovascular risk factors (Garber *et al.*, 2011; Scherr *et al.*, 2013; Williams, 2017). Participants were encouraged to work at an RPE of 12-14 with the resistance then adjusted to achieve this.

The intervention group undertook APT cycling out with their normal therapy times and at a time preferred by them. The intervention was completed daily (Monday to Friday) at the same time, or as close to that time as possible, and any deviations from this protocol recorded.

Cycling data were recorded following each session which included active and passive distance cycled, average rpm, resistance levels, right and left leg cycling symmetry. Data were recorded on an individual patient chip card which was inserted into the top of the bike prior to each session and stored the

participant's daily cycling programme. A paper copy of the cycling data was also stored within each participant's notes.

4.2.9 Advisory Group

An advisory group was formed with a local representative of the West branch of the MS Society, the research physiotherapist, an academic supervisor and two pwMS known to the researcher and the rehabilitation unit. Both pwMS were also familiar with the use of APT machines. This group was originally planned to be a 'virtual' group and meet via Skype, but all participants preferred to meet in person to participate. The group met three times over the year to discuss the project design, plan, results and future plans.

4.2.10 Data analysis

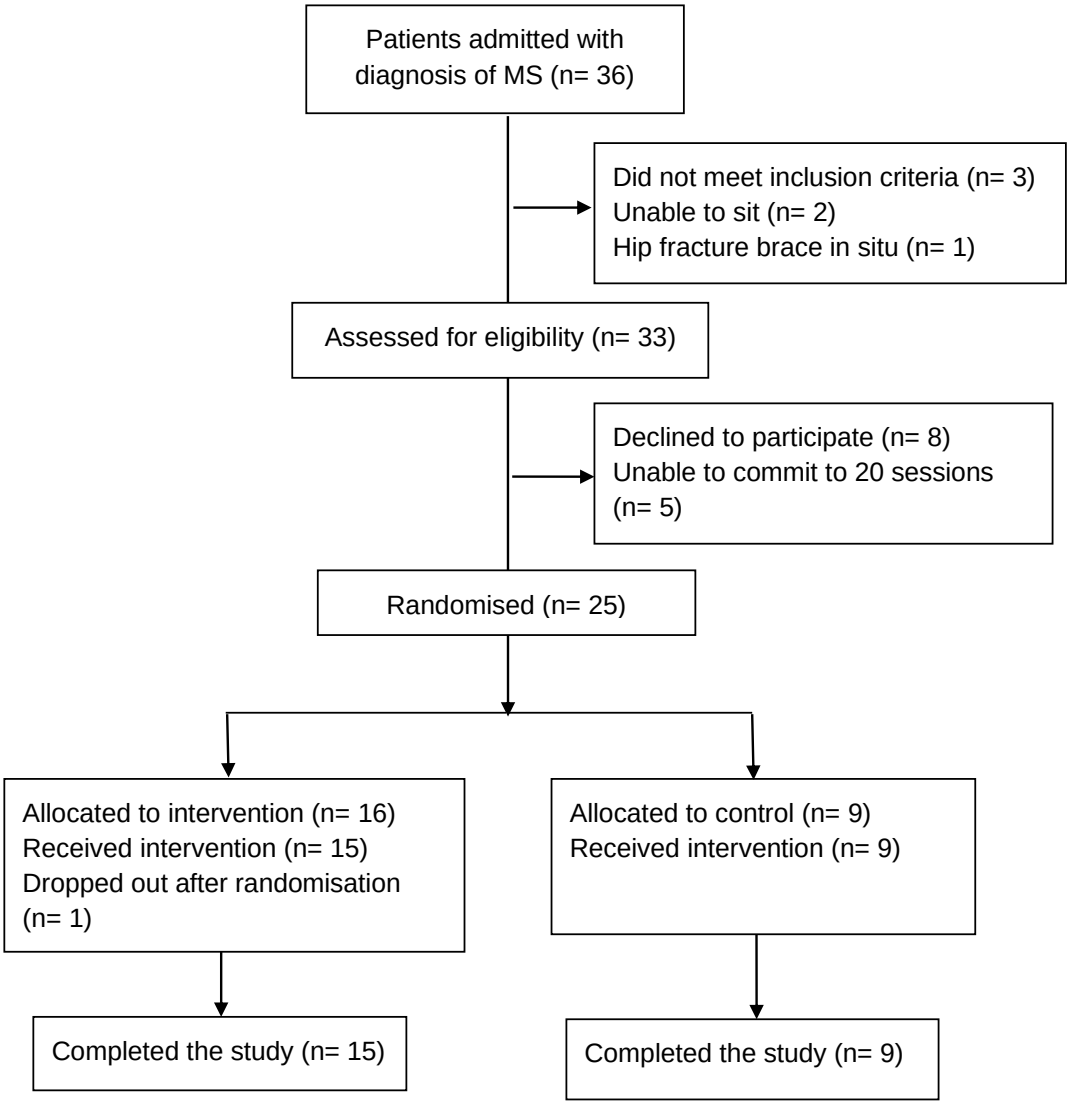
As a feasibility study, the analysis of the main outcome variables aimed to concentrate on descriptive statistics with the estimate and its 95% confidence interval presented. Demographics and outcome variables were summarised with group differences being tested using chi-square tests for categorical variables, two independent sample t-tests or Mann-Whitney tests where appropriate. Simple linear regression was used to assess if any significant increases occurred in the cycling outcomes in the intervention group (total distance, average rpm and power). A 5% level of significance was used, and all analysis was performed on either Microsoft Excel or IBM Statistical Package for the Social Sciences (SPSS) version 24.

4.3 Results

The study recruited participants from 1st July 2016 until 31st June 2017. Over this period 36 people were admitted to NRU with a diagnosis of MS, with 33 people meeting the inclusion and exclusion criteria and invited to take part.

Eight people declined for various reasons which included concerns about managing the intensity of the intervention, the effects on their fatigue and being unable to commit to the full intervention period. Twenty-five participants were recruited to the study with one participant dropping out the day after group allocation due to experiencing a relapse. After discussion with the research team, it was agreed this allocation should be re-used as the participant had not undertaken any assessments, and to allow maximum opportunity to test the feasibility of the intervention. The final recruitment and results are based on the remaining 24 participants with 15 randomly assigned to the intervention group and 9 to the control group, as illustrated in the consort diagram (Figure 4.1).

Figure 4.1 Study recruitment



4.3.1 Demographics

Demographic details for both groups are presented in Table 4.2. Overall, the group had an average age of 54.4 ± 9.1 years and had a median EDSS of 7.25 (range 6.0-8.5). The average time since diagnosis was 15.5 ± 10.5 years.

Table 4.2 Summary of participant demographics

	Intervention Group (n= 15)	Control Group (n= 9)
Gender (M/F)	6/9 (40%/60%)	3/6 (33%/67%)
Age (yrs) (mean ± SD)	54.9 ± 9.9	53.6 ± 8.0
Type of MS: PPMS SPMS RRMS	 3 (20.0%) 10 (66.7%) 2 (13.3%)	 2 (22%) 6 (67%) 1 (11%)
Years since diagnosis (mean ± SD)	14.6 ± 8.6	16.9 ± 13.5
EDSS (mean ± SD)	7.2 ± 0.8	7.3 ± 0.7
Marital status: Married/co habit Single Other	 11 (73.3%) 2 (13.3%) 2 (13.3%)	 8 (89%) 1 (11%) 0
Education status: University College Employed from school	 5 (33.3%) 2 (13.3%) 8 (53.3%)	 3 (33.3%) 3 (33.3%) 3 (33.3%)
Smoker: Yes No	 6 (40%) 9 (60%)	 2 (22%) 7 (78%)
Alcohol: Drinker Non- drinker	 8 (53%) 7 (47%)	 5 (56%) 4 (44%)

PPMS (primary progressive MS); SPMS (secondary progressive MS); RRMS (relapsing and remitting MS); EDSS (Expanded disability status scale)

4.3.2 Therapy input

The average number of therapy sessions for each discipline was calculated for each participant in each group during the study period (Appendix 8). Both groups received similar physiotherapy (PT) input with the intervention group receiving an average of 29 ± 3 sessions and the control group 29 ± 2 sessions

during the study period. When comparing occupational therapy (OT) input the intervention group however received 9 ± 6 sessions whereas the control group received 15 ± 9 sessions. In addition, the control group received on average 1 ± 2 session of speech and language therapy (SLT) and psychology and the intervention group received 1 ± 1 session of psychology.

4.3.3 Outcome measures

In the intervention group, 10 participants completed the assessments according to the protocol, on the day prior to the first session and the day after completing the 20th session. The remaining five participants completed the final assessment as close after the final session as possible. The final assessment fell on a Friday for two participants which meant they were re-assessed on the Monday. Three participants also had a delay of one or two days due to an inability to access exercise testing equipment. In the control group, seven participants were assessed as planned, and for two the 20th session fell on a Friday and so were re-assessed on the following Monday.

Outcome measures were assessed at the same time of day and in the same order for each participant. There was 100% (n=24) completion of MAS, MSSS-88, OUES, FIM, and MSQOL-54. Assessment of the T25FW was dependent on each participants ability to walk and only 46% (n=11) of the participants were able to walk at initial assessment. The average summary scores for all measures are presented in Table 4.3.

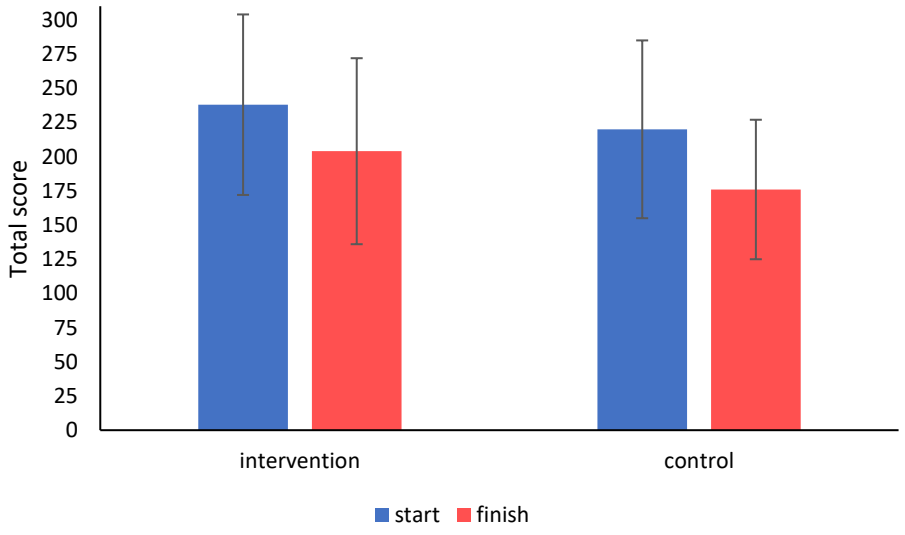
Table 4.3 Summary of outcome measures

Outcome measure (mean ± SD)	Intervention pre	Intervention post	Control pre	Control post
MSSS-88	238 ± 66	204 ± 68	220 ± 65	176 ± 51
T25FW(s)	60 ± 43 (n=8)	64 ± 56 (n=8)	39 ± 15 (n=3)	23 ± 12 (n=3)
FIM	98 ± 21	104 ± 19	88 ± 10	98 ± 15
MSQOL-54; PH MH	28 ± 14 52 ± 28	43 ± 17 63 ± 25	34 ± 20 54 ± 30	42 ± 16 65 ± 27
OUES	0.734 ± 0.286	0.829 ± 0.245	0.768 ± 0.405	0.746 ± 0.336

4.3.3.1 Multiple Sclerosis Spasticity Scale 88

Both groups reported a reduction in perceived spasticity, however there were no differences between groups (p=0.34). The average reduction in the scores for the intervention group was 34 ± 69 (95% CI:-4.3-71.5, p=0.78), and the control group 44 ± 60 (95% CI:-1.9-90.8, p=0.58) (Figure 4.2).

Figure 4.2 Change in MSSS-88 scores



4.3.3.2 Modified Ashworth Scale

Pre and post MAS scores were recorded for each participant and the median scores used to summarise the spasticity for each muscle group (Tables 4.4 and 4.5). Overall, there were low levels of median spasticity in both right and left legs, with little change noted over time. Due to this further analysis was not felt to be appropriate.

Table 4.4 Intervention group median MAS scores

Intervention group	Right Leg		Left Leg	
	Pre	Post	Pre	Post
Hip flexors	0	0	0	0
Hip extensors	0	0	0	0
Adductors	1	0	0	0
Quadriceps	1	1	0	0
Hamstrings	0	0	0	0
Gastrocnemius	1	1	1	1
Soleus	0	1	0	1
Invertors	0	0	0	0

Table 4.5 Control group median MAS scores

Control group	Right Leg		Left Leg	
	Pre	Post	Pre	Post
Hip flexors	0	0	0	0
Hip extensors	0	0	0	0
Adductors	1	0	1	0
Quadriceps	0	0	0	0
Hamstrings	0	0	0	0
Gastrocnemius	1	1	1	0
Soleus	1	1	1	1
Invertors	0	0	0	0

During the study period participants in both groups underwent medication changes or procedures that could have influenced spasticity as listed in Table 4.6.

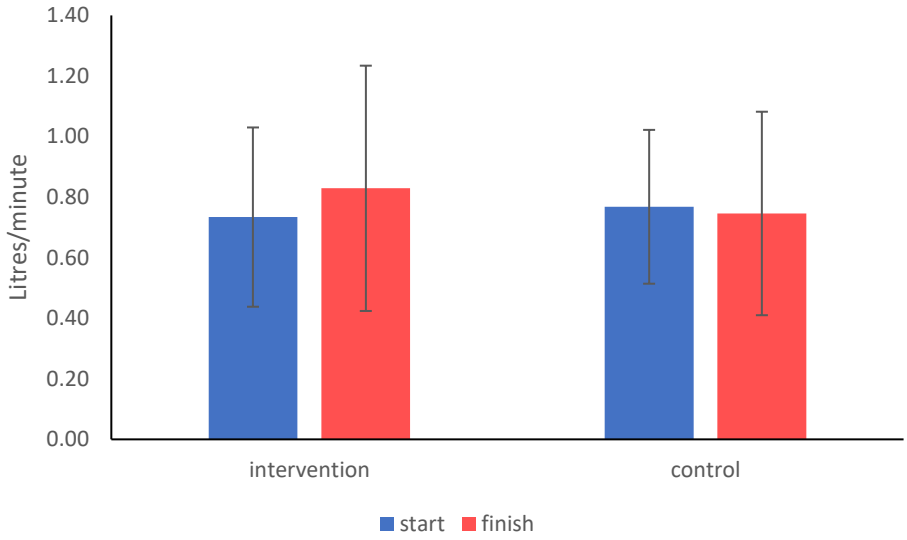
Table 4.6 Participant intervention and medication changes

Participant number	Changes or interventions during study period
P5	Gabapentin ↑ from 600mg tid to 700mg tid
P7	Botulinum toxin injection left hamstring, bilateral obturator nerve blocks with aqueous phenol
P8	Baclofen ↑ 5 mg night, started Gabapentin 100mg tid
P14	Tramadol ↑ 50mg am to 100mg tid, Ibuprofen and Paracetamol started qid
P16	Sativex ↓ reduced from 5 to 3 sprays, ITB pump ↓ 100mcg to 50mcg day
P20	Suprapubic catheter inserted week 3
P21	Gabapentin ↑ increased 300 to 400mg tid, Baclofen 10mg tid stopped

4.3.3.3 Oxygen Uptake Efficiency Slope

The OUES showed a small but non-significant improvement following the intervention while the control showed little change, however there was no group effect found (p=0.84). The average improvement in the intervention group was 0.095L/min ± 0.299 (95% CI:-0.260-0.070, p=0.24) and the control reduced by 0.022L/min ± 0.299 (95% CI:-0.154–0.198, p=0.78) (Figure 4.3).

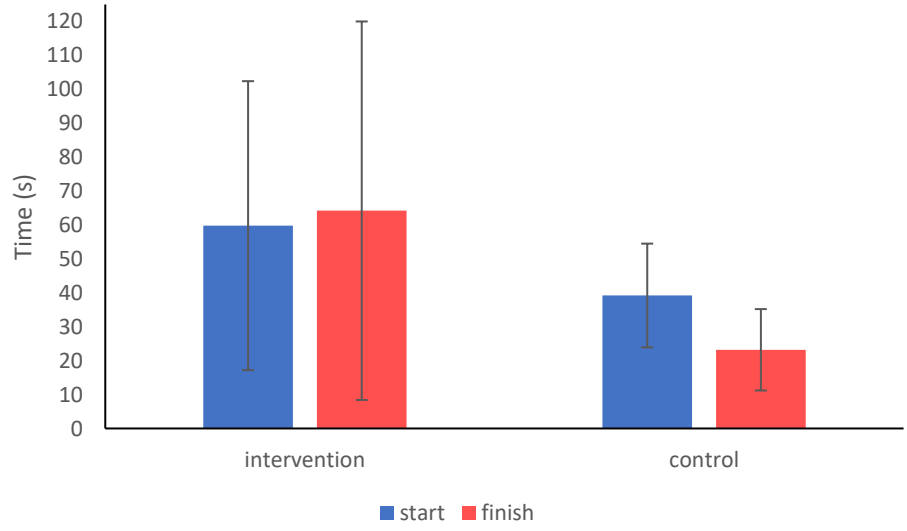
Figure 4.3 Change in OUES



4.3.3.4 Timed 25 Foot Walk

The intervention group was found to walk slower on average following the intervention with an increase in T25FW time of 4.4s ± 32.1s (95% CI:-31.3-22.5, p=0.71) (Figure 4.4). The control group demonstrated an improvement, with a reduction in time by 16s ± 22.7s (95% CI:-40.3-72.3, p=0.35). Again, there was no differences between groups (p=0.23).

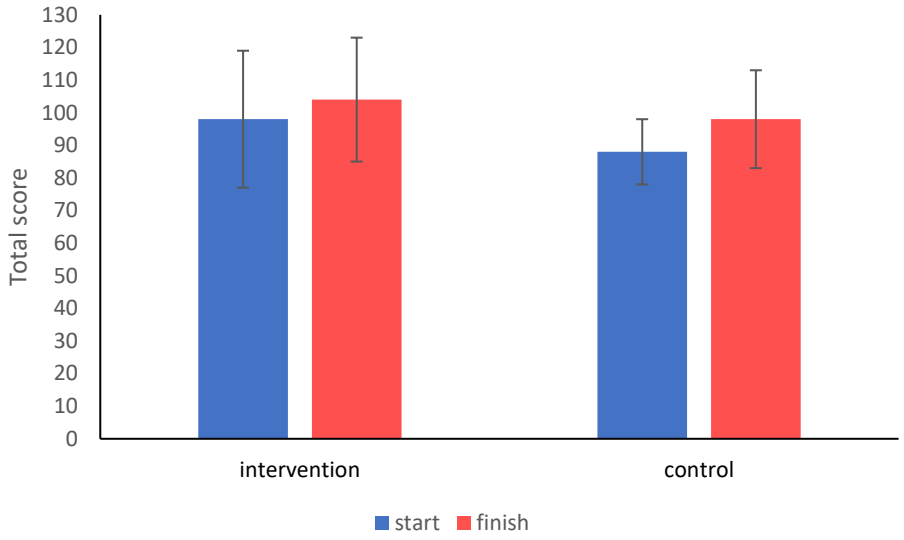
Figure 4.4 Change in T25FW time



4.3.3.5 Functional Independence Measure

On average the overall FIM score in the intervention group improved by 6 ± 8 (95% CI:1.8-10.9, p=0.1), and the control group by 10 ± 7 (95% CI:5.5-15.8, p=0.01) (Figure 4.5). There was a significant increase in overall score over time although no group effect was demonstrated (p=0.29).

Figure 4.5 Change in FIM scores



4.3.3.6 Multiple Sclerosis Quality of Life-54

There was also an improvement noted to both groups in the domains of physical and mental health (PH and MH) in the MSQOL-54, however no group effect was found in either (PH: p=0.63, MH: p=0.84).

In the PH domain the intervention group showed an increase of 15 ± 20 (95% CI:3.9-26.1, p=0.12) and the control group 8 ± 15 (95% CI:-3.4-19.7, p=0.14) (Figure 4.6).

In the MH domain the intervention group displayed an improvement of 11 ± 25 (95% CI:-2.8-25.4, p=0.11) and the control an improvement 11 ± 18 (95% CI:-2.5-25.4, p=0.9) (Figure 4.7).

Figure 4.6 Change in MSQOL-54 PH scores

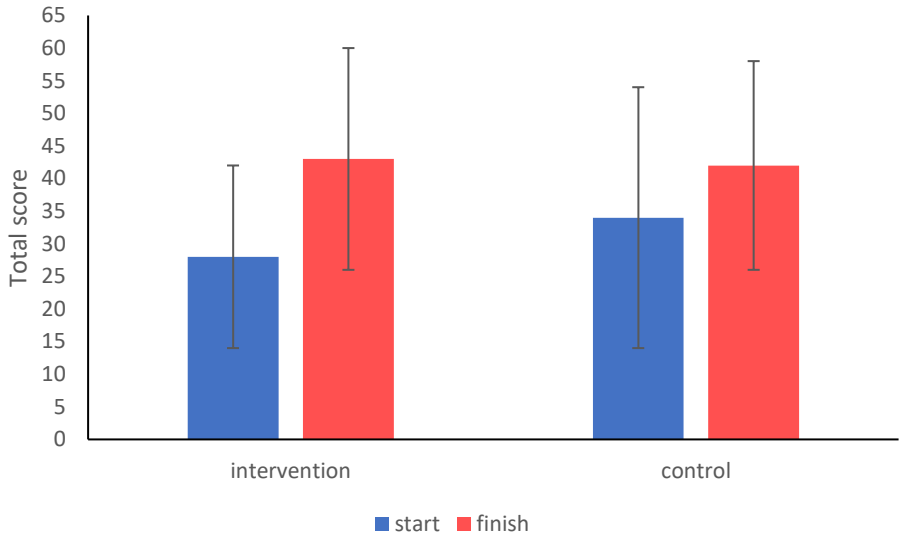
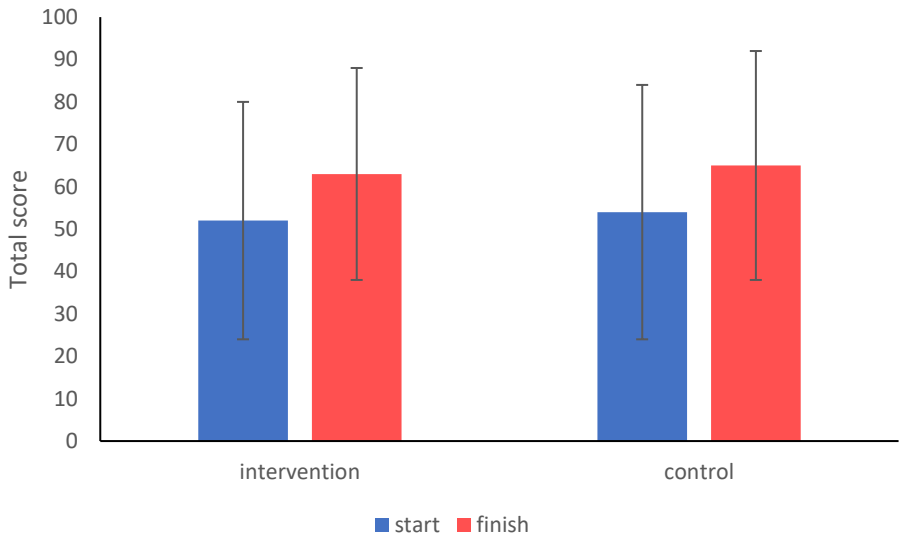


Figure 4.7 Change in MSQOL-54 MH scores



4.3.3.7 Intervention group cycling data

Cycling variables were collected over the 20 sessions as illustrated in Table 4.7. Data for power was missing for two participants on two occasions, so analysis for this variable is based on the other 13 data sets.

