Treadmill training augmented with real-time visualisation feedback and function electrical stimulation for gait rehabilitation after stroke: a feasibility study

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Declaration of Authenticity and Author's Rights

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Abstract

Motor rehabilitation typically requires patients to perform task-specific training, in which biofeedback can be instrumental for encouraging neuroplasticity after stroke. Treadmill training augmented with real-time visual feedback and functional electrical stimulation (FES) may have a beneficial synergistic effect on this process. This study aims to develop a multi-channel FES (MFES) system with stimulation triggers based on the phase of gait cycle, determined using a 3D motion capture system. A feasibility study was conducted to determine whether this enhanced treadmill gait training system is suitable for stroke survivors in clinical practice.

The real-time biomechanical visual feedback system with computerised MFES was developed using six motion-capture cameras installed around a treadmill. This system was designed to stimulate the pretibial muscle for correcting foot drop problems, gastro-soleus for facilitating push-off, and quadriceps and hamstring for improving knee stability. Dynamic avatar movement and step length/ratio were displayed on a monitor, providing patients with real-time visual biofeedback. Participants received up to 20 minutes of enhanced treadmill training once or twice per week for 6 weeks. Training programme, pre- and post-training ability, and adverse events of each participant were recorded. Feedback was also collected from participants and physiotherapists regarding their experience.

Eight out of ten participants fully completed their programme. In total, 67 training sessions were carried out. All participants had a good attendance

rate. The number and duration of training sessions ranged from 5 to 20, and 11 to 20 minutes, respectively. The MFES system successfully improved gait patterns during training, and feedback from participants and physiotherapists regarding their experience of the research intervention was overwhelmingly positive.

In conclusion, this enhanced treadmill gait training system is feasible for use in gait rehabilitation after stroke. However, a well-designed clinical trial with a larger sample size is needed to determine clinical efficacy on gait recovery.

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List of Abbreviations

10mWT	10-Meter Walk Test
1DS	First Double Support
2DS	Second Double Support
2MWT	2-Minute Walk Test
6MWT	6-Minute Walk Test
AC	Alternating Current
ACA	Anterior Cerebral Artery
AF	Anatomical Frame
AFO	Ankle-foot orthosis
AHA/ASA	American Heart Association/American Stroke Association
ASIS	Anterior Superior Iliac Spine
BBS	Berg Balance Scale
BI	Barthel Index
BWS	Body Weight Support
CAREN	Computer Assisted Rehabilitation Environment
CWS	Comfortable walking speed
DC	Direct Current
EMG	Electromyography
ENTRES	Enhanced Treadmill Gait Training with Lower Limb Support after Stroke
ESw	Early Swing
FAC	Functional Ambulation Classification
FES	Functional electrical stimulation

FMA-LE	Fugl Meyer Assessment for Lower Extremity
GF	Global Frame
GFR	Ground Reaction Force
IC	Initial Contact
ICC	Intra Class Correlation
IDE	Integrated Development Environment
ISB	International Society of Biomechanics
LSw	Late Swing
MCA	Middle Cerebral Artery
MFES	Multi-channel Functional electrical stimulation
NMES	Neuromuscular Electrical Stimulation
PC	Pulsed Current
PIG	Plug-in-gait
PSIS	Posterior Superior Iliac Spine
PSR	Paretic Step Ratio
RCT	Randomised Controlled Trial
RMI	Rivermead Mobility Index
SCM	Strathclyde Cluster Model
SLA	Step Length Asymmetry
SLR	Step Length Ratio
SS	Single Support
TENS	Transcutaneous Electrical Nerve Stimulation
TF	Technical Frame
TO	Toe Off

Chapter 1: Introduction and Literature Review

1. Introduction and Literature review

1.1. Stoke

1.1.1. Definition and Types

Stroke is one of the major health problems across the globe. The World Health Organization define stroke as “a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin”(1988, Aho et al., 1980).

There are two main types of stroke; ischemic and haemorrhagic. Ischemic stroke happens when blood supply to the brain is blocked due to plaque inside the artery (atherosclerosis) or a travelling clot (embolus). Haemorrhagic strokes are caused by bleeding from ruptured blood vessel within the brain (Intracerebral haemorrhage) or into the space between the brain and the skull (Subarachnoid haemorrhage) (Price et al., 2018).