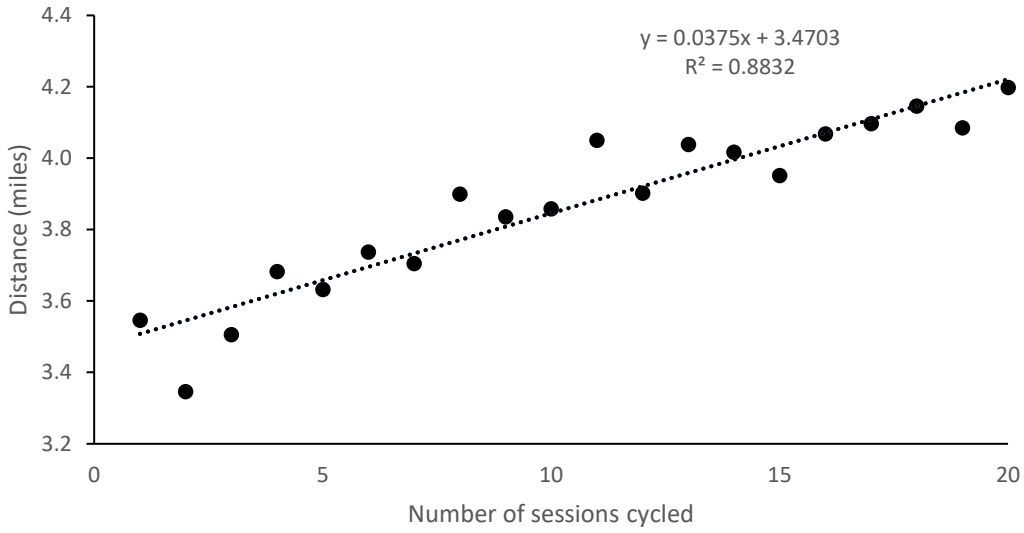
Table 4.7 Cycling variables - day 1 and 20

	1st session (day 1) (mean ± SD)	**20th session (day 20) (mean ± SD)**
Duration active (min)	25.9 ± 0.0	25.8 ± 0.7
Duration passive (min)	4.0 ± 0.0	4.2 ± 0.6
Distance active (miles)	3.4 ± 0.3	3.9 ± 0.5
Revolutions per minute (RPM)	42.2 ± 3.5	50.5 ± 16.5
Power (W) (n=13)	7.1 ± 3.9	13.6 ± 9.4
Resistance (kg)	0.9 ± 0.1	2.5 ± 0.5

Three variables were shown to have statistically significant improvements, with increases in average distance cycled (p=0.032), speed (p=0.026) and power output (p=0.006) found. Linear regression was used to illustrate these changes (Figures 4.8-4.10).

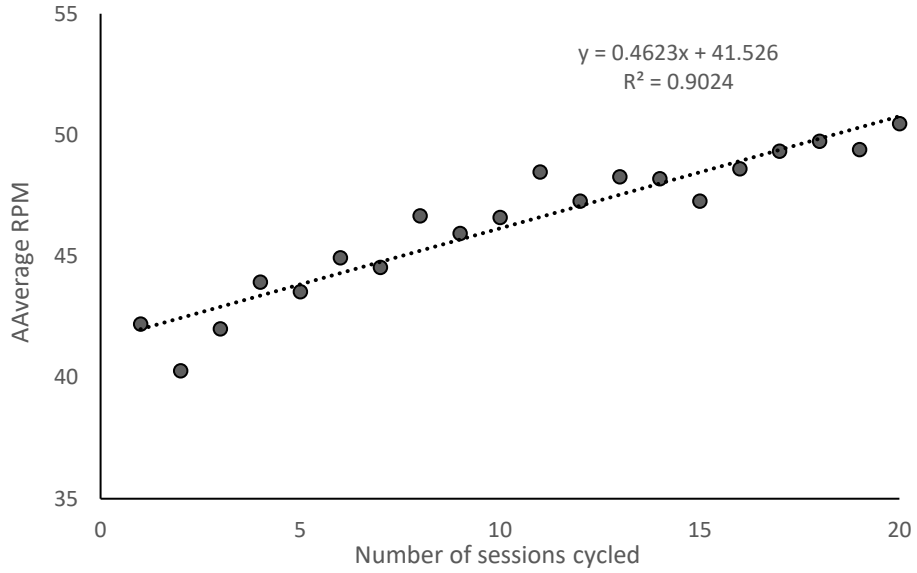
It was found that for each day cycled the average total distance increased by 0.04 miles (95% CI:3.75-3.97, beta 0.04, p<0.001).

Figure 4.8 Average total distance cycled



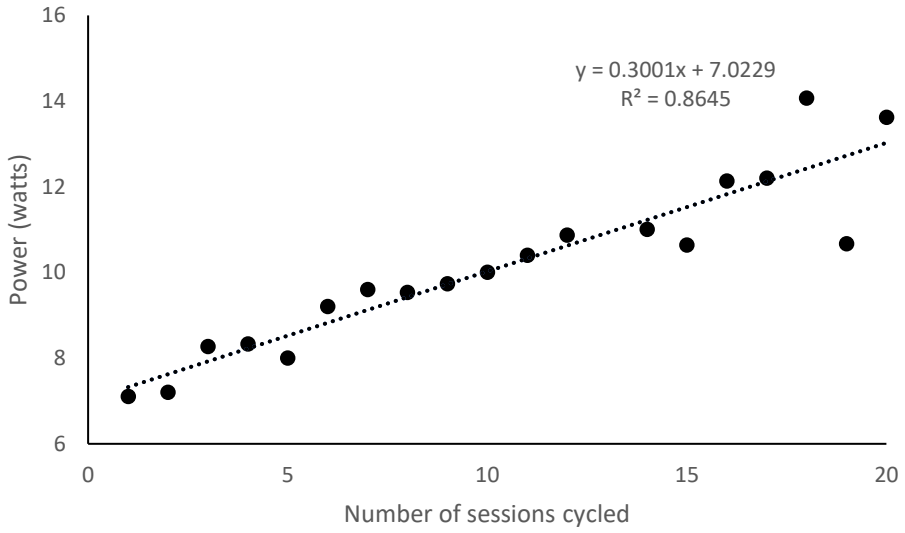
In addition, there was an average increase in speed by 0.46rpm each day cycled (95% CI:45.1-47.6, beta 0.46, p<0.001).

Figure 4.9 Average change in RPM



Lastly for each day cycled there was an average increase in power by 0.30W (95% CI:9.3-11.0, beta 0.30, p<0.001).

Figure 4.10 Average change in power



4.4 Discussion

The aim of this study was to assess the effects of lower limb APTs on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe MS, and to determine the feasibility of the intervention. The study reported 100% adherence to the intervention and participants were able to tolerate the intensity of a daily cycling programme without any adverse effects. Following the APT intervention, significant improvements were found to the average total distance cycled, speed and power output. However, this did not appear to translate to changes in any of the other outcomes measured. Both intervention and control groups demonstrated non-significant improvements in all of the outcomes measured. The results were felt to have been influenced by the design of the study and the outcome measures selected for use, which will be considered in more detail in the following sections.

4.4.1 Feasibility

During the study period 36 people with MS were admitted to the rehabilitation unit over the year, which was lower than predicted. A contributing factor was a change in medical personnel which limited admissions and the study period had

to be extended to increase recruitment. The original aim of the study was to recruit 30 participants, but the decision was made to reduce this to 25 (15 intervention, 10 control), with the aim of maximising the ability to test the feasibility of the intervention.

During the study period one participant drop out occurred, which happened the day after allocation to the intervention group and prior to the assessments. A decision was made to exclude this participant and re-allocate the place to maximise the ability to test the intervention. No other adverse effects were noted during the study period. There was also 100% completion rate of the outcome measures, which took on average 66 ± 10 minutes to complete.

4.4.2 Spasticity

Following the study period both groups reported an improvement in perceived spasticity levels (MSSS-88), although minimal change was found objectively using the MAS in either group.

As this was a feasibility study it was felt important to use both objective and subjective measures, as participant feedback was felt to be as important as clinical measures. However, the MSSS-88 was found to be time consuming to complete with little guidance regarding data analysis, especially on the walking section which participants could leave if immobile, detracting from its use. And although the MAS is the most clinically used measure of spasticity, it has its limitations. The scale can only quantify passive resistance to stretch, and does not differentiate spasticity from other causes of stiffness (Blackburn *et al.*, 2002; Damiano *et al.*, 2002; Pandyan *et al.*, 2003; Fleuren *et al.*, 2010; Kaya *et al.*, 2011). In addition, it has been reported to show poor sensitivity at grades 1, 1+ and 2 which increase the probability for error in scoring (Blackburn *et al.*, 2002; Pandyan *et al.*, 2003; Ansari *et al.*, 2006; Mutlu *et al.*, 2008; Craven *et al.*, 2010). The lack of sensitivity shown at these grades could also have contributed to the lack of change noted by this study, as the majority of the participants were noted to have MAS scores at these grades.

The lack of objective change in spasticity in the intervention group may be considered surprising given the significant improvements in cycling ability shown by this group. On average they were able to cycle faster, further and showed improved power output over the 20 sessions, suggesting a change in their ability to actively move their legs. This could be due to a combination of peripheral adaptions which will be discussed in section 4.4.3, and/or suppression of reflex improving ease and speed of active movement. Cycling causes repetitive shortening of the soleus and firing of the muscle spindles, resulting in an increase in presynaptic inhibition of soleus 1a afferents and a reduction in the reflex response (Tanuma *et al.*, 2017). Cycling also results in reciprocal activation of agonist and antagonist muscles bilaterally (Raasch *et al.*, 1999; Ambrosini, Peri *et al.*, 2020), aiding muscle activation and motor relearning. Repetitive practice is known to be an important component of motor relearning, and each of these mechanisms has the potential to improve muscle activity and function. This study however, did not detect any meaningful changes in either function or spasticity which may be due to the lack of responsiveness from the measures used.

Of note, during the study period several participants underwent changes to their medication or procedures that may have affected their levels of spasticity (n=7) (Table 4.6, section 4.3.3.2). Four participants were found to have shown a reduction in MAS by 1 in several muscle groups, however this did not change the median scores reported and overall these changes were felt unlikely to have contributed to the results.

Other studies have reported a significant reduction in spasticity following lower limb cycling in pwMS measured using the H-reflex and/or MAS (Rösche *et al.*, 1997; Motl *et al.*, 2006, 2007; Szecsi *et al.*, 2009). They did however re-assess these measures immediately after their intervention which this study did the day after completion of the intervention. This could have meant that any short terms effects on spasticity were lost.

Future studies should consider these points when choosing measures and study design. Assessing spasticity immediately following APT cycling should be considered. In addition, a more sensitive measure of spasticity such as the H-

reflex may also be more appropriate for use. The H-reflex measures alpha motor neuron excitability in the spinal reflex arc and so is considered a direct measure of spasticity (Voerman *et al.*, 2005; Burke, 2016, Hugos *et al.*, 2019). It requires specialist equipment and training to use, and as a result is likely to be a measure used within research settings rather than clinical practice. However, identifying a more appropriate measure of spasticity to be used within research is also key. As this will help identify interventions aimed at enhancing function and quality of life, which can then be used to inform everyday practice. Lastly, using a shorter, simpler patient reported outcome measure (PROM) should be considered such as a numerical rating scale, which has been shown to be valid and reliable when considering spasticity in pwMS (Farrar *et al.*, 2008; Anwar *et al.*, 2009).

4.4.3 Cardiovascular fitness

This study found that 20 sessions of APT cycling resulted in a small, non-significant improvement in cardiovascular fitness in the intervention group, while the control group showed little change.

This is the first study to have completed submaximal exercise testing using the OUES in people with moderate to severe MS. The participants were able tolerate and complete this test without issues, and the OUES appears to be an effective measure in this group. Due to the disability levels of the participants the CPET was completed within the rehabilitation unit, with the samples then transported off site for analysis within a University of Glasgow laboratory. This resulted in a slight delay in testing each sample and while this was unlikely to have had a major impact on the results, the process could have resulted in some leaking from the Douglas bags. Future studies should aim to have the appropriate equipment for analysis available on site to reduce the potential of this and improve accuracy.

The length of cycling and study period chosen for the study was a pragmatic choice. The study aimed to determine if people with MS could tolerate daily exercise in line with government guidelines on aerobic exercise (Davies *et al.*,

2019). The length of intervention was also chosen being mindful of the average length of stay within the rehabilitation unit to help maximise recruitment. In healthy adults, exercise interventions of as little as two weeks have been shown to improve aerobic fitness although they have used high intensity or interval training, where participants work for short periods at maximal or submaximal levels (MacInnis *et al.*, 2017; Hughes *et al.*, 2018). Changes associated with moderate intensity or continuous exercise have been reported to take much longer with studies suggesting 6-12 months can be required (Mezzani *et al.*, 2008; Latimer-Cheung *et al.*, 2013). However, Murias et al (2011) found a 12-week programme of cycling was sufficient to significantly improve cardiovascular fitness as long as the intensity is maintained and work rate progressed appropriately. This was demonstrated in older and younger participants using a thrice weekly cycling intervention, for 45 minutes at a power output that elicited 70% of VO_{2max}, with the intensity adjusted every three weeks to reflect changes in fitness.

Improvements in cardiovascular fitness occur through a series of peripheral and central adaptations that enable muscles to become more efficient, which improves performance and exercise capacity (Hawley, 2002; Coffey *et al.*, 2007; Rivera-Brown *et al.*, 2012). Peripheral adaptations are the first response to regular exercise training which produce several metabolic changes. The initial response triggers an increase in the number and size of mitochondria in the muscle fibres, which increases the mitochondrial enzyme content. These enzymes help oxidise fatty acids and pyruvate used within the Krebs cycle to produce energy or ATP (Holloszy *et al.*, 1984; Neufer, 1989; Hawley, 2002; Heinonen *et al.*, 2014). The increase in enzyme levels also reduce carbohydrate oxidation, glycogen and lactate production which results in a higher lactate threshold, and improved muscle performance (Hawley, 2002; Coffey *et al.*, 2007).

Exercise training also induces central adaptations within the cardiovascular system, by angiogenesis and arteriogenesis (Heinonen *et al.*, 2014). Angiogenesis leads to an increase in the volume of capillaries around the muscle, and arteriogenesis results in enlargement of the existing vessels enhancing venous return (Golbidi *et al.*, 2012). Alongside these changes an anti-

inflammatory response is stimulated, with an increase in plasma volume reducing blood viscosity which again facilitates improved blood flow. This increases the end-diastolic volume and contractility of the left ventricle, resulting in improved stroke volume and cardiac output (Rivera-Brown *et al.*, 2012; Heinonen *et al.*, 2014; Hellsten *et al.*, 2016). In combination these adaptations result in an increase in the mean blood transport time and oxygen delivery allowing for increased O_2 extraction (Neufer, 1989; Høier *et al.*, 2010; Heinonen *et al.*, 2014). This can however be affected by factors such as age, gender, race and genetics (Hautala *et al.*, 2009; Rivera-Brown *et al.*, 2012).

Passive exercise has been shown to trigger a similar physiological response to active exercise (Høier *et al.*, 2010, 2013). The studies by Høier et al. showed a small but significant increase in the volume of capillaries around muscle fibres after passive exercise indicating an angiogenic response being triggered. This was though found to be at a lesser rate than active exercise, indicating a longer intervention would be required to achieve similar central adaptations. It does however suggest that APT equipment could provide a valid way of improving health in people who are unable to actively exercise or at increased intensity due to a chronic condition or disability. The dose required to do so has yet to be established, and merits further research. In addition, long term adherence would also be needed to maintain this.

There are few studies that look at the effects of cardiovascular exercise in people with high levels of disability, with this study believed to be the first to do so using APT equipment. The small improvements found following the APT cycling suggest the intervention may have the potential to improve cardiovascular fitness, and further research is merited to establish the length and dose required to do so. A future study should consider an APT intervention of at least 12 weeks at moderate intensity and in line with the study by Murias et al (2011). It could also consider alongside a passive cycling intervention using a similar length and dose, to compare the effects.

4.4.4 Function

Function was measured using the FIM and T25FW in this study. The FIM was chosen as it is a generic measure of disability and has been found to be responsive to change in pwMS (van der Putten *et al.*, 1999). While both groups improved in their average FIM scores (intervention 6 ± 8, control 11 ± 7) no significant group effect was found. The minimal clinical important difference (MCID) for the FIM has been shown to represent a 22-point improvement in total score in stroke participants (Wallace *et al.*, 2002; Beninato *et al.*, 2006), but has yet to be studied in other populations. While this cannot be generalised to pwMS, if used as a baseline one participant from the intervention group achieved this.

Few cycling studies involving pwMS have included generic measures to consider function. One study used the London Handicap Scale, a scale similar to the FIM as it considers 12 items in relation to cognitive, physical and ADL's (Kileff *et al.*, 2005). Another used the MS Functional Composite, which is made up of the T25FW, 9-hole peg test and the Paced Auditory Serial Addition test, a cognitive test (Ratchford *et al.*, 2010). Measurement of walking ability is preferred by most studies, which is likely due to being identified as the most important function by pwMS (LaRocca, 2011). However, the majority of studies include participants with mild disability who are ambulant. Few have included people who are wheelchair dependent and who struggle to walk, and those that have included measures that considered muscle function at impairment or participation level instead (Ratchford *et al.*, 2010; Edwards *et al.*, 2018; Backus *et al.*, 2020).

The T25FW was also used by this study to assess walking ability, with a 20% improvement in time shown to be clinically meaningful (Goldman *et al.*, 2013; Motl, Cohen, *et al.*, 2017). Walking ability can be considered in relation to speed (10MWT, T25FW) with the average of two tests used, or by endurance measuring distance over time (2MWT, 6MWT). Only 46% of this study's participants (n=11) were able to complete the requirements of the T25FW at both assessments, with four from the intervention group and one from the control group achieving the threshold, reflecting a meaningful change in walking performance. In addition, by the end of this study a further four participants

were able to complete the walking test (three from the intervention group and one from the control), and with a longer intervention more may have managed this.

On average the control group showed a trend for improved walking speed, and the intervention group were slower. However, these times were influenced by the numbers of participants in the control group (n=3) and by two participants from the intervention group who were found to be slower at their final assessment (by 25s and 76s). The variation in performance could be explained by several factors. The intensity of a daily therapy programme and APT intervention may have contributed to fatigue in the intervention group. In addition, the order in which the measures were re-assessed at the end of the trial could also have affected the intervention groups performance of the T25FW. It was noted that the participants who performed slower in the walking test completed this following their CPET test, which again could have resulted in fatigue. Lastly, while both groups received the same volume of PT input (intervention group 29 ± 3 sessions, control 29 ± 2 sessions), the control group were noted to have received more OT input (intervention group 9 ± 6 sessions, control 15 ± 9 sessions). Each participants therapy programme was based on their rehabilitation goals, with treatment in each discipline focused around key areas. Analysis of each participants therapy programme was not undertaken and therefore cannot be ruled out as a contributing factor to these results. This should be considered by future studies as well as measures to consider fatigue.

While maintaining and improving mobility is a key goal for pwMS, for many with higher levels of disability this may not be possible and this should be considered when selecting measures. The T25FW did not capture the overall change in walking ability of the participants in this study, nor would any other walking measure and it does question its use in people with EDSS scores of 6.5-7.5. For these people it may be more appropriate to simply categorise ability and/or assistance required using the Functional Ambulatory Capacity, whilst recording a maximal distance or time able to walk. While for those with severe levels of disability (EDSS of ≥8.0) the focus of function may be more in relation to maintenance of UL function and self-care tasks, and so less of a key measure in relation to lower limb interventions.

4.4.5 Quality of life

Health related QOL (HRQOL) has been reported to be significantly lower for pwMS than other chronic diseases such as rheumatoid arthritis, diabetes, inflammatory bowel disease and depression (Campbell *et al.*, 2014). It has also been shown to correlate to disability, and measurement provides the opportunity to evaluate the impact of the disease as well as treatment interventions. This study found that while QOL improved in both groups, measured using the MSQOL-54, no group or interventional effect was noted.

Only three studies involving pwMS and cycling interventions have measured QOL (Mostert *et al.*, 2002; Rampello *et al.*, 2007; Çakt *et al.*, 2010). The MSQOL-54 was used by Rampello et al (2007) while the others used the SF-36, the measure the MSQOL-54 was developed from (Mostert *et al.*, 2002; Çakt *et al.*, 2010). Each study used interventions with high intensity and progressive workloads which lasted between 4-8 weeks and included participants with mild disability from MS (average EDSS range 3.5-4.6). While all reported significant improvements it was to differing subscales within each measure making it difficult to generalise or compare.

The MSQOL-54 was chosen by this study as it is disease specific but it does have its limitations. The threshold representing a meaningful change has yet to be established, and the length of time taken to complete the scale has also been raised as an issue (Fischer *et al.*, 1999; Freeman *et al.*, 2001). This study's participants agreed with this point as both measures (MSQOL-54 and MSSS-88) took 30 minutes on average to explain and complete, which they felt to be too long. It was also commented that sections of each measure, particularly around sexual function, were intrusive and not relevant to the intervention. Both points could have affected the scoring and the reliability of the results.

Other factors such as mood, fatigue, memory and recall have been found to affect the reliability of patient feedback (van Winsen *et al.*, 2010). Given the disability levels of the participants within this study, it is reasonable to assume participants could have been experiencing some of these symptoms. Although

this study did not include formal assessment of participant's cognition or fatigue levels, it was felt doing so would be important in future studies.

HRQOL remains an important measure in people with higher levels of disability however remains poorly studied and no scale has been identified as the most appropriate. The time taken to complete the scale should be considered when selecting a measure, and the MSIS-29 may be more appropriate to consider in future studies. The MSIS-29 is a shorter measure, has been shown to have good psychometric properties and considers both the physical and psychological impact of MS (Hobart *et al.*, 2001; Marrie *et al.*, 2021).

4.4.6 Study limitations

There were several limitations to this study, which include the sample size, the protocol adopted, the outcome measures used and that no formal process evaluation was undertaken.

The protocol adopted was that participants would be assessed the day after completion of the intervention. As a result, any short-term treatment effects from the cycling intervention on spasticity may have been lost. The design of this study was chosen for various reasons, which included clinician availability, time required to complete the assessment measures and concerns regarding participant fatigue. As the participants were already undergoing various therapies during the day it was not felt to be feasible to assess outcome measures immediately prior to or following the interventions. In addition, the measures used to assess spasticity may not have been sensitive enough to detect change in spasticity.

This study also only included participants who were inpatients in the NRU for ease and funding reasons. As a result each participant underwent an intensive period of therapy during the study period, which was felt to impact on the results of both groups. While peripheral adaptations may in part explain the improvements found in the intervention group, each group also received 29 ± 3 physiotherapy sessions, which may also have had a positive impact. Indeed both

groups showed improvements in all of the outcome measures over time, strongly suggesting therapy input had a beneficial effect.

Lastly, no formal process evaluation was used due to time constraints of the study. It is acknowledged this process would strengthen any future, larger studies.

This study has shown it is feasible for people with moderate to severe MS to manage a daily APT intervention in addition to an intensive inpatient therapy programme. However, future studies should consider using a community-based population to fully determine the effects of APT interventions.

4.5 Conclusion

This study has demonstrated that daily APT cycling for 30 minutes a day is a feasible and safe exercise option for pwMS. It produced no adverse effects or increase in symptoms, and participants were able to tolerate the intensity of treatment as demonstrated by 100% adherence to the intervention programme. Although the majority of outcome measures improved, this was the case for both intervention and control groups and it was difficult to separate the effects of the inpatient therapy programme and the APT intervention. The intervention group did show a small non-significant change in cardiovascular fitness compared to the control group. In addition, they were on average able to cycle further, faster and with increased power output, suggesting that APT interventions could be beneficial, and investigation of a longer intervention is merited.

A further, fully powered, study of APT cycling over a longer period of time and using community dwelling pwMS is merited to further determine the effects of APT cycling. From the data generated it was estimated that in a future RCT, due to the main outcome variability, 38 participants would be required in each group to detect significant group differences with an 80% power. In addition, the use of alternative outcome measures should be considered. For spasticity a more sensitive measure is needed and shorter PROM for HRQOL. Fatigue should also be included as well as assessment of cognition due to potential prevalence

in this disability group. Lastly, exit interviews with participants may also be useful in future studies as no participant feedback regarding the intervention was formally taken.

Chapter 5 The effect of a single session of APT cycling on spasticity in people with moderate to severe MS: a feasibility study

Spasticity is one of the most troublesome symptoms of MS and impacts on mobility, self-care and QOL, with studies reporting it to affect up to 85% of pwMS (Oreja-Guevara *et al.*, 2013; Flachenecker *et al.*, 2014; Milinis *et al.*, 2016). Spasticity can be measured by a variety of methods, and the method chosen is often based on the clinician's preference, convenience and setting of use (Blanchette *et al.*, 2017; Balci, 2018). The need for a more sensitive measure of spasticity was identified as a key area for further research in Chapter 3, and determining a better measure than the MAS is the focus of this third study.

5.1 The principles of measuring change

Measuring change is important in healthcare and research, and requires an instrument to have good psychometric properties, with reliability and validity considered the main qualities assessed (de Souza *et al.*, 2017). It is also suggested that the measure should have evidence of its use in the target population and have information regarding the feasibility available (Prinsen *et al.*, 2016). This includes availability, cost and ease of administration (Prinsen *et al.*, 2016).

Validity refers to the degree to which a test measures what it is intended to, with content, criterion and construct validity considered the essential components (Prinsen *et al.*, 2016). Reliability examines how stable, consistent and accurate a measure is by considering test/retest, internal consistency, inter-rater and intra-rater reliability (de Souza *et al.*, 2017; Koo *et al.*, 2016). Prinsen et al (2016) recommended that the most important components when choosing a measure are content validity followed by internal consistency (Table 5.1).

Table 5.1 Types of Validity and Reliability

Property	Definition
Validity	The degree a test measures what it is intended to measure.[a]
Content validity	The degree to which a test measures the concept it should measure. It evaluates the rigour of the method for which the instrument was created and the purpose of the measure for which it was proposed.[a]
Construct validity	The degree to which a test measures the construct of interest. It examines the theoretical relationship of the instrument items and concepts contained in the theory.[a]
Criterion validity	The degree to which the instrument produces results similar to other valid/gold standard instruments evaluating the same construct.[a]
Reliability	How stable, consistent and accurate a measure is. [b]
Test-retest reliability	Consistency of data taken from the same subject and conditions over time.[b]
Inter-rater reliability	Consistency of data from two or more raters measuring the same subject at same time.[b]
Intra-rater reliability	Consistency of data recorded by one rater at different times.[b]
Internal consistency	The extent to which all the items in a test measure the same concept.[b]

[a] de Souza *et al.*, (2017), [b] Koo *et al.*, (2016).

Content validity assesses how well a test measures the concept or characteristics it should measure. It is usually evaluated by comparing the instrument to another similar one, using correlation analysis and Pearson's correlation or Spearman rank correlation coefficient (Prinsen *et al.*, 2016; de Souza *et al.*, 2017). Both are reported as a number between -1-1, with the stronger the correlation the closer to ±1.

Internal consistency describes the extent to which all the items in a test measure the same concept and ensure the items are connected within the test (Taber, 2018). It is measured using Cronbach's alpha, expressed as a number between 0-1, with higher values indicating the measure is more consistent (Tavakol *et al*., 2011; Taber, 2018). Test/retest and rater reliability are illustrated by the intraclass correlation coefficient (ICC). Values of 0.5 or less are considered poor reliability, between 0.5 and 0.75 moderate, 0.75 and 0.9 good and above 0.9 excellent reliability (Koo *et al*., 2016).

Another important characteristic to consider is the responsiveness of the measure used, or its ability to detect change over time (Roach, 2006). Clinically this change is often considered using the minimal detectable change (MDC) and the minimal clinical important difference (MCID). The MDC is the smallest change in score detected after considering measurement error (Mouelhi *et al*., 2020). While the MCID is defined as the smallest change required to represent a meaningful change to a patient, or a change that is important to the patient (Mouelhi *et al*., 2020). Both help define how clinically useful a measure really is.

As mentioned in previous chapters, there are many methods used to measure spasticity with the evidence to support their use mixed (Table 5.2).

Table 5.2 Methods used to evaluate spasticity

Spasticity measure	Direct Measure	Valid	Reliable	MCID	Specialist training	Specialist equipment	Used clinically	Used in research	Used in pwMS
MAS	x	x	✓	✓	x	x	✓	x	✓
MTS	x	x	✓	?	x	x	✓	x	?
MSSS-88	x	✓	✓	?	x	x	✓	✓	✓
NRS	x	✓	✓	✓	x	x	✓	✓	✓
ArmA/LegA	x	✓	✓	✓	x	x	✓	✓	✓
LASIS	x	?	?	?	x	x	✓	✓	?
PRISM	x	✓	✓	?	x	x	?	✓	✓
PT	x	✓	✓	?	x	✓	?	✓	?
ID	x	?	✓	?	x	✓	x	✓	?
H-reflex	✓	✓	✓	?	✓	✓	x	✓	✓
sEMG	✓	✓	✓	?	✓	✓	x	✓	?
Hybrid	✓	✓	✓	?	✓	✓	x	✓	?

Abbreviation: ✓ - Yes, ✗ - No, ? – Unknown, ArmA – Arm activity measure, H-reflex – Hoffmans reflex, ID – Isokinetic Dynamometry, LASIS – Leeds Adult Spasticity Impact Scale, LegA – Leg activity measure, MAS - Modified Ashworth Scale, MCID – Minimal clinically important difference, MTS - Modified Tardieu Scale, MSSS-88 – Multiple Sclerosis Spasticity Scale 88, NRS – Numerical Rating Scale, PT – Pendulum test, PRISM – Patient Reported Impact Spasticity Measure, sEMG – surface Electromyogram.

5.2 Methods used to evaluate spasticity

The current measures listed in Table 5.2 can be categorised into clinical scales, biomechanical and neurophysiological methods. There are strengths and weaknesses for each method, with no one instrument being identified as gold standard in the measurement of spasticity. These methods will be discussed in more detail in the next few section.

5.2.1 Clinical scales

Clinical scales include objective/clinical rating scales and PROMs.

The MAS and Modified Tardieu Scale (MTS) are both examples of objective rating scales. The advantage of both measures are that they are quick, easy to use, require minimal equipment and frequently used in practice, making it possible to compare findings across studies. Evidence also exists to support the reliability of both scales. However, the validity of both measures is poor as both scales quantify muscle stiffness or resistance to stretch. They are also unable to differentiate the different causes of muscle stiffness and so do not directly measure spasticity.

As discussed in Chapter 4, the MAS scale is the most commonly used scale in clinical practice, and grades the resistance encountered during passive muscle stretch (Bohannon *et al.*, 1987; Pandyan *et al.*, 1999). It has been shown to have good inter-rater reliability in patients with central nervous system lesions (Bohannon *et al.*, 1987). However, studies have found it to correlate to muscle stiffness rather than spasticity (Bakheit et al 2003; Pandyan *et al.*, 2005; Biering-Sørensen *et al.*, 2006; Malhotra et al., 2008; Fleuren *et al.*, 2010). It has also been shown to lack sensitivity between grades (Pandyan *et al.*, 1999, 2003; Blackburn *et al.*, 2002; Ansari *et al.*, 2006; Mutlu *et al.*, 2008; Craven *et al.*, 2010).

The MTS considers four components during assessment; the range of movement at slow and at fast stretch, the angle of a catch when the limb is moved at speed and the resistance felt during the movement. As it assesses muscle response at different speeds it considers reflex hyperexcitability, a component of spasticity, which in theory suggests the MTS to be a more accurate measure of spasticity. However, its validity is unproven and evidence only exists to support its reliability. It has rarely, if ever, been studied in pwMS. The inter-rater reliability and test-retest agreement of the MTS was found to range from good to excellent by Li et al (2014) using stroke participants (n=51) (kappa range: 0.73-0.82), and by Akpinar et al (2017) who used people with SCI (n=65) (kappa range: 0.69–0.91). While Naghidi et al (2014) found no correlation between the MTS and neurophysiology methods (the H-reflex), when assessing wrist flexor

spasticity in stroke participants (n=20). They did however, state this could be due to the small sample used, and the low levels of spasticity of the participants.

PROMs used to evaluate spasticity include the Leeds Adult Spasticity Impact Scale (LASIS), Arm activity measure (ArmA), Leg activity measure (LegA), MSSS-88, Patient Reported Impact of Spasticity Measure (PRISM) and the Numerical Rating Scale (NRS). PROMs are used by clinicians to gain information on the impact of spasticity on HRQOL and to evaluate the effect of treatment (Hugos *et al.*, 2019). While they are considered important as they provide participant thoughts and feelings, they again do not directly measure spasticity. In addition, they are subjective and can be prone to bias so should be used in conjunction to other measures rather than in isolation (Balci, 2018).

The LASIS, ArmA and LegA were developed to measure change in limb function or care needs following treatment with focal treatment such as botulinum toxin (Ashford and Turner-Stokes, 2013; Ashford, Turner-Stokes, *et al.*, 2013; Ashford *et al.*, 2021). While no data exists on the psychometric properties of the LASIS, the ArmA and LegA have been studied in mixed neurological populations which include stroke, acquired brain injury and MS, and have been shown to be valid and reliable tools (Ashford, Turner-Stokes, *et al.*, 2013; Ashford *et al.*, 2021). Construct validity of the ArmA and LegA was supported with the ArmA found to moderately correlate with the LASIS for passive function (r=0.50) and active function (r=0.48). The LegA showed weak correlation to the MAS (r=-0.25) & moderate to goal attainment scale (r=-0.35) for passive function. While active function strongly correlated to the Rivermead Mobility Index (r=-0.89). In addition, test re-test reliability was also found to be excellent for the ArmA for both passive function (kappa= 0.90) and active function (kappa= 0.93) (Ashford, Turner-Stokes, *et al.*, 2013). As it also was for the LegA (passive function kappa= 0.83, active function kappa= 0.91, impact scale kappa= 0.82) (Ashford *et al.*, 2021).

The MSSS-88 and PRISM consider the patients perspective on the overall impact of spasticity on HRQOL (Balci, 2018). The MSSS-88 has been shown to be a valid and reliable measure in pwMS (Henze *et al.*, 2014; Rodic *et al.*, 2016; Freeman *et al.*, 2019), with its psychometric properties discussed previously in section

4.2.6.2. Its main limitation is around the time taken to complete it, as highlighted by the participants of the second study in this thesis (Chapter 4). The PRISM is a shorter and quicker scale to complete than the MSSS-88 and has been suggested as a better alternative as a result (Knežević *et al.*, 2017). It has been reported to show good test-retest across its subscales which include social embarrassment (ICC 0.82), need for intervention (ICC 0.85), daily activities (ICC 0.86), positive impact (ICC 0.86), need for assistance/positioning (ICC 0.88), psychological agitation (ICC 0.88) and social avoidance/anxiety (ICC 0.90) (Knežević *et al.*, 2015). These subscales also showed moderate to strong correlation with the MSSS-88, which ranged from 0.34-0.73 (Knežević *et al.*, 2017).

Lastly, the NRS is also used to measure specific symptoms relating to spasticity such as pain, spasm or leg stiffness/spasticity. While much of the evidence exists in relation to pain, it has also been shown to be valid and reliable when considering spasticity in pwMS (Farrar *et al.*, 2008; Anwar *et al.*, 2009). Farrar et al (2008) reported the scale to show good reliability when comparing two NRS scores one week apart (ICC 0.83). While Anwar et al (2009) reported the test re-test reliability of the NRS to also be good (r=0.67), with moderate correlation also found between the mean NRS and the MAS scores taken six weeks apart (week 0: r=0.46, p=0.006; week 6: r=0.45, p=0.01). One of its strengths is it is quick to complete and easy to use, highlighted as important following the study in Chapter 4.

5.2.2 Biomechanical measures

Biomechanical measures of spasticity include the pendulum test and isokinetic dynamometry, both of which measure mechanical response to movement. They do so by using device(s) that measure joint position, range of motion, angular speed and torque to quantify the resistance to movement or muscle tone (da Luz dos Santos *et al.*, 2017; Luo *et al.*, 2019). The strength of these measures is in the ability to standardise the speed and amplitude of the muscle stretch (Biering-Sørensen *et al.*, 2006). However, they require equipment which can be expensive, requires training and a space to use it which limits their clinical use

(Wood *et al.*, 2005; da Luz dos Santos *et al.*, 2017; Hugos *et al.*, 2019). Like clinical rating scales, they are also unable to differentiate between the different causes of muscle stiffness and resistance to stretch, and so do not directly measure spasticity. As a result they are often used in combination with neurophysiology, (surface electromyography (sEMG)), as a hybrid measure of spasticity.

The pendulum test is used to assess spasticity at the knee joint with the patient positioned in a supine, sitting or prone position. The leg is held in flexion or extension, depending on the muscle group being tested, and released to swing freely. Electro-goniometry measures the initial range of movement and on release if spasticity is present, the movement would 'catch' or stop, with that second angle measured and indicative of spasticity (Biering-Sørensen *et al.*, 2006). Video analysis of angular displacement and velocity can also be used to assist this process (Hugos *et al.*, 2019). Kim et al (2013) reported it to be valid and reliable in participants with acquired brain injury (n=31). Test-retest reliability was found to be excellent (ICC 0.95-0.97), with high correlation also reported when compared to sEMG recordings (r=-0.77—-0.85). The limitations though, are that it was designed to measure spasticity around the knee and requires the participants to be able to fully relax for it to be accurate (Biering-Sørensen *et al.*, 2006; Balci, 2018). Modified versions have also been developed to include measurement of the elbow flexors and extensors (Rahimi *et al.*, 2020), however the same limitations apply.

Isokinetic dynamometers measure the range of movement and torque while a limb is passively moved at a specific speed(s), with 30-120 degree/second being the commonly used parameters (Wood *et al.*, 2005). As the speed of movement increases, spasticity would be indicated by an increase in torque (Balci, 2018). Dynamometers are often used alongside neurophysiology measures such as sEMG to detect a lower stretch reflex threshold (Wood *et al.*, 2005; Malhotra *et al.*, 2008; Hugos *et al.*, 2019). The evidence for their use will be considered in the next section alongside neurophysiological methods.

5.2.3 Neurophysiological measures

Neurophysiology has been suggested to be the most precise method of measuring spasticity, as it directly measures the response of the nervous system through spinal reflex activity (Biering-Sørensen *et al.*, 2006; Malhotra *et al.*, 2008, 2009; Hugos *et al.*, 2019). Methods of doing so include measurement of the stretch reflex during passive muscle stretch, by tapping the tendon mechanically (T-reflex) or by electrical stimulation of a peripheral nerve (Hoffmans reflex or H-reflex) (Voerman *et al.*, 2005; Biering-Sørensen *et al.*, 2006).

Assessing the stretch reflex by passive muscle stretch and T-reflex are common components of a neurological examination undertaken by clinicians. During assessment through passive muscle stretch the muscle is moved at different speeds, with the response then scored using objective rating scales such as the MAS or MTS. However, as discussed in earlier sections, these measures lack sensitivity and validity. Surface EMG can also be used during this process to quantify the reactivity of the reflex, which is known to be hyperexcitable in people with spasticity (Voerman *et al.*, 2005). The stretch reflex response however is influenced by the frequency and speed of stretch, limb position, background muscle activity and the biomechanical properties of the muscle (Voerman *et al.*, 2005).

The T-reflex, better known as the patellar tendon or ankle reflex, evokes the stretch reflex via tapping the distal tendon of a muscle which stimulates the afferent nerve and muscle spindle. Reflex response can be compared although recording muscle activity using sEMG is suggested, with amplitude and latency of the response measured. Although it is quick to perform and painless, it requires practise to standardise the technique and so can be limited by the skill of the practitioner (Voerman *et al.*, 2005). It too is influenced by the force and frequency of the tap, background muscle activity and age. Due to this it has been reported to be less standardised and reproducible than other measures such as the H-reflex (Voerman *et al.*, 2005).

The H-reflex has been described by Burke (2016) as the electrical equivalent of the T-reflex, however it bypasses the muscle spindle and directly measures the alpha motor neuron pool in the spinal reflex. As a result, it is considered the

most direct measure of reflex activity and is more frequently used to measure spasticity (Voerman *et al.*, 2005; Burke, 2016; Hugos *et al.*, 2019).

The H-reflex is elicited by electrical stimulation of a mixed peripheral nerve, and requires the use of a stimulator, sEMG and an amplifier. As the H-reflex reflects the excitability of the alpha motor neuron pool within the reflex arc in the spinal cord, it provides information about changes within the nervous system.

The H-reflex is mostly studied in the soleus muscle by stimulating the posterior tibial nerve (Palmieri *et al.*, 2004; Voerman *et al.*, 2005). When stimulated at a low intensity the sensory 1a afferent fibres arising from the muscle spindle are first to be triggered due to being large in diameter (Figure 15 response 2). This response is relayed via the nerve to the alpha motor neurons in the spinal cord and at the correct intensity produces an H-reflex (Figure 15 response 3). However, the smaller diameter efferent fibres also become stimulated with higher intensities, which produce a muscle response (M wave) (Figure 15 response 1). This response is not reflexive as it does not pass through the spinal cord and, as each response is linked to the length of it path, a motor response or M wave appears first on the sEMG at 6-9 milliseconds with the H-reflex slightly later at 30 milliseconds (Palmieri *et al.*, 2004; Voerman *et al.*, 2005).

Figure 5.1 Illustration of Hoffmans reflex

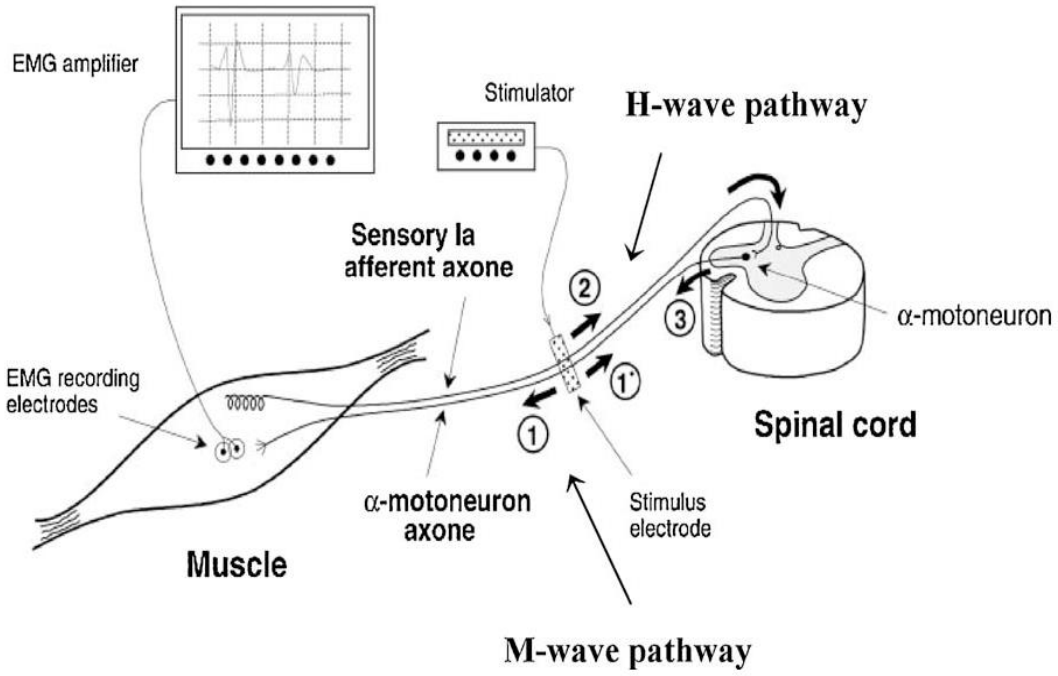


Figure reproduced from Chen et al (2011) with permissions from Elsevier.

Simplified H-reflex: Low intensity stimulation results in action potential on the 1a afferent axons (2). This causes an alpha motor neuron response to the target muscle (H-reflex) (3). Increased stimulation intensity generates a muscle response (M wave) (1), as well as in spinal cord (1*), causing antidromic collision with the spinal response (3).

With increased stimulation a threshold of the motor fibres is reached, and no further increase occurs in the M wave even at higher stimulation which is also referred to as M_{max}. In contrast as the H-reflex increases and reaches threshold, it then reduces and disappears at higher stimulation due to a process called antidromic collision (Palmieri *et al.*, 2004; Voerman *et al.*, 2005). This describes the process of rebound electrical activity, where activity travelling back down the alpha motor neuron collides with the reflex response (Figure 15 response 1^*). Higher stimulation results in reduced motor neuron response due to this blockage by the antidromic volley, which causes the progressive reduction of the H-reflex on sEMG until it disappears. However, the M wave remains stable and unaffected (Palmieri *et al.*, 2004; Voerman *et al.*, 2005).

The H-reflex can be measured using the latency, amplitude or as a ratio of maximal stimulation using the M wave, or M_{max}. As the M wave can be stabilised with stimulation and is not controlled by the spinal centres, it is considered the

more stable variable allowing the H_{max} to be matched to it (Palmieri *et al.*, 2004; Voerman *et al.*, 2005). The H_{max}/M_{max} ratio, often referred to as the H/M ratio, is preferred for use when data is measured on different days. This allows for slight changes in the position of the electrodes and the H-reflex is taken as a percentage of the M wave, using the M_{max} to improve the reliability (Palmieri *et al.*, 2004; Voerman *et al.*, 2005).

Both the H-reflex and H/M ratio however, can be easily influenced by factors such as the environment, position of testing, participant posture and eye position, which are known to affect the reflex. In addition, background muscle activity and cognitive processes such as expectation of stimulation or by even thinking about contracting the muscle have also been reported to have an effect (Hultborn *et al.*, 1987; Misiaszek, 2003; Palmieri *et al.*, 2004; Voerman *et al.*, 2005; Burke, 2016; Traverse *et al.*, 2018).

Studies have compared biomechanical and/or neurophysiology measures to clinical scales and reported them to be more sensitive (Malhotra *et al.*, 2008; Fleuren *et al.*, 2010; da Luz dos Santos *et al.*, 2017). As a comparison these studies used the Ashworth Scale (AS) and Modified Ashworth Scale (MAS), the scale it was developed from, to compare to.