1.1.2. Statistics

In 2013, Globally, prevalence of stroke was nearly 25.7 million survivors (71% with Ischemic stroke). There were almost 10.3 million new strokes (67% with Ischemic stroke) and 6.5 million deaths from stroke (51% with Ischemic stroke) (Feigin et al., 2015). In 2010, stroke was reported as the third highest cause of disability with 102,239 (95%CI: 90,472 – 108,003) in thousands of Disability-Adjusted Life-Years (DALYs) ,nearly as high as the

primary cause which is Ischemic heart diseases with 129,795 (95%CI: 119,218 – 137,398) in thousands of DALYs (Murray and Lopez, 2013).

For the UK, there are more than 100,000 new strokes each year among individuals who are 45 years old or more, and the prevalence will reach 1,424,100 cases in 2025 and 2,119,400 cases in 2035 (King et al., 2020). Also, based on health economic model, total costs of stroke for health care, social care, unpaid care, and lost productivity will increase from £26 billion in 2015 to £43 billion in 2025 and will reach to £75 billion in 2035 (King et al., 2020).

1.1.3. Clinical syndromes

Stroke results in a wide range of disabilities due to physical, psychological, and/or cognitive impairment depending on affected brain area. Major impairments of stroke are detailed below.

Motor control and Strength

This function is controlled by the primary motor cortex (M1 cortex) which is located along the cortex of the precentral gyrus anterior to the central sulcus. Axon fibres of these upper motor neurons descend along the internal capsule and cross to the contralateral side at the brain stem. They then descend to the corticospinal tract of the spinal cord. Thus, patients with stroke affecting the motor cortex have motor weakness on the contralateral side to the brain lesion.

The topography of motor control is illustrated by the motor homunculus (Figure 1.1). The medial aspect of motor cortex is supplied by the anterior cerebral artery (ACA) while the lateral aspect is supplied by the upper trunk of the middle cerebral artery (MCA). Therefore, patients with ACA stroke have contralateral hemiplegia and the lower extremities are more severely affected than the upper extremities, whereas those with MCA (upper division) stroke suffer from a contralateral hemiplegia in which the upper extremities are more severely affected than the lower extremities.

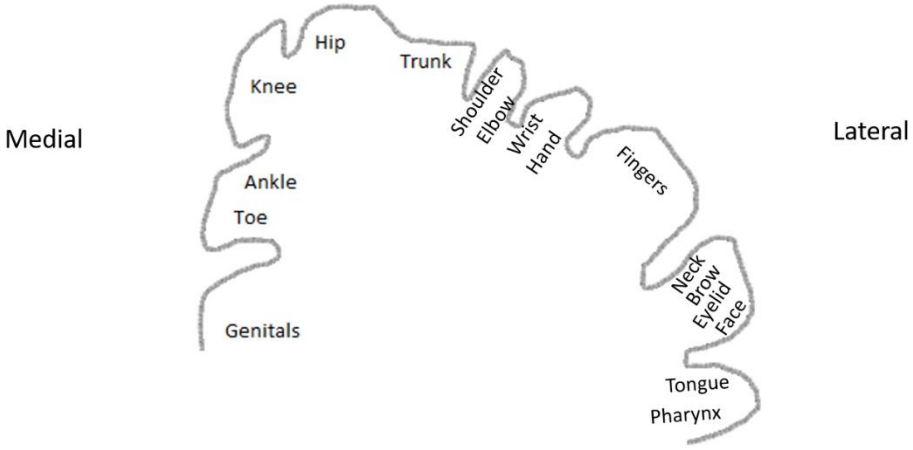


Figure 1.1: Motor homunculus (Coronal view of Frontal lobe)

Spasticity

According to the American Academy of Neurology, spasticity is a motor disorder that is characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of upper motor neuron syndrome (Lance, 1990). It is normally developed after an upper

motor neuron injury such as stroke due to loss of inhibitory control of α- and γ-motor neuron activity (Kheder and Nair, 2012, Chang et al., 2013). As neurological recovery progresses, spasticity will decrease, and voluntary movement becomes recovery. Spasticity usually remains if neurological recovery is not complete.

Motor coordination and balance

The premotor area located anterior to the precentral gyrus is the important part in motor planning. Multiple fibre tracts from this part descend along internal capsule (anterior limb) to the basal ganglion and the cerebellum, with sensory input from the vestibular, visual, and proprioceptive system. Damage of these areas such as cerebellar or brain stem stroke can result in problems of static and dynamic balance, and coordinated movement patterns (Konczak et al., 2010, Nouh et al., 2014).