Malhotra et al (2008) compared the MAS, to biomechanical methods (force transducer and electrogoniometer) and muscle activity (via sEMG) in participants with wrist spasticity following stroke (n=100). They identified spasticity to be present in 87 participants using sEMG and only 44 participants when using the MAS. However, biomechanical measures showed no consistent relationship with the MAS and sEMG. In addition, the MAS was shown to have poor sensitivity (0.5) and high specificity (0.92) in relation to muscle activity recordings from slow and fast stretch. The authors concluded that the MAS has limited sensitivity in the measurement of muscle activity. The study did show that the hybrid technique used may offer a more accurate approach to measuring spasticity, although requires further research before it can be used in clinical practice.

The study by Fleuren et al (2010) used three clinicians to assess knee extensors and elbow flexors in stroke participants (n=30). They reported moderate correlation between the AS and sEMG (r=0.56-0.66, p=0.05) and isokinetic

dynamometry (r=0.55-0.87, p=0.05). However, correlation between measures was found in the knee extensors but not the elbow flexors. While Du luz dos Santos et al (2017) also concluded that both biomechanical and neurophysiological approaches were more sensitive than the MAS. They completed a literature review on studies that compared the MAS to biomechanical methods (n=14), neurophysiology (n=3) and hybrid approaches, combination of both (n=9). They did however conclude that no method was identified as being superior.

The reliability and reproducibility of biomechanical and neurophysiology measures has been considered by two studies (Condliffe *et al.*, 2005; Dehno *et al.*, 2020). Dehno et al (2020) reported the reproducibility to be good when testing wrist spasticity in stroke participants (n=26) using isokinetic dynamometry. Testing took place on consecutive days, at four different speeds, with an ICC range of 0.76-0.85 reported. While Condliffe et al (2005) used both isokinetic dynamometry and sEMG and reported moderate to good reliability when testing elbow flexor spasticity (ICC range 0.63-0.85), although it should be noted this study had much smaller sample (n=9).

While studies often use a hybrid approach to measure spasticity, neurophysiological measures have been reported to be more precise, with the H-reflex the most used (Malhotra *et al.*, 2009; Balci, 2018; Hugos *et al.*, 2019).

5.2.1 The H-reflex as a measure of spasticity

Various studies have used the H-reflex to measure the physiological effects of cycling on the nervous system in healthy adults (Motl *et al.*, 2003, 2004; Mazzocchio *et al.*, 2006), as well as neurological conditions where the effects on spasticity are of interest (Motl *et al.*, 2006, 2007; Phadke *et al.*, 2009; Sosnoff *et al.*, 2010; Rayegani *et al.*, 2011).

Several of these studies considered the effects of a single session of active cycling for 20 minutes on spasticity (Motl *et al.*, 2006, 2007; Phadke *et al.*, 2009; Sosnoff *et al.*, 2010). Sosnoff et al (2010) involved participants with mild MS

(EDSS 1-4) and assessed the H-reflex before, 10 mins and 30 mins after cycling. They reported a significant reduction in both H/M ratio and MAS following cycling ($p<0.001$ both), with a moderate effect to the H/M ratio ($d=-0.52$ and -0.50). Overall an average reduction on 14% was reported to the H/M ratio. While the studies by Motl et al (2006, 2007) also included participants with mild MS (EDSS 0.5-4.5) and assessed the reflex before, 10 minutes, 30 minutes and 60 minutes after active cycling. The study in 2006 included a larger sample (n=27), while the 2007 study re-tested the method using a small sample of participants who were taking anti-spasticity medication (n=6). Both studies reported a significant reduction in H/M ratio following cycling. Motl et al (2006) reported this to be with a small to moderate effect ($p<0.001$, $d=-0.38$, -0.48, -0.54), while the 2007 study reported this to be with a moderate effect ($p<0.001$, $d=-0.52$, –0.56, –0.52). Overall, the 2006 study reported an average reduction in the H/M ratio of 15%, while the study in 2007 reported this to be by 20% reduction however did have a much smaller sample size.

The last study to compare a single session of cycling compared the effects to locomotor training, but using participants with incomplete SCI who could walk at least 10 metres with or without aid (ASIA C or D) (n=12) (Phadke *et al.*, 2009). They also measured paired H-reflex depression to assess change, which is when two successive stimuli are delivered with the reflex responses compared. The second response produces a smaller amplitude, dependent on the inter stimulus interval but is known to be impaired in SCI (Phadke *et al.*, 2009). Following the interventions, they noted that only the cycling intervention resulted in a significant reduction in the reflex depression, but only at one interstimulus interval (100m/s, $p=0.01$). Participants in this study with spasticity were also found on average to show a 19% reduction in the reflex amplitude, however this analysis only included a small number of participants (n=5).

Only one study used the H-reflex to measure spasticity following a prolonged cycling intervention (Rayegani *et al.*, 2011). They used an intervention of 60 minutes a day of passive APT cycling, which lasted for two months and included a larger more disabled group of SCI participants (n=63 ASIA A, n=1 ASIS B). They reported a significant reduction in H/M ratio following APT cycling, however did

not include sufficient statistical data to support this as they only reported the p value (p= 0.000).

While promising, the limitations of these studies are the small numbers of participants with lower levels of disability, and all but one involved participants who could walk and used an ergometer. As a result, the H-reflex remains untested in people with higher levels of disability from MS or as an outcome measure of studies involving APTs.

5.3 Study aims

As this is the first study to consider the H-reflex in people with moderate to severe MS using an APT the study aimed to;

1. Assess if spasticity, as measured by the H-reflex, is reduced following a single session of cycling using the APT

2. Determine if the H-reflex is a more sensitive and feasible measure of spasticity than the MAS and self-reported leg spasticity measured using the Numerical Rating Scale (NRS)

3. Evaluate the feasibility of a single session of lower limb APT cycling on spasticity in people with moderate to severe MS by recording; the number or participants who met the criteria for the study, the number who consented to participate and reasons for not, the ability to elicit an H-reflex, adverse effects and attrition rates

5.4 Methods

5.4.1 Study design and ethical approval

This was a pre and post study that recruited a convenience sample of people with moderate to severe MS. Ethical approval was granted from the West of

Scotland Research Ethics Committee reference 19/WS/0103 (Appendix 9). Research and development approval was also obtained through NHS Greater Glasgow and Clyde reference GN18PY384 (Appendix 10). Due to the outbreak of the Covid-19 pandemic the study was significantly delayed and an application to resume research activity was submitted and approved in July 2021 (Appendix 11). A further application to extend the study by one month was made due to the disruption caused by hosting the COP26 summit in Glasgow, the city where the study was being undertaken, and the impact to the surrounding hospital campus and transport system at that time.

5.4.2 Study recruitment

The study commenced on the 1st August 2021 and those attending as out-patients or admitted to NRU until the 30th April 2022 who fulfilled the inclusion and exclusion criteria were invited to take part. Participants were given a participant information sheet (Appendix 12) and given a minimum of a week to consider involvement in the study, to allow discussion with relatives if appropriate and to ask any questions they may have. Participants who agreed to take part gave written, informed consent (see Appendix 13). The study aimed to recruit 30 participants within this period which was felt to be achievable based on admission/attendance rates to NRU in 2019. During the same period in 2019 45 pwMS had attended the service as either an in or outpatient.

5.4.3 Inclusion and exclusion criteria

As in the previous study, the aim was to be as inclusive as possible, and the exclusion criteria were kept to a minimum. To be included in the study participants had to

- have a confirmed diagnosis of MS,
- be aged over 18 years,

- have an EDSS of between 6.0 (requires a walking aid-cane, crutch etc-to walk about 100m with or without resting) and 8.5 (essentially restricted to bed much of the day, have some effective use of arms and retains some self-care functions),

- have lower limb spasticity with a MAS score of ≥1 in any lower limb muscle group (as recorded during their initial physiotherapy assessment).

Participants were excluded if they

- had significant cognitive impairment such that they could not understand instructions,

- had visual impairment such that they could not see the screen on the APT,

- had co-morbidities which would preclude them taking part in exercise such as unstable cardiac or respiratory symptoms, lower limb fractures,

- had peripheral nerve injury, peripheral nerve disease/neuropathies or myopathy in the lower limbs,

- were unable to be seated appropriately in a chair or wheelchair for two hours due to body position or contractures,

- had broken or irritated skin in the right lower limb.

5.4.4 Study personnel

The research team consisted of the research physiotherapist (AB) and a research assistant, both of whom were experienced neurological physiotherapists and had experience of treating pwMS.

5.4.5 Baseline assessment

At baseline, demographic details were recorded on a participant demographic sheet (Appendix 14). This included data regarding each participant's age, sex, type of MS, time since diagnosis, EDSS, past medical history, medication and

social situation including home circumstance, marital status and whether they consumed alcohol or smoked. In addition, information on each participants ability to transfer and walk, if able, and the distance and equipment used to do so were also noted. The medical notes were consulted if the participant was unable to remember details such as type of MS, medication or time since diagnosis.

Outcome measures were documented in a data collection pack (Appendix 14) and in addition to these measures, the following feasibility outcomes were also recorded; the number of eligible participants approached to take part, the number who declined and reasons why, the number of participants who were able to elicit an H-reflex, adverse events and attrition.

5.4.6 Outcome measures

All the outcome measures were recorded immediately before the single session of APT cycling. The H-reflex was then measured again, immediately following cycling and where possible at 10, 20 and 30 minutes after completion of the cycling session. Upon completion of the H-reflex tests, the MAS and NRS were then re-assessed prior to finishing the study.

In addition, cycling variables were recorded from the APT including leg symmetry, active and passive distance cycled, resistance levels, average rpm and performance (overall power in watts) as described previously in section 4.2.8.

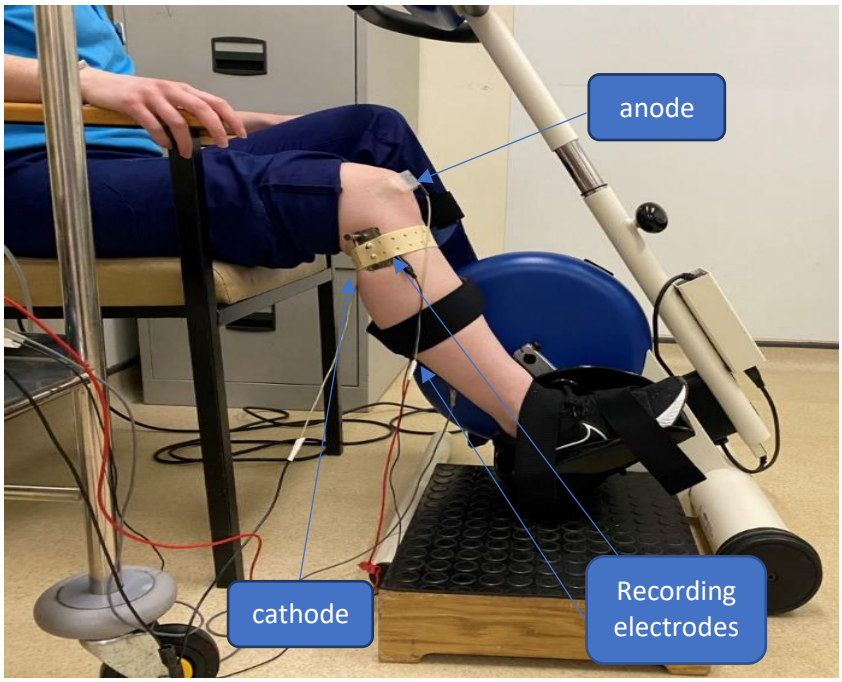
5.4.7 Primary outcome measure – Spasticity (Hoffman's Reflex)

The primary outcome was spasticity and assessed by the presence, amplitude and consistency of the H-reflex.

The H-reflex was recorded from the triceps surae muscle group by stimulating the posterior tibial nerve in the popliteal fossa of the participant's right leg.

After cleaning the skin with an alcohol wipe recording electrodes were applied to the soleus muscle and over the head of the fibula. Stimulation was applied with the cathode placed over the posterior tibial nerve at the back of the knee, and the anode positioned over the middle of the patella (Figure 5.2).

Figure 5.2 H-reflex electrode position



The nerve position was established by evoking a motor response and an initial H-reflex. The cathode was then fixed in place using an elastic strap and the reflex re-tested to ensure no movement had occurred. The tibial nerve was stimulated by 1ms square wave pulses delivered by a Digitimer DS7 isolated stimulator rated safe to use on humans. Twelve stimuli were applied with 10 seconds between each stimulus to minimise any effects of post-activation depression of the reflex (Hultborn *et al.*, 1996).

The H-reflex was recorded via the Delysis Bagnoli 2 EMG system, set at a gain of 1000, and recorded on a Cambridge Electronic Device micro. The EMG recordings were amplified and filtered at 15-500Hz and at a sample rate of 5000Hz. A stimulation intensity of 0.25mA was initially used and was steadily

increased by 0.25mA increments and adjusted to the level where the H-reflex was initiated. An 11% increase in stimulation intensity was then used for each H-reflex test (Palmieri *et al.*, 2004).

Each of the participant's data was kept in an individual paper file and stored in a secure filing cabinet, and EMG data from each assessment saved on the CED signal 2.16 software on a password protected laptop.

5.4.8 Secondary outcome measures: spasticity (MAS and NRS)

The other measures of spasticity were the MAS and NRS.

Measurement of the MAS was similar to the previous study described in Chapter 4, and followed the same procedure as described in section 4.6.2. The research physiotherapist measured the MAS in both legs, with the patient assessed in a semi recumbent position on a standard double plinth. Muscles tested included the hip extensors, hip flexors, adductors, quadriceps, hamstrings, gastrocnemius, soleus and the ankle invertors in that order. Each muscle group was tested by moving the participant's leg two to three times and any resistance to movement was scored according to the MAS, and recorded within the participants data collection pack.

The NRS was scored, with 0 representing no leg stiffness/spasticity and 10 the worst possible leg stiffness/spasticity, or as bad as it could be. The participants were asked to consider and give a verbal score of their leg stiffness/spasticity prior to and after completion of the APT cycling and H-reflex tests.

5.4.9 Pilot

Prior to commencing this study, a small pilot was completed using five healthy volunteers who worked in the NRU to help test and refine the protocol described in sections 5.5.7 and 5.5.10. Following this pilot, two changes were made to the H-reflex protocol described in section 5.5.7 to improve the measurement, data

recordings and time taken to complete each assessment. The first change was to the position of the distal recording electrode. During data analysis low quality recordings with poor signal were observed. The distal electrode was changed from the lateral malleolus to the fibular head to reduce movement artefact with a favourable effect. The second change was to the H-reflex measurements during testing. In line with the study protocol (Appendix 15) the study planned to measure the H-reflex latency, amplitude and complete a full recruitment curve at each time point. However, the total time required to complete these assessments was on average an hour. As a result, a decision was made to measure the H-reflex by its presence, amplitude and consistency to reduce the time required.

5.4.10 Study protocol

The cycling session and assessments were completed in a clinic room within the NRU. The participant was seated in a standard chair or their normal wheelchair which was positioned against the wall. Ankle splints (if worn) were removed prior to attaching the electrodes. The right hip and knee joint angles were positioned so that the participant was in a comfortable cycling position. The foot and ankle were held in a fixed position by the footplate and calf straps on the APT. During the H-reflex assessment a 10cm box was placed underneath the footplate to ensure the leg was stationary (Figure 5.3).

Figure 5.3 H-reflex assessment position

After measurement of the MAS, NRS and H-reflex, the participant was then asked to start cycling. The parameters for the cycling session were again kept similar to the APT protocol used in Chapter 4. The only change was to the length of active cycling time, which was increased to 30 minutes in line with suggested guidelines for aerobic exercise (Kalb *et al.*, 2020). The cycling session began with a two-minute warm up consisting of passive cycling, where the legs of the participant were moved by the APT at 10rpm. After two minutes an alarm sounded on the APT indicating the start of the active cycling. The participant was asked to cycle for 30 minutes and maintain a pedal rate that equated to moderate level intensity exercise (RPE 12-14), where 6 represents no exertion at all and 20 maximal effort (Williams, 2017). The resistance level on the APT started at level one and was increased or reduced according to the participant's RPE score, which was taken every three minutes during the cycling session. If the RPE fell below 12, the participant was asked to cycle faster, or the resistance increased by one level. Similarly, if the RPE was above 14, the participant was asked to either cycle slower or the level was reduced by one level. If the participant was unable to actively cycle at any point during the 30-minute exercise period, or if they had a spasm, the APT reverted to the passive

mode. The final phase was a cool down where participants again undertook two minutes of passive cycling at 10rpm.

5.4.11 Data analysis

The outcome variables were summarised numerically, and where appropriate graphically over time with the emphasis being on the pre-post data.

To analyse the data from the H-reflex the saved EMG recordings were used. Cursors in the signal software (version 2.16) were used to measure the peak-to-peak amplitude of H-reflex and M waves, and the latency which was measured from the start of stimulation to the onset of the initial deflection of the H-reflex. Means and standard deviations (SD) were calculated at each time point in Excel for subsequently analysis. A repeated measures ANOVA were complete to consider the H-reflex and M wave data over time.

The coefficients of variation (COV) were also calculated to assess reliability of the data using the mean and SDs at each time point, for both the H-reflex and M wave. The parameters were defined as excellent when the COV was less than 10%, good when the COV was between 10-20%, acceptable between 20-30% and poor when greater than 30%, similar to the study by Aronhime et al (2014).

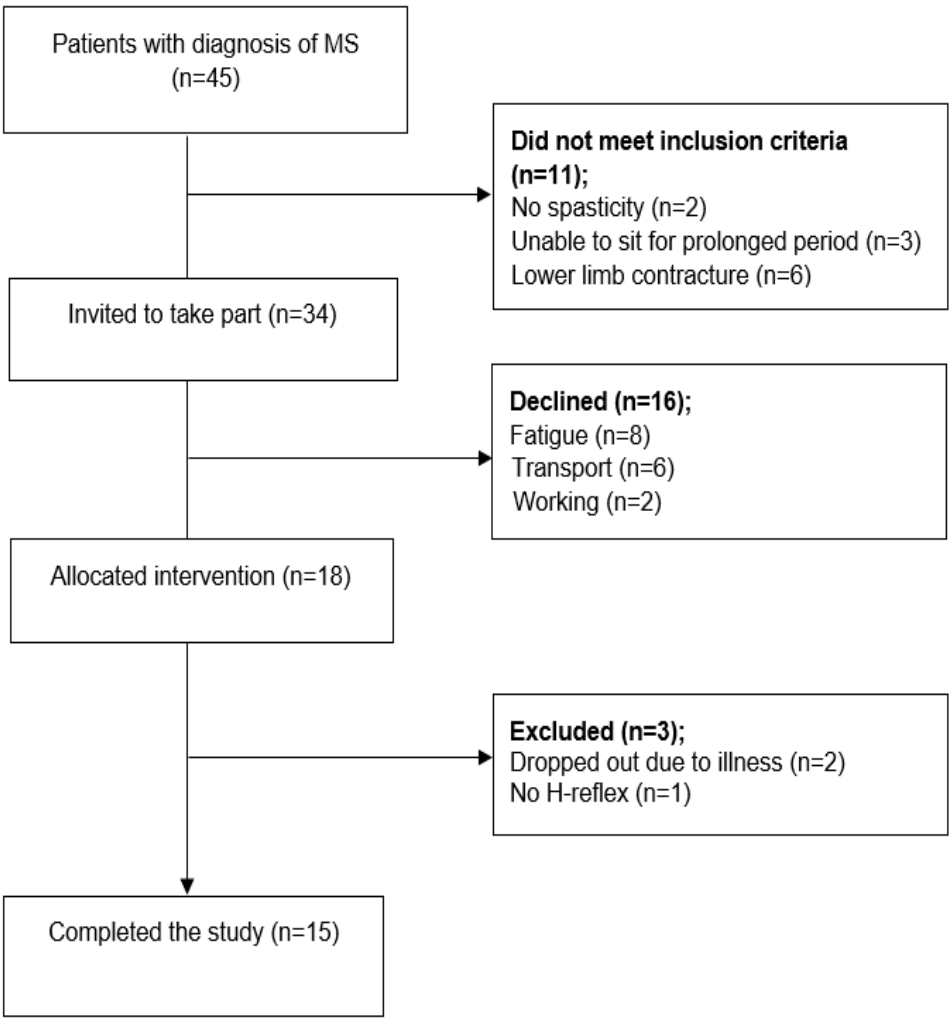
Descriptive statistics were used to analyse data from the MAS, with a paired t-test used for the NRS. All testing was performed in IBM SPSS version 28.0 and at the 5% level of significance.

5.5 Results

The study recruited participants from 1st August 2021 to 29th April 2022 and over this period 45 people with a diagnosis of MS were admitted to NRU or attended outpatient clinics. From this, 34 people met the criteria and were invited to participate, with 16 declining for reasons such as fatigue, transport issues or due to work commitments (Figure 5.4). Eighteen participants were recruited but

only 16 participated in the study, as two dropped out due to hospital admissions and one had no H-reflex on testing. The results presented in this section are based on the 15 participants who completed the study.

Figure 5.4 Study recruitment



5.5.1 Demographics

Demographic details for the study participants are presented in Table 5.3. Overall, the group had an average age of 56.0 ± 7.8 years and had a median EDSS of 6.5 (range 6.0-8.5). The average time since diagnosis was 19.2 ± 8.9 years.

Table 5.3 Participant demographics

	Study Group (n= 15)
Age (yrs) (mean ± SD)	
Female (n= 10)	57.1 ± 6.6
Male (n= 5)	52.6 ± 10.5
Type of MS (n (%)):	
PPMS	1 (7%)
SPMS	12 (80%)
RRMS	2 (13%)
Years since diagnosis (mean ± SD)	19.2 ± 8.9
EDSS (mean ± SD)	7.0 ± 0.9
Marital status (n (%)):	
Married/co habit	11 (73%)
Single	0 (0%)
Divorced	4 (27%)
Education status (n (%)):	
University	6 (40%)
College	5 (33%)
Employed from school	4 (27%)
Smoker (n (%)):	
Yes	3 (20%)
No	12 (80%)
Alcohol (n(%)):	
Drinker	11 (73%)
Non- drinker	4 (27%)

PPMS (primary progressive MS); SPMS (secondary progressive MS); RRMS (relapsing and remitting MS); EDSS (Expanded disability status scale)

5.5.2 Outcome measures

There was 100% completion of the MAS and NRS assessments pre and post APT cycling. There was also 100% completion of the H-reflex assessments at the pre, post and 10-minute post cycling time points (n=15). This reduced to 93% (n=14) at the 20-minute assessment and to 73% (n=11) at the final assessment 30

minutes after APT cycling. Reasons for stopping included the need to use the bathroom (n=3) and being too uncomfortable from prolonged sitting (n=1). No adverse effects were noted during the study.

Due to a fault in the signal programme EMG data during the H-reflex assessments could not be saved for one participant (P8). For this participant only the H-reflex amplitude data was recorded in the paper file at each time point and included in their analysis.

5.5.2.1 H-reflex

The H-reflex was found to be present in 15 participants. It was not possible to elicit in one participant (P7) therefore they did not continue to the cycling part of the intervention or complete any further measures. Nor was their data included in the analysis.

For each participant the average H-reflex and M wave amplitude, and the H-reflex latency was calculated (see Tables 5.4-5.6). The reliability of the data collected for each participant at each time point was also considered using the COV defined in section 5.4.11 (see Tables 5.7 and 5.8).

The average H-reflex latency was found to be consistent in 13 participants, with two displaying a much shorter time on sEMG (P12 and P14). Overall, the average H-reflex latency was found to be 31.4 ± 0.7ms (Table 5.4).