Sensation

The primary sensory cortex located posterior to the central sulcus in the postcentral gyrus receives pain and temperature sensation via the spinothalamic tract, and joint proprioception via the posterior column pathway. Injuries to the sensory pathways usually results in reduced or impaired sensation but sometimes patients with thalamic stroke can suffer from central neuropathic pain (Henry et al., 2008, Schott, 1996).

Language and communication

Aphasia is the major impairment of language after stroke and is commonly found among patients with a dominant (left) hemispheric lesion (Figure 1.2). The clinical characteristics are dependent on damaged areas. Patients with injury to Broca's area mainly present with the inability to produce language (Expressive aphasia) whereas injuries to Wernicke's area results in the inability to understand language (Comprehensive aphasia) (Sinanovic et al., 2011).

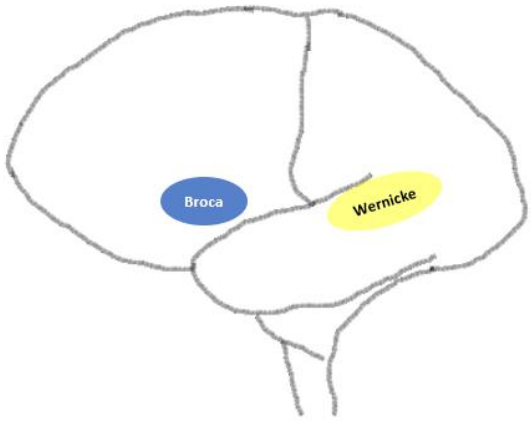


Figure 1.2: Broca's and Wernicke's area

Neglect syndrome

Neglect is a disorder of visual and spatial perception caused by temporoparietal stroke of the non-dominant hemisphere. Patients with hemispatial neglect are not able to report, respond, or orient to important or serious stimuli presented to the hemiplegic side although they have normal function of the visual, somatosensory, or motor system. Neglect causes poor

performance of sitting balance, visual perception, safety awareness and falling. Thus, neglect is an important predictor of poor outcome following rehabilitation (Dombovy et al., 1986, Jehkonen et al., 2000).

Swallowing problems

Swallowing difficulties also known as dysphagia is a common consequence of stroke and is associated with prolonged hospitalisation, care in a nursing home after discharge, poorer functional capacity, and increased mortality (Rofes et al., 2018). It can be found in 45% to 61% of patients with acute first stroke (Mann et al., 1999, Rofes et al., 2018). Fortunately, most stroke survivors with dysphagia recover the ability to have normal meals (Mann et al., 1999).

Although there are many sequelae after stroke, impairment or loss of motor control and strength seem to be the most common. The study of Lawrence et al. (2001) conducted among 1,259 registered patients with acute stroke revealed that common impairments were: upper limb weakness (77.4%), lower limb weakness (72.4%), urinary incontinence (48.2%), impaired consciousness (44.7%), dysphagia (44.7%), and impaired cognition (43.9%) (Lawrence et al., 2001).

Table 1.1**:** Prevalence of acute impairment and disability in first-in-a-lifetime stroke for 1,259 patients (Lawrence et al., 2001).

Impairment	n	%	Unable to assess N (%)
Upper limb motor deficit	975	77.4	39 (3.1)
Lower limb motor deficit	911	72.4	39 (3.1)
Urinary incontinence	607	48.2	80 (6.4)
Impaired consciousness (GCS<15)	563	44.7	34 (2.7)
Dysphagia	563	44.7	91 (7.2)
Impaired cognition (MMSE < 24)	522	43.9	400 (33.6)
Dysarthria *	494	41.5	280 (23.5)
Upper limb sensory deficit	381	30.3	255 (20.3)
Lowe limb sensory deficit	342	27.2	255 (20.3)
Visual field defect	328	26.1	271 (21.5)

* For 1,189 patients

1.1.4. Stroke recovery

Recovery from stroke has two main mechanism. The first is resolution of brain oedema, improvement of local circulation, reduction in inflammation toxin, and recovery of ischemic cortical neurons which normally leads to early spontaneous improvement. The second is neuroplasticity which is the ability of the cortical brain to modify its structure and function (cortical reorganization). It can occur in the early period but also continue for some

months. The evidence from both animal and human studies indicate that neuroplasticity depends on the degree of patient activity and on skill-specific training (Dimyan and Cohen, 2011). Hence, early, intensive, task-specific training is the key to stroke recovery and the foundation of stroke rehabilitation. However, very high dose intervention should not be carried out within 24 hours of stroke onset (group, 2015).