Table 5.4 Participant H-reflex latency

Participant number	H-reflex latency in milliseconds (ms)				
	Pre cycle (n=14)	Post cycle (n=14)	10min post cycle (n=14)	20min post cycle (n=13)	30min post cycle (n=10)
1	34.2	33.5	33.5	33.8	-
2	31.7	33.0	31.6	32.2	31.4
3	38.6	38.3	39.0	38.5	38.6
4	32.0	32.4	33.1	32.3	32.0
5	31.9	32.4	31.8	32.0	32.0
6	31.5	31.9	32.4	-	-
8	no data	no data	no data	no data	no data
9	32.5	33.6	32.6	32.8	-
10	39.2	36.8	38.5	39.2	39.2
11	32.1	30.9	31.2	31.4	31.7
12	17.2	17.8	17.6	17.8	18.1
13	36.7	36.2	36.6	37.0	36.6
14	11.3	12.1	12.9	11.9	-
15	34.6	33.7	33.8	33.9	34.0
16	32.6	31.7	32.5	32.3	32.3
mean	**31.2**	**31.0**	**31.2**	**31.2**	**32.6**
SD	**7.7**	**7.2**	**7.3**	**7.8**	**5.9**

NB - indicates no assessment, P7 excluded from analysis

The overall average H-reflex amplitude was found to be 0.27 ± 0.02mV (Table 5.5). When considering the H-reflex amplitude, on average it was found to have slightly increased following APT cycling at all time points. The average change at each time point was calculated and found to be; pre and post cycling by 0.02 ± 0.19mV (95% CI:-0.12–0.09, p=0.4); pre and 10 minutes by 0.03 ± 0.16mV (95% CI:-0.12–0.06, p=0.2); pre and 20 minutes by 0.02 ± 0.15mV (95% CI:-0.20–0.11, p=0.3); pre and 30 minutes by 0.04 ± 0.18mV (95% CI:-0.26–0.05, p=0.1). Using ANOVA with repeated measures the mean H-reflex amplitude over time was not found to be statistically significant ($F(1.949, 27.282) = 0.717$, $p=0.58$).

Table 5.5 Participant H-reflex amplitude

Participant number	H-reflex amplitude (mV)				
	Pre cycle (n=15)	Post cycle (n=15)	10min post cycle (n=15)	20min post cycle (n=14)	30min post cycle (n=11)
1	0.14	0.09	0.18	0.24	-
2	0.04	0.07	0.04	0.06	0.06
3	0.10	0.11	0.04	0.06	0.11
4	0.28	0.15	0.09	0.15	0.13
5	0.22	0.21	0.19	0.13	0.10
6	0.06	0.05	0.13	-	-
8	0.10	0.19	0.23	0.32	0.22
9	0.13	0.13	0.11	0.11	-
10	0.53	0.56	0.60	0.69	0.74
11	0.13	0.03	0.06	0.04	0.04
12	0.34	0.33	0.33	0.37	0.40
13	0.27	0.85	0.45	0.65	0.72
14	0.55	0.22	1.04	0.53	-
15	0.38	0.35	0.28	0.21	0.19
16	0.41	0.58	0.38	0.35	0.49
mean	**0.25**	**0.26**	**0.28**	**0.28**	**0.29**
SD	**0.17**	**0.24**	**0.27**	**0.22**	**0.26**

NB - indicates no assessment, P7 excluded from analysis

The overall average M wave amplitude was also calculated and found to be 5.45 ± 0.18mV (Table 5.6). On average the M wave showed a small reduction following APT cycling at all time points. The average at each time point was calculated and found to be; pre and post cycling by 0.06 ± 0.75mV (95% CI:-0.38–0.49, p=0.4); pre and 10 minutes by 0.08 ± 0.76mV (95% CI:-0.36–0.52, p=0.3); pre and 20 minutes by 0.31 ± 0.74mV (95% CI:-0.13–0.76, p= 0.08); pre and 30 minutes by 0.41 ± 0.78mV (95% CI:-0.15–0.97, p=0.06).

When using an ANOVA with repeated measures with a Greenhouse-Geisser correction, the mean M wave amplitude was statistically significant over time ($F(1.621, 21.074)= 4.340$, $p=0.03$).

Table 5.6 Participant M wave amplitude

Participant number	M wave amplitude (mV)				
	Pre cycle (n=15)	Post cycle (n=15)	10min post cycle (n=15)	20min post cycle (n=14)	30min post cycle (n=11)
1	6.85	7.27	7.70	7.87	-
2	7.15	7.23	7.22	7.19	7.08
3	7.42	7.42	6.89	7.12	7.03
4	3.36	4.17	3.82	4.35	4.44
5	7.86	6.85	7.01	6.81	6.82
6	5.35	6.85	6.84	-	-
8	No data	No data	No data	No data	No data
9	4.22	3.15	3.20	2.53	-
10	5.02	4.16	4.46	4.30	2.39
11	4.56	4.32	4.61	4.57	4.16
12	4.74	4.78	4.14	4.48	4.64
13	6.01	6.84	7.00	5.51	4.58
14	5.46	5.17	5.17	5.20	-
15	6.36	5.74	5.66	5.60	5.32
16	5.62	5.57	5.54	5.33	5.58
mean	**5.62**	**5.57**	**5.54**	**5.33**	**5.20**
SD	**1.36**	**1.49**	**1.54**	**1.55**	**1.49**

NB - indicates no assessment, P7 excluded from analysis

When considering the reliability of the data, the M wave and H-reflex recordings were considered individually at each time point and each participant was listed in order of reliability. Analysis of each participant's M wave data showed excellent reliability with low levels of variation found, and an overall mean of 0.57 ± 0.26% (range of 0-4%), reported in Table 5.7. However, analysis of the H-reflex showed less reliability, with a much higher degree of variation found with an overall average of 27.0 ± 2.09% (range of 4-67%), illustrated in Table 5.8. After taking advice no further analysis was warranted.

Table 5.7 M wave coefficient of variation

Participant number	Coefficient of Variation M wave (%)				
	Pre cycle (n=14)	Post cycle (n=14)	10min post cycle (n=14)	20min post cycle (n=13)	30min post cycle (n=10)
1	0	0	0	0	-
2	0	0	0	0	0
3	0	0	0	0	0
9	0	0	0	0	-
13	0	0	0	0	0
15	0	0	0	0	0
5	0	1	0	0	0
4	0	0	4	0	0
6	1	0	0	-	-
16	1	0	0	1	0
14	1	1	1	1	-
12	1	1	1	1	2
11	2	0	0	2	2
10	2	1	1	1	1
8	No data	No data	No data	No data	No data
mean	**1**	**0**	**1**	**0**	**1**
SD	**1**	**0**	**1**	**1**	**1**

NB - indicates no assessment, P7 excluded from analysis

Table 5.8 H-reflex coefficient of variation

Participant number	Coefficient of Variation H-reflex (%)				
	Pre cycle (n=15)	Post cycle (n=15)	10min post cycle (n=15)	20min post cycle (n=14)	30min post cycle (n=11)
9	4	5	4	38	-
12	5	4	4	24	22
10	17	43	23	12	14
15	19	20	13	16	17
4	19	52	35	51	42
5	20	67	28	31	31
14	22	25	38	17	-
13	24	10	20	18	20
3	25	26	59	50	33
11	27	19	24	27	-
8	29	21	14	10	17
16	33	21	32	40	20
6	38	36	40	-	-
1	53	34	42	24	-
2	56	24	74	28	27
mean	**26**	**27**	**30**	**28**	**24**
SD	**15**	**17**	**19**	**13**	**9**

NB - indicates no assessment, P7 excluded from analysis

5.5.2.2 MAS

Pre and post MAS scores were recorded for each participant and the median scores used to summarise the spasticity for each muscle group, illustrated in Table 5.9.

Table 5.9 Median MAS scores

Muscle group	Right Leg		Left Leg	
	Pre	Post	Pre	Post
Hip flexors	0	0	0	0
Hip extensors	0	0	0	0
Hip Adductors	1	1	1	1
Quadriceps	1	1	1	1
Hamstrings	0	0	1	1
Gastrocnemius	1.5	1.5	2	1.5
Soleus	1	1	1	1
Invertors	0	0	1	0

Overall, there were low levels of spasticity found in either leg and the only change noted was a reduction in the left gastrocnemius and ankle invertor muscles. Due to this no further analysis was felt appropriate.

5.5.2.3 Numerical Rating Scale

Pre and post NRS scores for leg spasticity were recorded for each participant and the average calculated, summarised in Table 5.10. The NRS reduced in nine participants and was no different in two participants. Four participants showed an increase in NRS scores following the APT cycling intervention, and two commented this was due to sitting for a prolonged length of time (P10 and P13). Overall, these changes were not found to be significant (95% CI:-0.46-1.86, df 14, t=1.3, p=0.11).

Table 5.10 NRS scores for lower limb spasticity

Participant number	Pre cycling	Post cycling	Change in score
1	7	5	↓ 2
2	4	3	↓ 1
3	3	2	↓ 1
4	3	2.5	↓ 0.5
5	8	3	↓ 5
6	2.5	1	↓ 1.5
8	4	2	↓ 2
9	6	4	↓ 2
10	3	6.5	↑ 3.5
11	7	7	0
12	2	2	0
13	3	4	↑ 1
14	6	7	↑ 1
15	7	4	↓ 3
16	6.5	8.5	↑ 2
mean	**4.9**	**4.2**	**0.7**
SD	**2.0**	**2.2**	**2.0**

P7 excluded from analysis

5.5.2.4 Cycling data

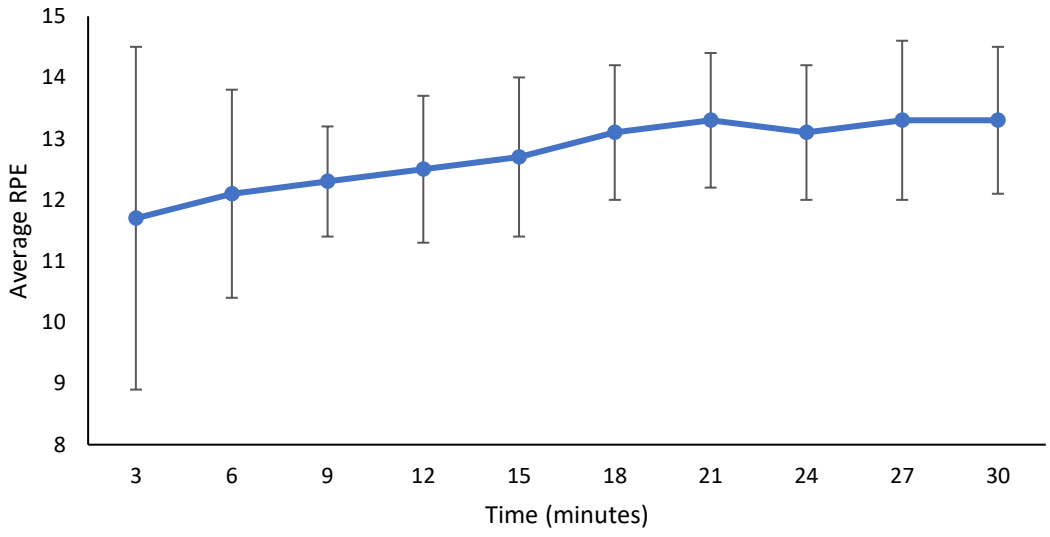
During the study fourteen participants were able to actively cycle for all or part of the APT intervention, while one completed the trial by passive cycling. Cycling variables are summarised in Table 5.11.

Table 5.11 Cycling variables

Cycling variables	mean ± SD
Duration active (min) (max 30mins)	26.3 ± 8.2
Duration passive (min) (max 30mins)	7.6 ± 8.2
Distance active (miles)	4.6 ± 2.5
Revolutions per minute (rpm)	47.9 ± 25.7
Power (W) (n=14)	5.6 ± 5.5
Resistance (kg)	1.8 ± 1.8

The average duration of active cycling during the intervention was 26.3 ± 8.2 minutes and the average total distance cycled by the 15 participants was 4.6 ± 2.5 miles. The average rpm was 48rpm (range 10-84), the median resistance was 1 (range 0-7) and the average RPE at each time check showed an overall upward trend, illustrated in Figure 5.5. When comparing lower limb symmetry during cycling the average percentage of activity in the right leg was 52% and in the left leg was 48%.

Figure 5.5 Average participants RPE



5.6 Discussion

Overall, the study did not find spasticity, as measured by the H-reflex, to be changed following 30 minutes of APT cycling in people with moderate to severe MS. Nor did the study show a change in self-reported spasticity or the MAS, however the participants were noted to have low levels of spasticity in both legs.

During the study period 34 people attended NRU inpatient and outpatient services and met the criteria to take part in the study. Eighteen participants agreed to participate, with reasons for not including concerns about fatigue and inability to get transport to and from the hospital site where the study was held. Two also dropped out due to hospital admissions which then precluded their involvement.

The H-reflex was found and elicited in 15 participants with only one found to have no H-reflex during the initial tests. There was a 73% completion rate of all of outcomes measured, with four participants unable to fully complete the H-reflex assessments due to the need to use the bathroom or being uncomfortable from sitting. The length of time taken to find and elicit an initial H-reflex varied across the participants, with the shortest being 10 minutes and the longest 45 minutes. No adverse effects were found during the study and the H-reflex protocol was felt to be reliable, illustrated by the stability of the M wave amplitude data obtained during each participant's assessments. However, the H-reflex amplitude data was found to be less reliable, with large variations found during the assessments for most participants. And while the H-reflex was found to be safe and feasible in people with moderate to severe MS, its suitability as a measure of spasticity in this group remains questionable, which will be discussed in the next few sections.

This study found the H-reflex latency to be within normal levels with an average mean onset of 31.4 ± 0.7ms. This is different to other studies involving people with spasticity who reported the latency of the H-reflex to be shortened (Levin *et al.*, 1993; Bakheit *et al.*, 2003; Tekgül *et al.*, 2013). This difference may be due to levels of spasticity of the participants, as the other studies involved participants with higher levels of spasticity and a median MAS score of 2 (Levin

et al., 1993; Bakheit *et al.*, 2003; Tekgül *et al.*, 2013). The overall average H-reflex amplitude was found to be 0.27 ± 0.02mV, with a small increase to the amplitude over time when comparing pre and post APT cycling data (range 7-19%). However, a large range was found across the participants at these time points, which reduces the meaningfulness of these figures.

The H-reflex amplitude is also known to be increased in people with spasticity (Palmieri *et al.*, 2004; Voerman *et al.*, 2005). Most studies have reported the change in reflex using the H/M ratio, with few reporting this using the change in reflex amplitude like this study chose to. Only two studies involving a cycling intervention and participants with spasticity reported the change in amplitude like this study. However, one reported no data to compare to and the other reported paired reflex depression thus precluding comparison (Phadke *et al.*, 2009; Rayegani *et al.*, 2011). The only other data found was from a study by Goulart et al (2000) who assessed the effects of postural adjustments in healthy participants (n=15), considering the H-reflex amplitude and latency while in supine, sitting and standing positions. They reported the average amplitude of their participants in supine to be 5.93 ± 0.78mV, in sitting to be 6.32 ± 1.05mV and in standing to be 6.85 ± 1.22mV, all of which are much higher values than found in this study.

Like the first study (Chapter 4), participants were found to have low levels of spasticity on initial assessment and minimal change was noted to the MAS and self-reported spasticity using the NRS. This again could be due to the lack of sensitivity shown by the MAS (Blackburn *et al.*, 2002; Pandyan *et al.*, 2003; Ansari *et al.*, 2006; Mutlu *et al.*, 2008; Craven *et al.*, 2010). It could also be due to the sample the study used, as it was recruited by convenience and so not fully representative of the local MS population. The NRS was selected for use as a PROM due to being easy to follow, quick to undertake and its proven validity and reliability in pwMS with spasticity (Farrar *et al.*, 2008; Anwar *et al.*, 2009). The meaningful change in NRS score has been established as a reduction of 18% (Farrar *et al.*, 2008) which five participants achieved in this study. And like the first study, although several patient's perceived there to be a change in their lower limb spasticity, the same change was not found objectively.

The MAS was used by this study alongside the H-reflex to be comparable with other studies measuring spasticity in pwMS or using APTs (Motl *et al.*, 2006, 2007; Sosnoff *et al.*, 2010; Rayegani *et al.*, 2011). However, the data reported by these studies was inconsistent, with detail often missing on the protocol of measurement including the actual testing position for both H-reflex and MAS. Several studies documented that the MAS was assessed in the right calf muscle and in the same position as the H-reflex assessment, without further clarification (Motl *et al.*, 2006, 2007). While Sosnoff et al (2010) only reported they measured the most affected leg of each participant, and Rayegani et al (2011) included no details regarding MAS testing. Similarly, the consistency and detail reported during H-reflex testing was also limited. Most studies reported the equipment used and stimulation parameters, but the test position was simply reported as being in a comfortable and semi-reclined position (Motl *et al.*, 2006, 2007; Phadke *et al.*, 2009; Sosnoff *et al.*, 2010). While the only study to use an APT and a more disabled population made no mention of the H-reflex test position, equipment, parameters or procedure itself (Rayegani *et al.*, 2011).

The most frequent method of analysis of the H-reflex was by using the H/M ratio (Motl *et al.*, 2006, 2007; Sosnoff *et al.*, 2010; Rayegani *et al.*, 2011), with Rayegani et al (2011) also reporting the change in reflex amplitude. While Phadke et al (2009) reported the change in H-reflex amplitude by using paired H-reflex depression instead. For data analysis, one study used the average of four recordings (Phadke *et al.*, 2009) and three used the average of five (Motl *et al.*, 2006, 2007; Sosnoff *et al.*, 2010), while only one study commented on the reliability of the recordings obtained during testing (Motl *et al.*, 2006) without presenting data to support this. While all the studies reported a significant reduction in spasticity using the H/M ratio, the lack of detail reported must question the reliability of the results. All but one of these studies used an ergometer and it is unclear how each minimised limb or postural movement between intervention and testing in a semi-reclined position, both of which are known to influence the reflex (Misiaszek, 2003; Palmieri *et al.*, 2004; Voerman *et al.*, 2005).

It has been suggested the ideal position to complete this test should be in a semi-reclined position with the head resting on a pillow, the hip and knee

flexed, and the ankle fixed in a neutral position (Burke, 2016). However, it was not possible to do this during the study without moving each participant. The decision was made to complete the H-reflex assessments while attached to the APT and in a seated position to prevent electrode displacement and minimise a change in background muscle activity. The right lower limb was fixed in position using a wooden step under the APT foot plate, which held the foot in a neutral position.

However, several issues with the testing and cycling position became apparent during the study which may have contributed to the results obtained. The first was the seating position of the participants. Those who were able to walk used a standard chair (n=9), while the other participants used their own wheelchairs which included an attendant propelled (n=1), self-propelled (n=3) and electric powerchairs (n=2). The chairs were stabilised against the wall but were different in height, support and backrests, altering the position of the participant in relation to the wall and the APT. This precluded head support and for smaller patients the position required to facilitate cycling precluding the right leg being fixed using the wooden box. Wedges and weights were required underneath the footplate to help fix and stabilise the leg. As the H-reflex is known to be influenced by factors such as change in head, body position and background muscle activity (Misiaszek, 2003; Voerman *et al.*, 2005), the difficulties with positioning described could have contributed and influenced the data collected.

A second issue was the time taken to complete the outcome measures and the intervention. The shortest duration was 75 minutes, with the longest 150 minutes. This was in part due to the disability levels of the participants, as for several equipment was required to aid transfer between their chair and bed. It was also due to the time taken to set up the equipment and complete the initial H-reflex test. While the right leg was fixed in position as described previously, the left leg was not and following completion of the H-reflex tests several participants reported their legs to feel stiffer from holding this position for a prolonged period. Several participants also reported discomfort from sitting in one position for so long, which also impacted on the completion of the post cycling tests. One person required to stop before the end due to this discomfort

and three due to the need to use the bathroom. The time taken to complete the intervention and outcome measures was not reported to be an issue by other studies, nor was participant comfort. So, it could be assumed this may be due to the increased disability levels of the participants in this study.

The method of measuring the H-reflex could also be considered a potential contributing factor for some of the issues highlighted by this study. The H/M ratio is the most frequently used method of measurement by studies. However, due to the challenges of finding and completing the H-reflex tests, the researcher opted to focus on measuring the presence, amplitude and consistency of the H-reflex. This was in part due to the time taken to complete the measurements as well as the difficulty in finding the reflex in many participants. And while the H/M ratio is reported to be the more reliable test, this is more important when testing on different days and used to standardise the electrode position. Overall, this was not thought to have impacted on the data obtained, as the same variability in the participants data would also have been reflected in the H/M ratio. However, this precluded comparison with other studies and should be considered by future studies to allow this.

And finally, the environment used to complete the study was identified as another issue. Due to Covid-19 restrictions the only space permitted for use was a clinic room next to the ward reception area. This area was noisy and frequent interruptions during and between H-reflex tests occurred. This again could have affected background muscle activity and postural tone of the participants, and so influencing the results.

Overall, the testing position, comfort of the participants and length of time taken to complete the cycling and H-reflex tests were felt to be the main contributing factors to the data obtained. This could be addressed by use of a tilt in space wheelchair or electric recliner chair to provide a more supportive and comfortable position for testing and between measures. This could then be adjusted to facilitate the cycling intervention. Furthermore, measuring the H/M ratio would ensure the reliability of the electrode position between positional adjustments from testing and cycling. In addition, the study time could be reduced by either reducing the intervention length, the number of assessments taken and by being more specific in MAS measures. Other studies that

successfully showed a reduction in spasticity using the H-reflex used a cycling intervention of 20 minutes and assessed the MAS in the calf muscles of the testing leg (Motl *et al.*, 2006, 2007; Sosnoff *et al.*, 2010). This study chose to follow a similar protocol for MAS assessment and cycling length as Chapter 4 to plan for larger RCT. However, this did contribute to the length of the trial for each participant. A shorter intervention length, assessing only the MAS in the soleus muscle from the testing leg, alongside a more comfortable testing position may help improve the stability of the data.

While adopting these changes may help reduce the influences known to cause variation in the H-reflex, its potential use as a measure of spasticity remains questionable. It is highly affected by the central nervous system and for people with higher levels of disability who already display high variability from their pathology and symptoms, it may be less appropriate to use. In addition, the expertise, equipment and time taken to complete it make it less useful. Many hours are required to become competent and proficient in testing the H-reflex. Even after extensive training this process was found to be challenging in many of the participants. From the current body of evidence, a combination of biomechanical and neurophysiology methods appear to be the most reliable method to assess spasticity. However, the evidence for use in people with higher levels of disability are limited and the same issues apply regarding skill, training, costs and space requirements to use them. Studies continue to highlight measurement of spasticity to be problematic and further research is needed to identify a more accurate way of doing so across all levels of disability.

5.6.1 Study limitations

There were several limitations of this study. The Covid-19 pandemic delayed the start by a year and had an impact on recruitment when the restrictions eased. Most of the participants were recruited from outpatient clinics and, due to the lack of funding for this study, had to be able to make their own way to hospital. As a result, the sample used cannot be considered fully representative of the more disabled MS population.

The participants recruited by the study were also found to have low levels of spasticity on assessment. This study chose to include participants with an MAS of ≥1, with the aim of being as inclusive as possible. However, recruiting participants with higher levels of spasticity may have been better to help to determine any interventional effects. This should be considered by future studies.

The study made several deviations from the planned protocol illustrated in Appendix 15. The NRS was planned to be taken before and after the APT cycling, and then again following completion of the study and after the MAS was assessed. However, this was only taken twice, before APT cycling and after completion of the MAS. This may have resulted in data on the immediate effects of APT being lost. In addition, it was agreed the researcher would focus measuring the presence, latency and change in H-reflex amplitude only. This was due to the time taken to find the H-reflex and the complexity in doing so. This limited the comparability of the results to other studies.

The equipment used may also have limited the study. The equipment was old and dated, resulting in compatibility issues. The software required to record the EMG data was only compatible with older versions of Microsoft and could only be used with one laptop within the department. This laptop failed during one participant's trial (P8) preventing data being saved for analysis. In addition, the electrode used to record the H-reflex was secured using an elastic strap which was difficult to complete by one person. This process often resulted in displacement and loss of response, and repeating the process again. This added to the time taken to complete the assessments.

The study was also limited by the availability of the clinician and the room used. The only space available for use was a clinic room outside the NRU ward and next to the reception area, as restrictions prevented access to quieter spaces within the ward. This area was busy, noisy and frequent interruptions to the room during the study occurred. In addition, this room was only available for use on four sessions a week, and due to the clinician's existing NHS workload this restricted the study to one morning a week. All were felt to impact on the study.

Similar to the study in Chapter 4, no formal process evaluation was undertaken as recommended by the Medical Research Council (Moore *et al.*, 2015). Again this should be considered for any future studies. Lastly, the researcher completed all the outcome measure assessments as well as overseeing the cycling intervention which could have introduced potential bias (Smith *et al.*, 2014).

5.7 Conclusions

Overall, the study showed that a single session of APT cycling did not change spasticity in people with moderate to severe MS. Furthermore, it was not possible to determine if the H-reflex was a more sensitive measure of spasticity in people with moderate to severe MS. Testing was found to be feasible and produced no adverse effects, although the data obtained from the H-reflex was highly variable. It was felt that other factors may have influenced this variability such as the participant position, comfort and length of time required to complete the measures.

Future studies should consider the number of assessments and length of intervention, as well as the testing position, to improve the comfort of the participants in people with higher levels of disability. The suitability of the H-reflex as a measure of spasticity in this group of participants though remains unproven. Further research is needed to establish if this is a suitable outcome in people with moderate to severe spasticity or to identify a more appropriate measure of spasticity for use.

Chapter 6 General discussion, conclusion and recommendations

6.1 Overall discussion

The aim of this thesis was to investigate the effects of lower limb APT cycling in people with moderate to severe MS. The focus was the effects on spasticity, however the effects on cardiovascular fitness, function and quality of life were also of interest. This was undertaken by evaluating the literature, completing a systematic review and two quantitative studies.

A systematic review of the effects of cycling using lower limb APTs in people with neurological conditions was undertaken after completing a literature review. Although the focus of the PhD was pwMS, very little evidence on APT cycling in pwMS exists and so the search was expanded to include other common neurological conditions. This review included 12 articles, six using FES assisted cycling and six APT cycling alone. A meta-analysis demonstrated a statistically significant improvement in walking endurance in a small number of studies involving stroke participants. However, the effects on other outcomes were less clear as the included studies featured heterogeneous designs, used differing outcome measures, exercise prescriptions and participant disability levels, which made comparison difficult. In addition, few studies considered whether FES assisted cycling is more beneficial than APT cycling alone. The review highlighted the need for further research using RCTs, similar outcome measures, larger sample sizes and comparing both FES assisted and APT cycling interventions to fully establish the effects.

A study was carried out to evaluate the feasibility of a lower limb APT intervention in people with moderate to severe MS on the outcomes of interest (spasticity, cardiovascular fitness, function and quality of life). A four-week intervention was felt appropriate as it was the first study of its kind to use a daily APT intervention in this population, and adherence and tolerance were unknown. The study recruited from an inpatient rehabilitation unit, which had an average length of stay of seven weeks. Therefore the four-week intervention also allowed adequate time to screen, recruit and complete the study during their stay.

The study participants undertook a daily rehabilitation programme specific to their needs, with the APT group also receiving a daily cycling intervention out with this. The study demonstrated that daily cycling for 30 minutes was a feasible and safe exercise option for people with higher levels of disability from MS. It resulted in no adverse effects or increase in symptoms, and the participants were able to tolerate the intensity of treatment with 100% adherence to the intervention. Although not powered to demonstrate significance, most outcome measures showed improvements, which was found in both control and intervention groups. The APT cycling group was found to be able to cycle faster, for longer and with a higher power output by the end of the intervention. However, as this did not translate to a meaningful change in any of the outcomes used it was felt this could be due to the study design and the lack of sensitivity of certain measures used. A fully powered study of APT cycling over a longer of period of time and using community dwelling people was recommended to fully determine the effects of the APT intervention. A study of this scale was out with the confines of this PhD, however one of the main issues the study raised was that alternative, more sensitive methods of measuring spasticity was required.

The final study was conducted to consider a more suitable measure of spasticity. This study aimed to determine if neurophysiology (H-reflex) assessment was feasible and a more sensitive method of measuring of spasticity after a single session of APT cycling in people with moderate to severe MS. While the H-reflex was found to be safe and feasible, it was not found to be a more sensitive measure of spasticity than the MAS or NRS following APT cycling, as no measure showed any change. However, it was also noted that the participants had low levels of spasticity as a group. The procedure was found to be time consuming to complete, and the data obtained highly variable, which was felt to be influenced by factors such as the position and comfort of the participants, and length of assessment. Further research is merited using a more comfortable and supportive position to fully determine the use of H-reflex as a spasticity measure in this group of participants. As a result, the most appropriate measure of spasticity has yet to be identified in this population.

The order in which these studies was conducted is due to this thesis starting as an MSc in research and then continued as a PhD. The initial funding was gained to complete a four-week intervention study in people with moderate to severe MS. As this was the first study to do so it was felt appropriate to consider the feasibility of the study in people with moderate to severe MS, as well as the effect of the APT intervention on the outcomes of interest and their suitability.

Eldridge et al (2016) advised that the purpose of a feasibility study is to consider organisational and contextual factors study such as recruitment, retention, data collection and sample size, which is needed to inform a future pilot. While the purpose of a pilot study is to test the feasibility of the intervention and outcome measures prior to a RCT. However, there is often overlap in healthcare studies due to the time required to complete this, especially when involving people with higher levels of disability. Such studies in MS are limited due to the complexities and variability in the condition, the limited availability of participants and accessibility. Therefore, it was felt appropriate to consider these areas within one study. The CONSORT 2010 checklist was consulted and followed to ensure appropriate information was recorded and reported accordingly (Appendix 17).

As the APT study demonstrated the need to identify a more sensitive measure of spasticity, additional funding was gained to enable a study to consider the H-reflex as a measure of spasticity. This measure had not been used in people with higher levels of disability from MS, and so the aim was to test the outcome measure in this population. This study involved a single session of APT cycling to include a larger population, and assess the outcome at different time points and so length of the APT intervention was not relevant.

6.2 Contribution to knowledge

Research studies involving people with moderate to severe MS are limited and are frequently acknowledged as an area to address in future research. Many barriers to exercise exist for this group and so identifying the optimum type and dose of exercise is important.

All three studies have made an original contribution to the evidence base regarding exercise interventions and APT use in people with moderate to severe MS. The systematic review evaluated the use of APT cycling with and without electrical stimulation in neurological conditions, the first to consider and compare both. The second study was the first to consider a prolonged programme of APT cycling in people with moderate to severe MS. The third study aimed to consider the effects of a single session of APT cycling on spasticity using the H-reflex, and again was the first to do so in people with moderate to severe MS.

While no firm conclusions can be made by these studies, this thesis has identified that lower limb APT cycling is a safe and feasible treatment option for pwMS. In addition, the H-reflex is also a safe and feasible outcome measure to use in people with moderate to severe MS. Both studies have also added to the evidence base by using participants with higher levels of disability from MS. Lastly, like other studies this thesis corroborates the challenge of accurately and reliably measuring spasticity. Further research is needed to fully determine if the H-reflex is a more sensitive measure of spasticity or to identify a more appropriate method, as well as explore the potential benefits of APT cycling in people with higher levels of disability from MS.

6.3 Implications for practice

APTs are commonly used within gym and rehabilitation settings, and people with MS often privately purchase them to use at home. This study highlighted that cycling at a moderate intensity for 30 minutes, five times a week was safe and feasible for people with higher levels of disability and resulted in small improvements to cardiovascular fitness and cycling parameters. Research has also shown that passive exercise triggers a similar physiological response to active exercise although at a slower rate (Høier *et al.*, 2010, 2013), and so has the potential to improve health outcomes when sustained over a longer period.

Clinicians and pwMS may wish to consider regular sessions of APT cycling at moderate intensity where possible, using RPE to guide the rpm and resistance

level when cycling to optimise its effects. In addition, clinicians should consider the use of the MAS as an outcome measure in clinical practice and research. Spasticity continues to be challenging to quantify and measure, and the gold standard method of doing so has yet to be established. The MAS continues to be frequently used even though it lacks reliability and sensitivity, and clinicians should stop using it and develop a more robust measure instead.

6.4 Recommendations for future research

Suggested areas for further research;

- To determine the optimum dose, intensity and frequency of APT interventions to improve spasticity, cardiovascular fitness, function and QOL in people with moderate to severe MS

- To compare the effects of FES assisted cycling to APT cycling, and establish the most effective intervention for pwMS

- To identify valid, reliable and sensitive outcome measures that can be used in studies involving people with moderate to severe MS, especially related to spasticity, function and quality of life.

6.5 Conclusion

Exercise is an important component of managing MS, however this can be challenging for people with moderate to severe MS. Accessibility and symptoms can impact, and adaptive equipment is often required to do so. Research involving people with higher levels of disability from MS is also limited and the optimum type and dose of exercise to improve health, symptoms and function has yet to be identified. APTs are frequently used by pwMS as well as in rehabilitation settings, and although the evidence to support their use is limited it suggests they may have the potential to improve walking performance and spasticity. This thesis has shown that APT cycling is safe and feasible in people

with moderate to severe MS, and further research is merited to fully explore the potential benefits as an exercise intervention for those with higher levels of disability.

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Appendix 1 Search strategy for systematic review

Search strategy as performed in Medline, CINAHL, Embase, Epistemonikos and Google.

1.	motomed.tw.or”leg bike*”.mp.
2.	"active passive trainer*".mp.
3.	"lower body ergometer".mp.
4.	(ergometer adj (leg or lower or cycl$)).tw.
5.	"biofeedback cycle train*".tw.
6.	"passive cyclic exercise".mp.
7.	cyclo-ergometer.mp.
8.	"robot assisted therapy".mp.
9.	"robot assisted movement".mp.
10.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11.	exp Neurological Rehabilitation/
12.	exp Neurology/
13.	exp Craniocerebral Trauma/
14.	((head or brain) adj (injur* or trauma or damage*)).tw.
15.	exp Stroke Rehabilitation/ or exp Stroke/
16.	stroke*.tw.
17.	"cerebrovascular accident*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18.	exp Multiple Sclerosis/
19.	"multiple sclerosis".tw.
20.	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21.	10 and 20
22.	exp Electric Stimulation Therapy/
23.	functional electrical stimulation.tw.
24.	fes.tw.
25.	22 or 23 or 24
26.	exp Bicycling/
27.	(cycl$ or bike$ or ergomet$).tw.
28.	26 or 27
29.	fesc.tw.
30.	25 and 28
31.	29 or 30
32.	exp Spinal Cord Injuries/
33.	exp Quadriplegia/
34.	exp PARAPLEGIA/
35.	(spinal cord adj2 (injur$ or lesion$ or impair$)).tw.
36.	sci.tw.
37.	(tetraplegi$ or quadriplegi$ or paraplegi$).tw.
38.	32 or 33 or 34 or 35 or 36 or 37
39.	10 or 31
40.	20 or 38
41.	39 and 40

Appendix 2 Ethics approval study two

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 5
West of Scotland Research Ethics Service
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SW

Miss Alison Barclay
Therapy Department
PDRU
Queen Elizabeth University Hospital
G514TF

Date 26 April 2016

Direct line 0141 232 1809
E-mail WoSREC5@ggc.scot.nhs.uk

Dear Miss Barclay

Study title: **The effect of cycling using active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with Multiple Sclerosis.**
REC reference: **16/WS/0084**
IRAS project ID: **200448**

The Research Ethics Committee reviewed the above application at the meeting held on 20 April 2016. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mrs Sharon Macgregor, WoSREC5@ggc.scot.nhs.uk. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

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

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

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must

confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

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

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

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

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

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

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

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).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study 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).

Summary of discussion at the meeting (for information only)

Social or scientific value; scientific design and conduct of the study

It was noted that there was no discussion of the effect size required for a sample size computation. However, this was acceptable as the researchers are greatly limited by the number of patients available. Also, the cycling was not thought to be overly burdensome or risky for participants. No issues were raised regarding the statistics.

The Committee suggested that it might be beneficial to see if the cycling resulted in a sustained improvement once the intervention had stopped, and that the researchers might therefore consider a further assessment some time after the intervention had ended. However, this was a suggestion only and did not influence the Committee's decision.

Dr Paul advised that you do not have the funding or time to do this, but that this suggestion had also been raised during an internal review.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

It was noted that this study will be quite a big time commitment for participants, which may be acceptable for in-patients. However, if patients are expected to carry on with the study if they are discharge, this could be very onerous.

You advised that only in-patients will be included in the study. The average stay for patients is 4-8 weeks so this should be plenty of time to complete the study.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

It was not clear from the application how capacity will be assessed.

The researchers advised that patients will have the MOCA done by a clinician when they are first admitted as part of standard care. Capacity and cognition will then be assessed by the therapists in various ways using their clinical judgement (ie checking patient's understanding; being able to follow instructions).

The Committee asked whether the control group participants be offered the trainer treatment once the study is finished.

Miss Barclay confirmed that this could be made available if a patient requests it.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Other [MSQOL54]		31 March 2016
Participant consent form	1	31 March 2016
Participant information sheet (PIS) [PIS]	1	31 March 2016
REC Application Form [REC_Form_01042016]		01 April 2016
Research protocol or project proposal [Study Protocol]	1	31 March 2016
Summary CV for Chief Investigator (CI) [Lorna Paul CV]		31 March 2016
Summary CV for student [Alison Barclay CV]		31 March 2016
Summary CV for supervisor (student research) [Niall MacFarlane CV]		21 March 2016
Validated questionnaire [MSSS88]		31 March 2016

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

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

After ethical review

Reporting requirements

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

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

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

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

16/WS/0084	**Please quote this number on all correspondence**

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

Yours sincerely

Dr Stewart Campbell
Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Ms Emma-Jane Gault, University of Glasgow
Mr Paul Dearie, Greater Glasgow & Clyde NHS
Dr Lorna Paul, University of Glasgow

West of Scotland REC 5

Attendance at Committee meeting on 20 April 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Stewart Campbell	Consultant Physician & Gastroenterologist **(CHAIR)**	Yes	
Dr Roddy Chapman	Consultant Anaesthetist	No	
Dr James Curran	GP	Yes	
Dr Gillian Harold	Consultant Radiologist	Yes	
Mrs Naomi Hickey	Research Nurse	Yes	
Dr Gillian Kerr	Consultant Physician	Yes	
Dr Ahmed Khan	Consultant Psychiatrist	No	
Professor Doreen McClurg	Reader	No	
Professor Eddie McKenzie	Statistician	No	
Canon Matt McManus	Parish Priest (Vice-Chair)	Yes	
Ms Janis Munro	Key Account Manager	Yes	
Mrs June Russell	Retired (Research Chemist)	Yes	
Mr Charles Sargent	Retired	Yes	
Dr Marcel Strauss	Consultant Radiologist	Yes	
Mrs Liz Tregonning	Retired (Special Needs Teacher) (Alternate Vice-Chair)	No	

Also in attendance:

Name	*Position (or reason for attending)*
Dr Judith Godden	Scientific Officer/Manager
Mrs Sharon Macgregor	Co-ordinator

Written comments received from:

Name	*Position*
Professor Eddie McKenzie	Statistician

Appendix 3 Ethics amendment study two

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

Miss Alison Barclay
Therapy Department
PDRU
Queen Elizabeth University Hospital
G514TF

West of Scotland REC 5
West Ambulatory Care Hospital
Dalnair Street
Yorkhill
Glasgow
www.nhsggc.org.uk

Date 07 November 2016
Direct line 0141-232-1806
e-mail Wosrec5@ggc.scot.nhs.uk

Dear Miss Barclay

Study title: **The effect of cycling using active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with Multiple Sclerosis.**
REC reference: **16/WS/0084**
Amendment number: **REC Ref AM01**
Amendment date: **01 November 2016**
IRAS project ID: **200448**

Summary of Amendment;

This minor amendment refers to the extension of the intervention aspect of the project from December 2016 until April 2017.

Thank you for your letter of 01 November 2016, 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*
Notice of Minor Amendment [Email from student]	REC Ref AM01	01 November 2016

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.

16/WS/0084:	Please quote this number on all correspondence

Yours sincerely

On behalf of
Sophie Bagnall
Assistant Coordinator

Copy to: *Mr Paul Dearie, NHS Greater Glasgow & Clyde*
Miss Alison Barclay

Appendix 4 NHSGGC R&D approval

Coordinator/administrator: Paul Dearie / RP
Telephone Number: 0141 232 1810
E-Mail: Paul.Dearie@ggc.scot.nhs.uk
Website: www.nhsggc.org.uk/r&d

Clinical Research & Development
West Glasgow ACH
Dalnair Street
Glasgow G3 8SJ
Scotland, UK

11/05/2016

Ms Alison Barclay
PDRU, Queen Elizabeth University Hospital
1345 Govan Road
Glasgow
G51 4TF

NHS GG&C Board Approval

Dear Ms Barclay

Study Title:	The effect of cycling using active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with Multiple Sclerosis.
Principal Investigator:	Ms Alison Barclay
GG&C HB site	QEUH
Sponsor	NHS GG&C
R&D reference:	GN15PY148
REC reference:	16/WS/0084
Protocol no: (including version and date)	Version 1 - 31/03/2016

I am pleased to confirm that Greater Glasgow & Clyde Health Board is now able to grant **Approval** for the above study.

Conditions of Approval

1. **For Clinical Trials** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004
   a. During the life span of the study GGHB requires the following information relating to this site
      i. Notification of any potential serious breaches.
      ii. Notification of any regulatory inspections.

It is your responsibility to ensure that all staff involved in the study at this site have the appropriate GCP training according to the GGHB GCP policy (www.nhsggc.org.uk/content/default.asp?page=s1411), evidence of such training to be filed in the site file.

2. **For all studies** the following information is required during their lifespan.
   a. Recruitment Numbers on a quarterly basis
   b. Any change of staff named on the original SSI form
   c. Any amendments – Substantial or Non Substantial
   d. Notification of Trial/study end including final recruitment figures

e. Final Report & Copies of Publications/Abstracts

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.

I wish you every success with this research study

Yours sincerely,

Paul Dearie
Research Co-ordinator

CC: Dr Lorna Paul, Dr Niall MacFarlane, Ms Emma-Jane Gault

Appendix 5 Study two participant information leaflet

The effect of cycling using active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with Multiple Sclerosis.

Why have I been approached about this study?
We are inviting you to participate in this study as you have Multiple Sclerosis (MS) and have been identified by your healthcare professional as someone who would be suitable for inclusion in this study. This study is a collaboration between NHS Greater Glasgow and Clyde and the School of Medicine at the University of Glasgow; it is funded by the Chartered Society of Physiotherapy Charitable Fund. This study will also contribute towards an MSc by Research for Alison Barclay, Physiotherapist, Physically Disabled Rehabilitation Unit.

Before you decide whether or not to take part it is important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

Thank you in advance for taking the time to read this information leaflet.

What is the purpose of the study?
We do not have enough evidence to support the benefits of exercise for people with Multiple Sclerosis (MS) who have higher levels of disability. Those with higher levels of disability also find it more difficult to exercise because of their symptoms, difficulty in getting to exercise locations or access issues within e.g. sports centres. Cycling is often feasible for this group of people and can improve fitness, muscle and bone strength, spasticity and function. Lower limb active passive trainers (APT) such as the Motomed, provide cycling from a seated position. The speed, resistance and how much help the APT gives during cycling can be adjusted depending on each person's ability. The Motomed APT is shown below;

Patients who have used APTs reported improvements in spasticity in their legs and tightness and generally felt better after using it but there are almost no studies that have

looked into the effects of APTs for people with MS. Furthermore people affected with MS often buy an APT for more regular home use, despite the lack of evidence to support its use.

There is therefore a need to investigate the use of APTs in people with MS especially those with higher levels of disability who have limited options for exercising. This study will investigate the effectiveness of APTs to help manage symptoms associated with MS.

Do I have to take part?
No; taking part in research is entirely voluntary; therefore it is up to you to decide. You should read this information leaflet and if you are interested in taking part you should advise the research physiotherapist. When you are assessed for the project you will be screened to make sure it is safe and suitable for you to take part in the study. If you wish to go ahead you will be asked to sign a consent form to show that you agree to take part. You would still continue to receive your normal therapy, interventions and medications under the care of the rehabilitation team according to standard clinical practice. If you decide to take part you are still free to withdraw at any time and without giving a reason. Your decision will not have any effect on the standard of care you receive.

What will happen to me if I take part?

If you agree to take part you will be randomly assigned to either a control group or intervention group by selecting an envelope that will advise you which group you are in. If you are in the control group you will receive your normal care which includes e.g. review of medication, nursing care, physiotherapy, occupational therapy etc. as appropriate. If you are assigned to the intervention group you will receive your normal in-patient care plus a four-week programme of exercise on the APT from Monday to Friday each week. Each exercise session will begin with a 2-minute warm up, where yours legs are assisted to move by the APT at 10 revolutions per min (rpm). Next, we will ask you to cycle for up to 26 minutes, at a speed you feel able to complete, and using the feedback on the display to help with this. If you are unable to actively cycle at any point during the 26-minute exercise period, or if your legs spasm, the Motomed APT will cycle for you. The final phase is a cool down where you will have 2 minutes of passive cycling where again the APT will do the cycling for you at 10rpm.

For all those who take part in the study at your first appointment, you will be asked some questions to ensure you are eligible to take part in the study. If you are eligible and wish to take part, you will be asked to provide written informed consent. You will then be assessed by a physiotherapist who will complete various questionnaires and outcome measures with you. This will involve completing a walking test if you are able, and two questionnaires, an assessment of your muscle tightness and assessment of fitness. The assessment will take no longer than an hour. These measures will be re-assessed in a similar way four weeks later.

What are the possible disadvantages or risks of taking part?

There are no major risks in taking part in this study. Regular exercise is a key part of the management of MS. Some people may notice muscle soreness or tiredness which is generally short lasting. In addition all cycling sessions with be monitored by a physiotherapist to ensure participants' safety.

What are the possible benefits of taking part?

We hope taking part in the study will improve your health and condition as the existing evidence suggests regular exercise is helpful. The information obtained from this study may also help improve the treatment of other people with MS.

What about expenses or payments involved with taking part in the study?

You will not be paid for participating in the study.

What happens when the research study stops?

As this is a small study, if the results are positive, it is likely that we will need to perform a larger trial before we can state for certain the benefits of APT's for people affected by MS. However the data from this pilot study will help to inform a larger trial.

Will my taking part in this study be kept confidential?

Yes, all information collected from you during the study will be kept strictly confidential and treated with normal ethical and legal practice for data collection. With your permission we will inform your Rehabilitation Consultant about your involvement in this study. In addition representatives of the Sponsor NHS Greater Glasgow and Clyde, may access your medical notes where they relate to the study in order to monitor that the study is being carried out properly. Also, with your permission we will transfer the data collected during the study anonymously for analysis.