For the natural history of stroke recovery, the Copenhagen stroke study – a large, prospective, community-based cohort study of acute stroke patients – is one of the most common references (Jørgensen et al., 1995a, Jørgensen et al., 1995b, Jørgensen et al., 1995c). In this study the patients received acute treatments as well as a conventional rehabilitation programme in a stroke unit. The results showed that most of the stroke survivors with initially severe or very severe neurologic deficits still had moderate neurological or functional deficits or worse at discharge. The time course of neurological recovery was strongly associated with the initial stroke severity. The results demonstrated that 95% of stroke survivors with mild to moderate severity achieved their best neurological level within 10 to 11 weeks after stroke onset but patients with severe to very severe stroke seem to need more time to reach their best recovery (within 13 to 15 weeks) (Figure 1.3) (Jørgensen et al., 1995c). Moreover, the proportion of stroke survivors who could return to independent walking level was greater in patients who had less severe lower extremities weakness at stroke onset (Figure 1.4) (Jørgensen et al., 1995a). These results indicate that rehabilitation programmes should be started as soon as possible when the patients are

safe to do so, and that stroke severity is a strong predictor of subsequent walking level.

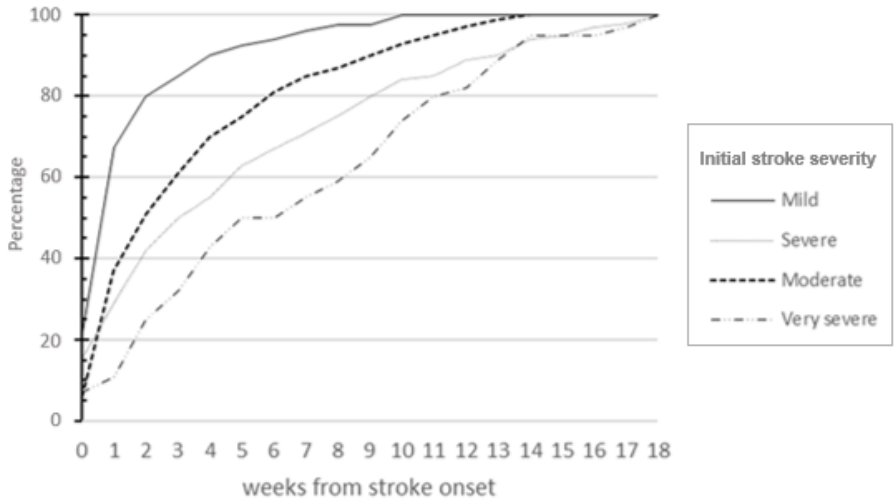


Figure 1.3: The time course of neurological recovery in relation to the initial stroke severity. The vertical axis is the cumulative percentage of stroke patients achieving their best outcome. Adapted from Jørgensen et al.,(1995c)