What will happen if I don't want to continue in the study?
You can withdraw at any time without giving us any reason. Any information collected prior to your withdrawal will still be used.

What If there is a problem?
Should you have a concern about any aspect of the study, in the first instance you should contact the research physiotherapist, using the contact details below, who will do their best to answer any questions. If this does not resolve the issue, and you would like to formally complain you can do this through the NHS Complaints Procedure, details can be obtained from the Patients, Relations and Complaints Office in Scotland. Independent advice about the study can be obtained from Heather Cameron tel: (0141) 201 0488.

What happens to the results of the research study?
It is intended that the results of the study will be published in medical literature and/or presented at healthcare conferences. All data will be anonymised before this and no-one will be able to identify you. Should you wish to know the results of the study then we will send you a summary of the main findings once the research is complete.

Who is organising funding the research?
This study is funded by Chartered Society of Physiotherapy Charitable Fund.

Who has reviewed this study?
All research in the NHS is looked at by the Research Ethics Committee, an independent group of people who aim to protect patient safety, rights, well-being and dignity. This study has been reviewed and given favourable opinion by the West of Scotland Research Ethics Committee.

Participation, further information and contact details.
Should you wish to take part in this study or if you require any further information about this research study please contact:

Alison Barclay
Highly Specialist Physiotherapist
Therapy Department,
PDRU,
Queen Elizabeth Hospital,
1345 Govan Road,
Glasgow

Tel: **01412012655**
Email:
Alison.barclay@ggc.scot.nhs.uk

G514TF

Thank you for taking the time to read this information leaflet

Appendix 6 Study two consent form

NHS Greater Glasgow and Clyde

University of Glasgow

Patient Identification Number for this study:

STUDY CONSENT FORM

Title of Project:The effect of cycling using active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with Multiple Sclerosis (MS).

Name of Researcher: Alison Barclay

Please initial boxes

1. I confirm that I have read and understand the participant information sheet (v 1 dated ……) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. All data (personalised and study data) collected up to the point of withdrawal from the study will be retained until the end of the study. ☐
3. I understand thatrelevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team or from regulatory authorities. I give permission for these individuals to access my records. ☐
4. I agree to my Rehabilitation Consultant being informed of my participation in this study ☐
5. I give permission for data collected during the study to be transferred anonymously for analysis. ☐
6. I understand that this research is part of an MSc degree ☐
7. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Researcher	Date	Signature
Witness	Date	Signature

*1 copy for participant and 1 copy for researcher

Appendix 7 Study two data collection pack

Participant Demographic sheet

Participant No; _____

Date; _____

Time; _____

Date of admission; _____

DOB/Age; _____

Sex (please circle); M F

Type MS (please circle); PPMS SPMS RRMS Benign MS

EDSS score; _____

Time since diagnosis; _____

PMH;

DH;

SH; _____

_____

Mobility status; Walking aid; _____

Splints (please circle); Yes No

Distance able to mobilise; _____

Smoker (please circle); Yes No

Number a day; _____

Alcohol intake; Yes No (Units per week); _____

Post code;

Level of education; University College Further Education High school

Participant number; _____ Date; _____

Modified Ashworth Scale

Time; _____

Muscle Group	Right	Left
Hip flexors		
Hip extensors		
Adductors		
Quadriceps		
Hamstrings		
Gastrocnemius		
Soleus		
Invertors		
Comments		

Grading/Description

0: No increase in tone,
1: Slight increase in muscle tone, manifested by a catch and release or by min resistance at the end of ROM when the affected group is moved into flexion or extension
1+: Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of ROM
2: More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3: Considerable increase in muscle tone, passive movement difficult,
4: Affected part(s) rigid in flexion or extension

OUES

Exercise Testing

Participant no _____

Date & Time _____

	Gas concentration	Gas Volume	Gas Volume + 1	Temperature	HR (sats machine/)
At rest (2 mins)					
2 min warm up passive					
2 mins cycling resist 0					
2 mins cycling resist 1					
2 mins cycling resist 2					
2 mins cycling resist 3					

Exercise Testing

Participant no _____

Date & Time _____

	Gas concentration	Gas Volume	Gas Volume + 1	Temperature	HR (sats machine/)
At rest (2 mins)					
2 min warm up passive					
2 mins cycling resist 0					
2 mins cycling resist 2					
2 mins cycling resist 4					
2 mins cycling resist 6					

Timed 25ft Walk

Time; _____

- Measure a 25ft (7.62m) distance in a quiet corridor or gym
- Mark the floor with tape on the start and 25ft lines
- Place a chair at each side of the start and 25ft lines
- Assistive devices can be used but should be kept consistent and documented
- If physical assistance is required to walk then the test should not be performed
- The test should be performed at the fastest speed possible but safely
- Start timing when the individual is instructed to 'Go' and their leading foot crosses the starting line
- Stop timing when the individual's leading foot crosses the 25ft line
- During the test do not offer words of encouragement or body language to speed up
- The test is administered twice with the participant walking back the same distance

Instructions

"The object of the test is to walk at your fastest but safe speed".

Start of test
"Start now, or whenever you are ready"

Trial 1 time	
(s)	
****Two Minute Rest Between Walks****	
Trial 2 Time	
(s)	
Walking aid	
None [0] 1 stick/crutch [1] 2 sticks/crutches [2] 3 wheeled walker [3] 4 wheeled walker [4]	
Assistive device	
None [0] AFO [1] FES [2]	

Notes;

Functional Independence Measures (FIM)

	Start Date; **Time;**	**Finish Date;** **Time;**
Self-Care		
Eating		
Grooming		
Bathing		
Dressing - upper body		
Dressing – lower body		
Toileting		
Sphincter		
Bladder Mx		
Bowel Mx		
Transfers		
Bed, chair, wheelchair		
Toilet		
Tub, shower		
Locomotion		
Walk/wheelchair		
Stairs		
Communication		
Comprehension		
Expression		
Social cognition		
Social interaction		
Problem solving		
Memory		
TOTAL FIM Score		

Levels
Independent
7 Complete Independence (Timely, Safely)
6 Modified Independence (Device)
NO HELPER, Modified Dependence
5 Supervision (Subject = 100%+)
4 Minimal Assist (Subject = 75%+)
3 Moderate Assist (Subject = 50%+)
Complete Dependence
2 Maximal Assist (Subject = 25%+)
1 Total Assist (Subject = less than 25%
Note: Leave no blanks. Enter 1 if patient is not testable due to risk

MSSS-88

This questionnaire asks how **bothered** you have been by your spasticity **in the past two weeks**.

- **By spasticity we mean muscle stiffness and spasms.**

- By **bothered** we mean how distressed or upset you have been by any of the following problems.

- For each statement, please **circle** the **one** number that best describes how you feel.

- Please answer **all** questions even if some seem rather similar to others, or irrelevant to you.

Section 1:

This section concerns muscle stiffness.

As a result of your *spasticity*, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Extremely bothered
01. Stiffness when walking?	1	2	3	4
02. Stiffness anywhere in your lower limbs?	1	2	3	4
03. Stiffness when you are in the same position for a long time?	1	2	3	4
04. Stiffness first thing in the morning?	1	2	3	4
05. Tightness anywhere in your lower limbs?	1	2	3	4
06. Your lower limbs feeling rigid?	1	2	3	4
07. Stiffness when standing up?	1	2	3	4
08. Tightness in your muscles?	1	2	3	4
09. Stiffness that is unpredictable?	1	2	3	4
10. Feeling that your muscles are pulling?	1	2	3	4
11. Stiffness in your whole body?	1	2	3	4
12. Your whole body feeling rigid?	1	2	3	4

Section 2:

This section concerns pain and discomfort.

As a result of your *spasticity*, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Extremely bothered
13. Feeling restricted and uncomfortable?	1	2	3	4
14. Feeling uncomfortable sitting for a long time?	1	2	3	4
15. Painful or uncomfortable spasms?	1	2	3	4
16. Pain when in the same position for too long?	1	2	3	4
17. Feeling uncomfortable lying down for a long time?	1	2	3	4
18. Difficulties finding a comfortable position to sleep in bed?	1	2	3	4
19. Pain in the muscles on getting out of bed in the morning?	1	2	3	4
20. Pain in the muscles provoked by movement?	1	2	3	4
21. Constant pain in the muscles?	1	2	3	4

Section 3:

This section concerns muscle spasms.

As a result of your *spasticity*, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Extremely bothered
22. Spasms that come on unpredictably?	1	2	3	4
23. Powerful or strong spasms?	1	2	3	4
24. Spasms when first getting out of bed in the morning?	1	2	3	4
25. Spasms provoked by changing positions?	1	2	3	4
26. Spasms provoked by movement?	1	2	3	4
27. Spasms where your leg kicks out in front of you?	1	2	3	4
28. Spasms provoked by certain positions?	1	2	3	4
29. Spasms disturbing sleep?	1	2	3	4
30. Spasms when doing certain tasks?	1	2	3	4
31. Spasms when travelling over bumps or cobbles?	1	2	3	4
32. Spasms where your knees pull up?	1	2	3	4
33. Spasms causing legs to hit things?	1	2	3	4
34. Spasms provoked by touch?	1	2	3	4
35. Spasms pushing you out of a chair or wheelchair?	1	2	3	4

Section 4:

This section concerns the effect of spasticity on your daily activities.

As a result of your spasticity, how much have you been limited in your ability over the past two weeks to carry out the following daily activities?	Not at all limited	A little limited	Moderately limited	Extremely limited
36. Putting on your socks or shoes?	1	2	3	4
37. Doing housework such as cooking or cleaning?	1	2	3	4
38. Getting in and out of a car?	1	2	3	4
39. Getting in and out of shower and/or bath?	1	2	3	4
40. Sitting up in bed?	1	2	3	4
41. Getting into or out of bed?	1	2	3	4
42. Turning over in bed?	1	2	3	4
43. Getting into or out of a chair?	1	2	3	4
44. Getting dressed or undressed?	1	2	3	4
45. Getting on or off the toilet seat?	1	2	3	4
46. Drying yourself with a towel?	1	2	3	4

Section 5:

This section concerns the effect of spasticity on your ability to walk.

If you cannot take any steps at all, even with help, please tick this box and ignore questions 47 to 56. ☐

As a result of your spasticity, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Extremely bothered
47. Difficulties walking smoothly?	1	2	3	4
48. Being slow when walking?	1	2	3	4
49. Having to concentrate on your walking?	1	2	3	4
50. Having to increase the effort needed for you to walk?	1	2	3	4
51. Being slow when going up or down stairs?	1	2	3	4
52. Being clumsy when walking?	1	2	3	4
53. Tripping over or stumbling when walking?	1	2	3	4
54. Feeling like you are walking through treacle?	1	2	3	4
55. Losing your confidence to walk?	1	2	3	4
56. Feeling embarrassed to walk?	1	2	3	4

Section 6:

This section concerns the effect of spasticity on your body movement.

As a result of your spasticity, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Extremely bothered
57. Difficulties moving freely?	1	2	3	4
58. Difficulties moving smoothly?	1	2	3	4
59. Limited range of movement?	1	2	3	4
60. Difficulties moving parts of your body?	1	2	3	4
61. Difficulties bending your limbs?	1	2	3	4
62. Your body being resistant to movement?	1	2	3	4
63. Your body or limbs feeling locked?	1	2	3	4
64. Awkward or jerky movement?	1	2	3	4
65. Difficulties straightening your limbs?	1	2	3	4
66. Difficulties relaxing parts of your body?	1	2	3	4
67. No control over your body?	1	2	3	4

Section 7:

This section concerns the effect of spasticity on your feelings.

As a result of your spasticity, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Extremely bothered
68. Feeling frustrated?	1	2	3	4
69. Feeling less confident in yourself?	1	2	3	4
70. Feeling inadequate?	1	2	3	4
71. Feeling low?	1	2	3	4
72. Feeling irritated?	1	2	3	4
73. Feeling angry?	1	2	3	4
74. Feeling depressed?	1	2	3	4
75. Loss of self-worth?	1	2	3	4
76. Feeling like a failure?	1	2	3	4
77. Feeling frightened?	1	2	3	4
78. Crying (tearful)?	1	2	3	4
79. Feeling panicky?	1	2	3	4
80. Feeling nervous?	1	2	3	4

Section 8:

This section concerns the effect of spasticity on your social functioning.

As a result of your spasticity, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Extremely bothered
81. Difficulties going out?	1	2	3	4
82. Feeling isolated?	1	2	3	4
83. Feeling vulnerable?	1	2	3	4
84. Difficulties finding energy for other people?	1	2	3	4
85. Feeling reluctant to go out?	1	2	3	4
86. Feeling less sociable?	1	2	3	4
87. Difficulties with relationships with other family members?	1	2	3	4
88. Difficulties interacting with people?	1	2	3	4

MSQOL-54

This survey asks about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3, ...)

If you are unsure about any answers, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need helping reading or marking the form.

1. In general, would you say your health is; (circle one number)

Excellent 1

Very good.....2

Good.....3

Fair.....4

Poor.....5

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

Much better now than a year ago.....1

Somewhat better now than one year ago.....2

About the same.....3

Somewhat worse now than one year ago.....4

Much worse now than one year ago.....5

3-12. The following question are about activities you might do during a typical day. Does **your health** limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing several flights of stairs	1	2	3
7. Climbing one flight of stairs	1	2	3
8. Bending, kneeling or stooping	1	2	3
9. Walking more than a mile	1	2	3
10. Walking several blocks	1	2	3
11. Walking one block	1	2	3
12. Bathing and dressing yourself	1	2	3

13-16. During the **past 4 weeks** have you had any of the following problems with your work or other regular daily activities **as a result of you physical health**?

	YES	NO
13. Cut down on the amount of time you could spend on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

17-19. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious).

	YES	NO
17. Cut down on the amount of time you could spend on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

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

Not at all 1

Slightly.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

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

None 1

Very mild.....2

Mild.....3

Moderate.....4

Severe.....5

Very severe.....6

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

Not at all 1

Slightly.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

23-32. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks .....**

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you ever been a nervous person?	1	2	3	4	5	6
25. Have you ever felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you ever felt calm and peaceful?	1	2	3	4	5	6
27. Did you have lots of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6
32. Did you feel well rested on waking in the morning?	1	2	3	4	5	6

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

All of the time 1

Most of the time.....2

Some of the time.....3

A little of the time.....4

None of the time.....5

34-37. How TRUE or FALSE is each of the following statements for you.

	Definitely True	Mostly True	Not sure	Mostly False	Definitely False
34. I seem to get sick a little easier than other people	1	2	3	4	5
35. I am as healthy as anybody I know	1	2	3	4	5
36. I expect my health to get worse	1	2	3	4	5
37. My health is excellent	1	2	3	4	5
27. Did you have lots of energy?	1	2	3	4	5
28. Have you felt downhearted and blue?	1	2	3	4	5
29. Did you feel worn out?	1	2	3	4	5

Health Distress

How much of the time during the **past 4 weeks** ….

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
38. Were you discouraged by your health problems?	1	2	3	4	5	6
39. Were you frustrated about your health?	1	2	3	4	5	6
40. Was your health a worry in your life?	1	2	3	4	5	6
41. Did you feel weighed down by your health problems?	1	2	3	4	5	6

Cognitive Function

How much of the time during the **past 4 weeks** ….

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
42. Have you had difficulty concentrating and thinking?	1	2	3	4	5	6
43. Did you have trouble keeping your attention on an activity for long?	1	2	3	4	5	6
44. Have you had trouble with your memory?	1	2	3	4	5	6
45. Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?	1	2	3	4	5	6

46-50. The next set of questions are about your sexual function and your satisfaction with your sexual function. Please answer as accurately as possible about your function **during the last 4 weeks only**.

How much of a problem was each of the following for you **during the past 4 weeks**?

MEN	Not a problem	A little of a problem	Somewhat of a problem	Very much a problem
46. Lack of sexual interest	1	2	3	4
47. Difficulty getting or keeping an erection	1	2	3	4
48. Difficulty having an orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

WOMEN	Not a problem	A little of a problem	Somewhat of a problem	Very much a problem
46. Lack of sexual interest	1	2	3	4
47. Inadequate lubrication	1	2	3	4
48. Difficulty having an orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

50. Overall, how satisfied were you with your sexual function **during the past 4 weeks?**

Very satisfied 1

Somewhat satisfied.....2

Neither satisfied nor dissatisfied.....3

Somewhat dissatisfied.....4

Very dissatisfied.....5

51. During the **past 4 weeks** to what extent have problems with your bowel or bladder function interfered with your normal social activities with family, friends, neighbours or groups?

Not at all 1

Slightly.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

52. During the **past 4 weeks**, how much did pain interfere with your enjoyment of life?

Not at all 1

Slightly.....2

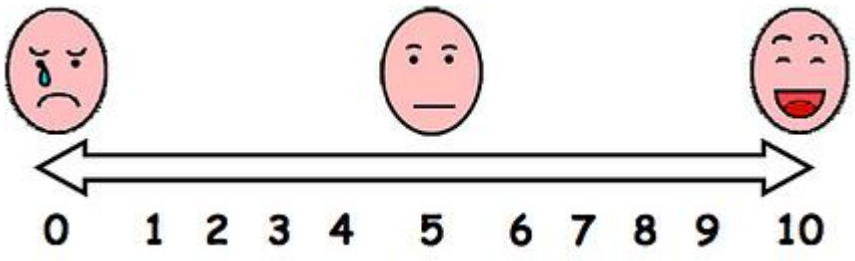
Moderately.....3

Quite a bit.....4

Extremely.....5

53. Overall, how would you rate your own quality-of-life?

Circle one number on the scale below;



Worst possible QOL Best possible QOL

(As bad as or worse

than being dead)

54. Which best describes how you feel about your life as a whole?

Terrible 1

Unhappy.....2

Mostly dissatisfied.....3

Mixed – about equally satisfied and dissatisfied.....4

Mostly satisfied.....5

Pleased.....6

Delighted.....7

LL APT Data Collection Sheet

Participant no _____

Time _____

Session number	Duration of activity; active	Duration of activity; passive	% activity with L leg	% activity with R leg	Total distance cycled	Distance active	Distance passive	Average RPM	RPE score	Resistance level
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
20										

Appendix 8 Study two participant therapy sessions

Intervention group

Participant Number	PT sessions	OT sessions	SLT sessions	Psychology sessions
P01	27	11	0	0
P03	28	22	1	4
P06	32	3	0	1
P07	20	9	0	0
P08	30	4	0	1
P09	24	4	0	3
P12	31	9	0	0
P15	32	3	0	0
P16	30	13	0	0
P18	25	12	0	1
P19	30	3	0	0
P21	30	14	1	2
P22	32	18	0	0
P23	29	4	0	0
P24	30	8	0	0
total	430	137	2	12
average	28.7	9.1	0.1	0.8
median	30	9	0	0

Control group

Participant Number	PT sessions	OT sessions	SLT sessions	Psychology sessions
P02	29	12	0	0
P04	25	14	0	2
P05	29	14	5	4
P10	30	15	0	0
P11	31	4	0	1
P13	26	14	0	0
P14	32	33	0	0
P17	26	22	0	4
P20	30	4	1	0
total	258	132	6	11
average	28.7	14.7	0.7	1.2
median	29	14	0	0

Appendix 9 Ethics approval study three

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

Dr Stuart Gray
Institute of Cardiovascular and Medical Sciences
University of Glasgow
Glasgow
G12 8TA

West of Scotland REC 3
West of Scotland Research Ethics Service
West Glasgow Ambulatory Care Hospital
(former Royal Hospital for Sick Children Yorkhill)
Dalnair Street
Glasgow G3 8SJ
www.nhsggc.org.uk

Date 4th July 2019
Direct line 0141 232 1803
E-mail WOSREC3@ggc.scot.nhs.uk

Dear Dr Gray

Study title:	**Does a single session of cycling using lower limb active passive trainers reduce spasticity, as measured by the H-reflex, in people with moderate to severe Multiple Sclerosis?**
REC reference:	**19/WS/0103**
IRAS project ID:	**255621**

The Proportionate Review Sub-Committee of the West of Scotland REC 3 reviewed the above application on 04 July 2019.

Provisional opinion

The Sub-Committee would be content to give a favourable ethical opinion of the research, subject to clarification of the following issues and/or the following changes being made to the documentation for study participants:

Number	Action Required
1	The wrong category was ticked in the filter page of the IRAS Application so as a result question 19b – clinical interventions – was missing so details of the interventions should be submitted in the same format as question 19a. As the IRAS Application Form did include the detailed information of the clinical interventions it was agreed that you do not require to revise the Form.
2	The recruitment and consent arrangements require to be clarified together with who would take consent in the gym setting. Participants must be able to opt in. Also who would assess capacity as cognition could be an issue in people with MS. A flow chart would be helpful in this regard.
3	An explanation of what is involved in measuring the H Reflex is required together with whether there are any potential risks to participants with this procedure.
4	An explanation of what is involved in 'small stimulation' is required and how often the measures will be taken.
5	Changes to the Participant Information Sheet (PIS)
	An explanation of 'Spasticity' should be given early on in the PIS. At 'What will happen to me if I take part' it states 'how stiff your feel'. This should be 'how stiff you feel'. There should be more detail about what is involved in 'small stimulation to be applied to the nerve at the back of the knee' as it states that this could be 'a little

	uncomfortable' and the participant can withdraw from the study. The PIS should explain that the plan is to do outcome measures 5 times in the 2 hours and then 4 times post cycle. It should also be made very clear that if the participant gets significant cramping/painful spasms then they can stop and are able to withdraw from the study if they wish and not just that the bike will continue to cycle for them. It states that the study has been reviewed by the 'West of Scotland Research Ethics Committee'. This should be revised to state 'West of Scotland Research Ethics Committee 3'.
6	Changes to the Consent Form
	The version number is missing. It only states 'version' with no number.

When submitting a response to the Sub-Committee, the requested information should be electronically submitted from IRAS. Please refer to the guidance in IRAS for instructions on how to submit a response to provisional opinion electronically.

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

Authority to consider your response and to confirm the final opinion on behalf of the Committee has been delegated to the Chair.

Please contact the REC Manager if you need any further clarification or would find it helpful to discuss the changes required.

The Committee will confirm the final ethical opinion within 7 days of receiving a full response. A response should be submitted by no later than 03 August 2019.

Extract of the meeting minutes (if applicable)

Documents reviewed

The documents reviewed were:

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_19062019]		19 June 2019
Participant consent form	1.0	10 April 2019
Participant information sheet (PIS)	1.0	10 April 2019
Research protocol or project proposal [Protocol]	1.0	10 April 2019
Summary CV for Chief Investigator (CI) [CV for CI]		
Summary CV for student [CV for student]		
Summary CV for supervisor (student research) [CV for supervisor]		

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

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.