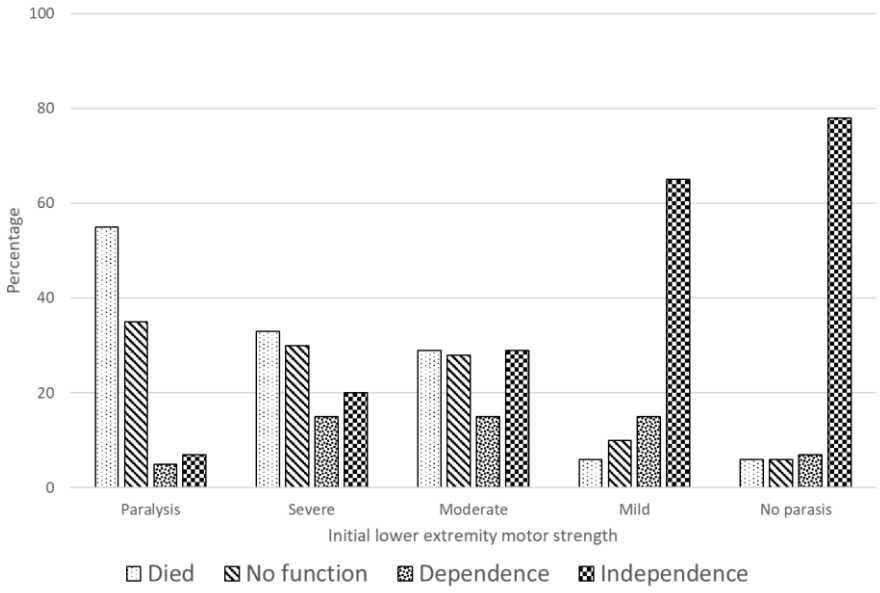


Figure 1.4: Final walking function in relation to initial lower extremity motor strength. Adapted from Jørgensen et al.,(1995a)

1.1.5. Gait abnormality after Stroke

The loss of or difficulty walking is one of the most common disabilities after stroke. The study of Mehrholz et al. (Table 1.2), which was carried out among 55 patients who had a new, first-time cerebral stroke, showed that all stroke survivors were categorized into non-functional or dependent ambulators before starting a 4-week inpatient rehabilitation programme. They also had reduced walking speed and reduced step length. At 6-month follow-up, most of the stroke patients were able to walk independently but some of them did not reach community ambulation levels (Mehrholz et al., 2007). Even though a variety of neurological impairments can cause gait difficulties, motor recovery and the degree of muscle weakness seem to be the major contributions to this problem (Cho et al., 2014, Belda-Lois et al., 2011).

Table 1.2**:** Walking ability of Stroke survivors in the study of Mehrholz J et al.

Parameters	**At baseline**	**At 2 weeks**	**At 4 weeks**	**At 6-month follow-up**
FAC (score, 0 – 5)	0.44 ± 0.69 (0, 0 – 3)	1.22 ± 1.32 (1, 0 – 5)	1.98 ± 1.50 (2, 0 – 5)	2.79 ± 2.12 (4, 0 – 5)
6MWT (m)	15.9 ± 34.3 (0, 0 – 175)	50.9 ± 81.1 (15, 0 – 315)	83.9 ± 107.8 (40, 0 – 460)	112.3 ± 143.9 (60, 0 – 560)
Walking velocity (m/s)	0.07 ± 0.14 (0.01, 0.01 – 0.82)	0.19 ± 0.28 (0.08, 0.01 – 0.96)	0.33 ± 0.46 (0.15, 0.01 – 1.96)	0.38 ± 0.51 (0.15, 0.00 – 1.96)
Step length (m)	0.09 ± 0.13 (0.00, 0.00 – 0.48)	0.18 ± 0.19 (0.18, 0.00 – 0.61)	0.27 ± 0.20 (0.22, 0.00 – 0.74)	0.28 ± 0.26 (0.26, 0.00 – 0.16)

Value are mean ± SD (median, range); FAC = Functional Ambulation Classification; 6MWT = 6-minute walk test.

Changes in temporo-spatial parameters

The reduced walking speed was associated with a decrease in both stride length and cadence. Patients with a slow walking speed (< 0.4 m/s) showed not only considerably prolonged duration of the pre-swing phase, but also poor weight-bearing on the hemiplegic side. Among stroke survivors having walking speed less than 0.8 m/s, time spent during the swing phase on the hemiplegic side seem to be similar to normal people although the percentage of swing phase in the gait cycle was reduced (Figure 1.5) (De Quervain et al., 1996).