19/WS/0103	**Please quote this number on all correspondence**

Yours sincerely

Mrs Liz Jamieson
REC Manager
On behalf of Mrs Rosie Rutherford, Chair

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms Emma-Jane Gault, University of Glasgow

West of Scotland REC 3

PRS Sub-Committee of the REC meeting held in correspondence on 04 July 2019

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Daniel Boyle	Scriptwriter	Yes	
Dr Anne-Louise Cunnington	Consultant Geriatrician and Vice Chair	Yes	
Dr Linsay McCallum	Consultant Physician	Yes	
Mr Ben Parkinson	Lecturer in Nursing and Alternate Vice Chair	Yes	
Mrs Rosie Rutherford	Volunteer - Lay Plus Member and Chair	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Liz Jamieson	REC Manager

Appendix 10 Study three R&D approval

Coordinator: Mr Graeme Piper
Telephone Number: 0141 314 0222
E-Mail: Graeme.Piper@ggc.scot.nhs.uk
Website: https://www.nhsggc.org.uk/about-us/professional-support-sites/research-innovation/

Clinical Research & Innovation
Dykebar Hospital, Ward 11
Grahamston Road
Paisley, PA2 7DE
Scotland, UK

19 July 2021

Ms Alison Barclay
PDRU
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow G51 4TF

NHS GG&C Board Approval

Dear Ms A Barclay,

Study Title:	Does APT cycling reduce spasticity in people with Multiple Sclerosis
Principal Investigator:	Ms Alison Barclay
GG&C HB site	Queen Elizabeth University Hospital
Sponsor	NHS Greater Glasgow and Clyde
R&I reference:	GN18PY684
REC reference:	19/WS/0103
Protocol no: (including version and date)	V1; 10/04/2019

I am pleased to confirm that Greater Glasgow & Clyde Health Board is now able to grant **Approval** for the above study.

Conditions of Approval

1. **For Clinical Trials** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004

   a. During the life span of the study GGHB requires the following information relating to this site
      i. Notification of any potential serious breaches.
      ii. Notification of any regulatory inspections.

It is your responsibility to ensure that all staff involved in the study at this site have the appropriate GCP training according to the GGHB GCP policy (www.nhsggc.org.uk/content/default.asp?page=s1411), evidence of such training to be filed in the site file.

2. **For all studies** the following information is required during their lifespan.
   a. First study participant should be recruited within 30 days of approval date.
   b. Recruitment Numbers on a monthly basis

NHS
Greater Glasgow and Clyde

c. Any change to local research team staff should be notified to R&D team
d. Any amendments – Substantial or Non Substantial
e. Notification of Trial/study end including final recruitment figures
f. Final Report & Copies of Publications/Abstracts
g. You must work in accordance with the current NHS GG&C COVID19 guidelines and principles.

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.

I wish you every success with this research study

Yours sincerely.

Mr Graeme Piper
Research Co-ordinator

CC: Emma Jane Gault (GU), Stuart Gray,

Appendix 11 Study three ethics amendments

Amendment Tool

v1.6 06 December 2021

For office use

QC: No

Section 1: Project information

Short project title*:	Does cyling using lower limb APT reduced spasticity in pwMS.
IRAS project ID* (or REC reference if no IRAS project ID is available):	255621
Sponsor amendment reference number*:	GN18PY384 AM01
Sponsor amendment date* (enter as DD/MM/YY):	18 March 2022
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	The research study was proposed to run at the QEUH, Glasgow over an 8 month period, and is due to finish on 31/3/22. However during the study period the city hosted COP-26 within venues surrounding the hospital site, and directly impacted on the recrutiment and participation of patients during that time. Therefore I would like to extend the study by one month to account for this and to maximise potential recrutiment & participants. The study would therefore end on 30/4/22.

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	No	No	**Yes**	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		**No**	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		**No**	
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		**No**	
Did the study involve children OR does the amendment introduce this?:	Yes		**No**	
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**		No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes		**No**	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	No	No	**Yes**	No
Which nations had participating NHS/HSC organisations prior to this amendment?	No	No	**Yes**	No
Which nations will have participating NHS/HSC organisations after this amendment?	No	No	**Yes**	No
Does this study only involve a single participating NHS organisation in Scotland?	**Yes**		No	

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1				
Area of change (select)*:	Study Design			
Specific change (select - only available when area of change is selected first)*:	Extension to study duration that will not have any additional resource implications for participating organisations - Please specify in the free text below			
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	The study predominantly involves the researcher. Permission has been granted by management of the department to extend the length of the study without issue due to this.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	No	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Add another change	

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name [first name and surname]:*	Emma-Jane Gault
*Email address**:	emmajane.gault@glasgow.ac.uk

Lock for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Lock for submission

After locking the tool, proceed to submit the amendment online. The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																	
	UK wide:						England and Wales:				Scotland:				Northern Ireland:			
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	IMPPS	IRAS and HCRW Approval	REC (AWA)	PBPP	SPS (RAEC)	NHS organisation	HSC REC	HSC Data Guardians	Prisons	National coordinating function	Category:
Change 1:						(Y)								(Y)					C
Overall reviews for the amendment:																			
Full review:						N								N					
Notification only:						Y								Y					
Overall amendment type:	Non-substantial, no study-wide review required																		
Overall Category:	C																		

Appendix 12 Study three participant information sheet

NHS Greater Glasgow and Clyde

University of Glasgow

Participant Information Sheet

Does a single session of cycling using lower limb active passive trainers reduce spasticity, as measured by the H-reflex, in people with moderate to severe Multiple Sclerosis ?

Why have I been approached about this study?
We are inviting you to participate in this study as you have Multiple Sclerosis (MS) and have been identified by your healthcare professional as someone who would be suitable for inclusion in this study. This study is a collaboration between NHS Greater Glasgow and Clyde (NHSGGC), the School of Life Sciences at the University of Glasgow and Glasgow Caledonian University; it is funded by NHSGGC Endowment Fellowship Fund. This study will also contribute towards a PhD for Alison Barclay, Physiotherapist, Physically Disabled Rehabilitation Unit (PDRU).

Before you decide whether or not to take part it is important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

Thank you in advance for taking the time to read this information leaflet.

What is the purpose of the study?
Spasticity is a common symptom of MS. Spasticity is a term used to describe muscle stiffness or spasms and makes the muscles feel more rigid. It can be difficult to treat and manage. Cycling delivered by Active Passive Trainers (APT) is one exercise option offered within rehabilitation settings and provide cycling from a seated position. The speed, resistance and how much help the APT gives during cycling can be adjusted depending on each persons ability. The Motomed APT is shown below;

Anecdotally people with MS report they feel better and their spasticity reduces after APT cycling. However, there is a lack of evidence to support this as spasticity can be difficult to measure. Often measures of spasticity used in clinical practise don't always reflect objective or perceived changes by patients.

A recent research study, based within the PDRU at the QEUH, looked at the effectiveness of a four week programme of cycling using an APT (MOTOmed) on spasticity, fitness, function and quality of life in people with moderate to severe MS. The results showed that while the majority of outcome measures improved, this occurred in both the usual care and the APT groups. The participants significantly improved in their ability to cycle faster and further over the 20 sessions on the APT. This suggests a change in their ability to actively move their legs, however this change was not reflected in the measures of spasticity used. One of the key recommendations from the study was to consider a different way to measure spasticity, which is the purpose of this study.

Do I have to take part?
No; taking part in research is entirely voluntary; therefore it is up to you to decide. You should read this information leaflet and if you are interested in taking part you should advise the research physiotherapist. When you are assessed for the project you will be screened to make sure it is safe and suitable for you to take part in the study. If you wish to go ahead you will be asked to sign a consent form to show that you agree to take part. You would still continue to receive your normal therapy, interventions and medications under the care of the rehabilitation team according to standard clinical practice. If you decide to take part you are still free to withdraw at any time and without giving a reason. Your decision will not have any effect on the standard of care you receive.

What will happen to me if I take part?
If you agree to participate in the study you will be asked some questions to ensure you are eligible to take part. If you are eligible and wish to take part, you will be asked to provide written informed consent. Prior to starting the cycle session a physiotherapist will complete three different measures to assess the spasticity or stiffness in your legs. These measures will be repeated a further four times at the end of cycling.

For the first measure the physiotherapist will move your legs to assess the stiffness in your legs. For the second measure you will then be asked to score how stiff you feel your legs are on a scale of 0-10. And for the third measure the physiotherapist will measure the electrical activity in a muscle in the back of your calf. To do this a small electrode will be placed at the back of your knee, in the middle of you calf and over your ankle. A small electrical current or stimulation will be delivered under the electrode at the back of your knee which feels similar to the feeling of flicking a finger on the skin. This will be repeated 10 times over a minute to measure the activity in the muscle. The whole process should take no longer than 2 minutes to complete.

You will then be asked to cycle which will start with a 2 minute warm up, where your legs are assisted to move by the APT at 10 revolutions per minute (rpm). Next we will ask you to cycle for up to 30 minutes, at a speed you feel able to complete, and using the feedback on the display to help with this. If you are unable to actively cycle at any point during the 30 minute exercise period, or if your legs spasm, the Motomed APT will cycle for you. You will be asked to rate how difficult you find cycling the APT at regular intervals during the cycling session. The final phase is a cool down where you will have 2 minutes of passive cycling where again the APT will do the cycling for you at 10rpm.

After completing cycling the physiotherapist will then re-measure the tests to assess leg stiffness. Firstly you will then be asked to score how stiff your feel your legs are on a scale of 0-10, then the test to measure the electrical activity in the muscle in the back of your calf will be repeated. Both of these tests will be repeated again after 10 minutes, 20 minutes and 30 minutes. Lastly the physiotherapist will then re-measure the stiffness in your legs by moving them.

The whole session will take no longer than two hours. If at any part of the process you get any symptoms such as cramping or spasms, or you find the process too uncomfortable you can stop and withdraw from the study.

What are the possible disadvantages or risks of taking part?
There are no major risks in taking part in this study. Some people may find the nerve stimulation a little uncomfortable, this will last for only a few seconds. If you feel this is too uncomfortable to continue you can stop and withdraw from the study.

What are the possible benefits of taking part?
We hope taking part in the study will help gain further information on the use of APT cycling which may also help improve the treatment of other people with MS.

What about expenses or payments involved with taking part in the study?
You will not be paid for participating in the study.

What happens when the research study stops?
The results of this study will help inform a larger trial before we can be more confident of the benefits of APT's for people affected by MS.

Will my taking part in this study be kept confidential?
Yes, all information collected from you during the study will be kept strictly confidential and treated with normal ethical and legal practice for data collection. With your permission we will inform your Rehabilitation Consultant about your involvement in this study. In addition representatives of the Research Team and Sponsor NHS Greater Glasgow and Clyde, may access your medical notes where they relate to the study in order to monitor that the study is being carried out properly. Also, with your permission we will transfer

the data regarding the measures we have collected during the study anonymously for analysis.

What will happen if I don't want to continue in the study?
You can withdraw at any time without giving us any reason. Any information collected prior to your withdrawal will still be used.

What If there is a problem?
Should you have a concern about any aspect of the study, in the first instance you should contact the research physiotherapist, using the contact details below, who will do their best to answer any questions. If this does not resolve the issue, and you would like to formally complain you can do this through the NHS Complaints Department, tel: (0141) 201 4500. Independent advice about the study can be obtained from Karen Scott, AHP Team Lead, PDRU tel: (0141) 201 2655.

What happens to the results of the research study?
It is intended that the results of the study will be published in medical literature and/or presented at healthcare conferences. The results will also contribute towards a PhD for Alison Barclay, Physiotherapist, Physically Disabled Rehabilitation Unit (PDRU). All data will be anonymised before this and no-one will be able to identify you. Should you wish to know the results of the study then we will send you a summary of the main findings once the research is complete.

Who is organising funding the research?
This study is funded by NHS Greater Glasgow and Clyde.

Who has reviewed this study?
All research in the NHS is looked at by the Research Ethics Committee, an independent group of people who aim to protect patient safety, rights, well being and dignity. This study has been reviewed and given favourable opinion by the West of Scotland Research Ethics Committee 3.

Participation, further information and contact details.
Should you wish to take part in this study or if you require any further information about this research study please contact:

Alison Barclay
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Research Centre,
College of Medical, Veterinary
and Life Sciences,
University of Glasgow,
G12 8TA

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Thank you for taking the time to read this information leaflet

Appendix 13 Study three consent form

NHS Greater Glasgow and Clyde

University of Glasgow

Patient Identification Number for this study: ☐

STUDY CONSENT FORM

Title of Project: Does a single session of cycling using lower limb active passive trainers reduce spasticity, when measured by the H-reflex, in people with moderate to severe Multiple Sclerosis ?

Name of Researcher: Alison Barclay

Please initial boxes

1. I confirm that I have read and understand the participant information sheet (v3 dated 10.9.19) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. All data (personalised and study data) collected up to the point of withdrawal from the study will be retained until the end of the study. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by the research team or from regulatory authorities. I give permission for these individuals to access my records. ☐
4. I agree to my Rehabilitation Consultant being informed of my participation in this study. ☐
5. I give permission for data collected during the study regarding the outcome measures used to be transferred anonymously for analysis. ☐
6. I understand that this research is part of a PhD degree. ☐
7. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Researcher	Date	Signature

*1 copy for participant and 1 copy for researcher

Appendix 14 Study three data collection pack

Participant Demographic Sheet

Participant No; Date; Time;

DOB/Age;

Sex (please circle); M F

Type MS (please circle); PPMS SPMS RRMS Benign MS

EDSS score;

Time since diagnosis;

PMH;

DH;

SH;

Mobility;

Walking aid

Splints (please circle); Yes No

Distance able to mobilise;

Smoker (please circle); Yes No

Number a day;

Alcohol intake; (please circle); Yes No

Number a week;

Post code;

Level of education; University College Further Education High school

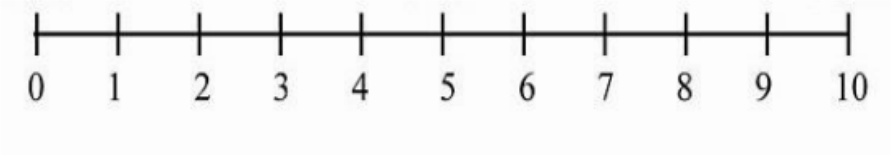
Participant number: Date:

Numeric Rating Scale of Spasticity

Please circle/score how much leg tightness/spasticity you have

Before cycling

No leg tightness/ spasticity — Moderate leg tightness/ spasticity — Worst possible leg tightness/ spasticity



Pre MAS

	R	L
HF		
HE		
ADD		
QUADS		
HAMS		
GASTROC		
SOLEUS		
TP		
TF		

H-reflex study pre and post LL APT cycling

Participant no: **Date & time:**

Stimulus setting:

Start time: **Start time:**

Pre cycle **After cycle**

Stim no	Cr 1	Cr 2	Value	Stim no	Cr 1	Cr 2	Value
1				1			
2				2			
3				3			
4				4			
5				5			
6				6			
7				7			
8				8			
9				9			
10				10			
11				11			
12				12			
		Average				Average	

Start time: **Start time:**

10 min post cycle **20 min post cycle**

Stim no	Cr 1	Cr 2	Value	Stim no	Cr 1	Cr 2	Value
1				1			
2				2			
3				3			
4				4			
5				5			
6				6			
7				7			
8				8			
9				9			
10				10			
11				11			
12				12			
		Average				Average	

H-reflex study pre and post LL APT cycling

Participant no:

Start time:

30 min post cycle

Stim no	Cr 1	Cr 2	Value
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
		Average	

LL APT Data Participant no _____ Date & Time _____

% of activity passive:

% of activity active:

Total distance cycled:

Total distance (passive):

Total distance (active):

Time active:

Time passive:

% activity with left leg:

% activity with right leg:

Power (Watts):

Average RPM:

Resistance at end:

Appendix 15 Study three protocol

Study Design
A pre-post study

Aim
The aim of this study is to assess the effects of a single session of cycling using an APT on lower limb spasticity, by measuring the H-reflex, in people with moderate to severe MS.

Research questions
Primary Research Objectives

- Explore the feasibility of measuring the H-reflex before and after APT cycling in people with moderate to severe MS
- Compare changes in H-reflex and H/M ratio to changes in other measures of spasticity after one session of APT cycling in people with moderate to severe MS

Secondary Research Objectives

- Inform the recruitment strategy for a future trial by determining (a) what proportion will agree to participate in the study (b) how many participants are able to elicit an H-reflex (c) how many adverse events such as hyper-reflexia occur (d) reasons for not participating in the project.

Plan of Investigation
Thirty people with MS admitted as either inpatients or outpatients to the PDRU at the QEUH in Glasgow will take part in the study. They will complete a single session of APT cycling for 34 minutes (2 minutes warm up, 30 minutes active cycling, 2 minutes cool down). Outcome measures will be assessed pre and post cycling.

Study sites
PDRU, Queen Elizabeth University Hospital

Inclusion Criteria
Participants will be included if they

- have a confirmed diagnosis of progressive MS
- are aged over 18 years
- have an Expanded Disability Status Scale (EDSS) of between 6.0 (Requires a walking aid - cane, crutch, etc - to walk about 100m with or without resting) and 8.5 (Essentially restricted to bed much of day. Has some effective use of arms retains some self care functions)
- have lower limb spasticity with an MAS score of ≥1 (on initial physiotherapy assessment)

Exclusion Criteria
Participants will be excluded if they have

- cognitive impairment (cannot understand instructions)
- other co-morbidities which would preclude them taking part in exercise
- visual impairment (such that they cannot see the screen on the APT)

- peripheral nerve injury, peripheral nerve disease/neuropathies or myopathy in the lower limbs
- broken or irritated skin over the lower limb

Subject recruitment and consent
All those admitted to PDRU, and who fulfil the inclusion and exclusion criteria will be invited to take part in the study. All participants will be required to provide written, informed consent.

Study intervention
On admission to PDRU people with MS will be assessed by a physiotherapist and if found to have lower limb spasticity will be invited to take part in the study. Spasticity will be indicated by a MAS score of ≥ 1, as manifested by a catch and release or by minimal resistance at the end of the range of motion when the knee and ankle is moved in flexion or extension. Participants will then complete a single session of lower limb APT cycling outwith their physiotherapy programme. Spasticity will be assessed by measurement of MAS, Numeric Rating Scale (NRS) and H-reflex before and after the APT cycling.

Each participant will be seated in a standard chair or their normal wheelchair which will be positioned against the wall (see below). They will be encouraged to relax, and rest their head back against a pillow positioned against the wall. Ankle splints (if worn) will be removed prior to attaching the electrodes. The right hip and knee joint angles will be positioned that participant is in a comfortable cycling position. The foot and ankle position will be held in a fixed position by the footplate and straps on the APT.

After measurement of MAS, NRS and H-reflex (described below) each participant will then start cycling. The cycling session will begin with a 2 minute warm up consisting of passive cycling, where the legs of the participant are moved passively by the APT at 10 revolutions per min (rpm). Next the participant will cycle for 30 minutes at resistance level one. They will be encouraged to cycle in a symmetrical pattern using feedback from the display screen, and at a pedal rate that equates to moderate level intensity which they will be encouraged to try and maintain throughout the session. This intensity is indicated by a Rating of Perceived Exertion (RPE) score of between 12-14. Participants will be asked to state their RPE score every three minutes during the cycling session. If the RPE falls below 12 the participant will be asked to cycle faster and if above 14 to cycle slower. If the participant is unable to actively cycle at any point during the 30 minute exercise period, or if they have a spasm, the Motomed APT will revert to the passive mode. The final phase is a cool down where participants again will have 2 minutes of passive cycling at 10rpm.

Screening and baseline assessments
At baseline, demographic details will be recorded; age, sex, type of MS, time since diagnosis, EDSS, use of walking/mobility aids. Medications will also be recorded.

Study outcome measures
The primary outcome measure will be the H-reflex. The H-reflex is a measure of reflex spinal excitability and is recorded from the triceps surae muscle group by stimulating the posterior tibial nerve in the popliteal fossa in the right leg of each participant. Unipolar stimulation will be applied with the cathode placed over the posterior tibial nerve at the back of the knee and laterally positioned, and the anode positioned over the middle of the patella. The tibial nerve will be stimulated by 1 ms square wave pulses delivered by a Digitimer DS7 stimulator. Ten stimuli will be applied with 10 seconds between each stimulus to eliminate any effects of post-activation depression of the reflex. Recording electrodes spaced 1cm apart will be applied on the skin overlying triceps surae. The H-reflex will be recorded via the Delysis Bagnoli and recorded on a Cambridge Electronic Device micro. An H-reflex recruitment curve will be produced by progressively increasing the stimulus intensity until the H-reflex is eliminated by the recruited maximum M-response. H-reflexes utilised during the test period will be obtained by stimulating at an intensity that elicits an H-reflex on the upward slope of the recruitment curve. H/Mmax ratio will be used to evaluate any alterations in H-reflex excitability.

Spasticity will also be measured using the MAS in the right knee and ankle muscles. The MAS is a six point ordinal scale (0-4) which grades the resistance during passive muscle stretching. For example the participant will sit with their knees bent, the therapist will slowly straighten and bend their knee and the amount of resistance they feel to the movement represents the tone or spasticity within the muscles. In this scale 0 represents no increase in tone and 4 is graded where the affected part is rigid and very hard to move.

In addition a NRS score regarding the stiffness of the participants leg(s) will be taken as a self reported outcome measure. The NRS is scored from 0-10 where 0 represents no leg stiffness to 10 representing worst possible leg stiffness or as bad as it could be. Participants will be asked to give their leg stiffness or tightness a number on this scale.

All of the outcome measures will be recorded immediately before and after completion of the cycling session. In addition the H-reflex and NRS will be taken again 10, 20 and 30 minutes after completion of the cycling session.

Data will also be taken from the APT following the session: symmetry, distance cycled and performance (overall power in watts).

Data management
Participant data will be made anonymous; coding will be used to identify participants within the data set. Any information pertaining to the participant's identity will be stored in a locked filing cabinet in a locked room at the study site. Anonymised data will be stored on an NHS password protected computer Only the research team and regulatory authorities will have access to the data collected for the study.

Following completion of the study the anonymised data will be stored on a data storage device, this will be labelled and stored in a locked filing cabinet in a locked room within the clinical site for 10 years.

Statistical analysis
The outcome variables will all be summarised numerically, and where appropriate graphically over time with the emphasis being on the pre-post data. The paired analysis of the H/M ratio, H-reflex, M wave and MAS will be performed either using paired t-tests or paired Wilcoxon tests dependent on the symmetry of the data. For the additional data collection at 10, 20 and 30 minutes after completion, these variables will be analysed using either a parametric one factor repeated measures ANOVA or a Friedman test. All testing will be performed on IBM SPSS v25.0 and at the 5% level of significance.

Criteria for termination of the study
We do not anticipate stopping the trial early. The main technical challenge is eliciting an H-reflex. We do not anticipate this to be an issue as we have ethical approval from Glasgow Caledonian University to undertaken a study on healthy volunteers prior to starting this study.

Safety and risk assessment
The study exclusion criteria will ensure people with special exercise needs or for whom this type of exercise may be associated with some risk are not included. Some people may perceive the stimulus from assessing H-reflex to be uncomfortable. If they report this to be intolerable they will be able to stop and withdraw from the study at that point.

Serious Adverse Events (SAE) will be recorded and the CI at the PDRU will notify the project sponsor (within 24 hrs).

Study timetable
The study aims to recruitment participant over a 4 month period.

Funding
The study has been funded by NHS GG&C Endowments Fellowship.

Dissemination
The results of this study will help support a larger grant application to the MS Society to fund an RCT of a three month programme of exercise using APT to reduce spasticity, in community dwelling patients.

Participants will be sent a lay summary of the findings. We will present the findings at appropriate conferences, such as Chartered Society of Physiotherapy Conference or MS Frontiers, and the local Best Practise Study Days. We will also aim to publish the findings in a relevant scientific journal. Lastly the results of the study will also contribute towards a PhD thesis.

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Appendix 17 CONSORT 2010 Checklist

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	
	2b	Specific objectives or research questions for pilot trial	
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
	4c	How participants were identified and consented	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	
Sample size	7a	Rationale for numbers in the pilot trial	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the pilot trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
	19a	If relevant, other important unintended consequences	
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	
Protocol	24	Where the pilot trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	
	26	Ethical approval or approval by research review committee, confirmed with reference number	

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.