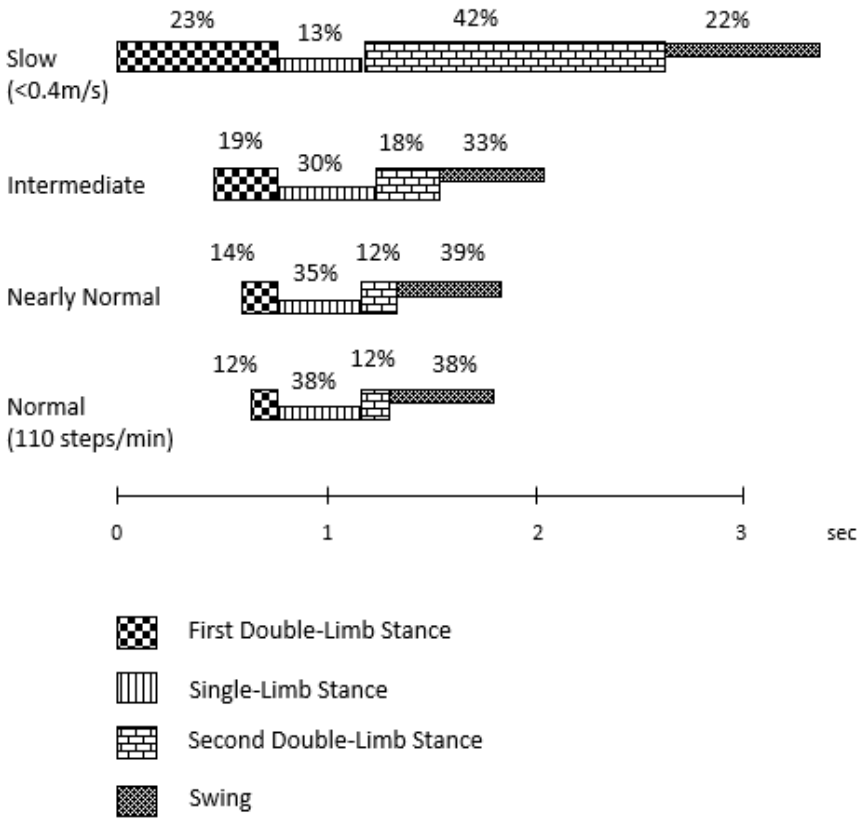


Figure 1.5: The percentage of the gait cycle for each walking speed. Adapted from De Quervain et al. (1996)

Step length asymmetry (SLA) is a frequently reported gait characteristic for stroke patients. The study of Balasubramanian and colleagues (Balasubramanian et al., 2007) recruited 49 chronic stroke patients to determine the relationship between SLA and walking ability. In this study, step length ratio (SLR) (the hemiplegic step length divided by the non-hemiplegic step length) was used to determine SLA. The results reported that 24 patients (49%) had no SLA ($0.9 < SLR < 1.1$), and among 25 patients with a significant SLA, 21 patients had $SLR > 1.1$ and only 4 patients had $SLR < 0.9$ (Balasubramanian et al., 2007).

In another study by Allen and colleagues (Allen et al., 2011), SLA was defined by paretic step ratio (PSR) – the paretic step-length divided by the stride length. The study found that among 29 patients who had household walking status, only 4 patients (13.8%) had no SLA ($0.465 < PSR < 0.535$) and the majority of patients with SLA had $PSR > 0.535$ (84%, 21/25) (Allen et al., 2011). In conclusion, as the non-hemiplegic leg can provide good stability when the hemiplegic leg is swung forward, the hemiplegic leg typically has better advancement during the swing phase than the non-hemiplegic leg.

Changes in Kinematics

A delay in initiating hip flexion during the pre-swing phase on the hemiplegic side was found in stroke survivors who had a slow walking speed. Some patients had a severe delay and only began hip flexion at or shortly after toe-off. In addition, poor advancement of hip flexion, knee flexion and

ankle dorsiflexion throughout the swing phase was observed (De Quervain et al., 1996).

During stance phase, the range of hip extension was decreased, and was related to one of four coupling patterns between the knee and ankle (De Quervain et al., 1996).

1. Extension thrust pattern was an extension thrust of the knee immediately after foot contact and increased plantar flexion of the ankle at foot contact, then decreased dorsiflexion.
2. Stiff knee pattern in which the knee remains in a position of 20 – 30 degrees of flexion of knee, with neutral or slight plantarflexion of the ankle.
3. Buckling knee pattern was characterized by an increased excursion of knee flexion during weight transfer, with the flexed position continued during the entire stance phase, and an increased excursion of ankle dorsiflexion.
4. Normal knee pattern showed almost normal flexion-extension pattern of the knee with slightly increased knee flexion and ankle dorsiflexion during some parts of stance phase.

Hence among chronic stroke survivors, a reduction in range of hip extension during stance phase on the hemiplegic leg, as well as, a decreased range of hip flexion, knee flexion, and ankle dorsiflexion during swing phase were found.

However, patients with good motor recovery had better gait characteristics. Chen et al (2003) assessed gait performance among 35 patients with stroke 6 months after stroke onset compared with 15 healthy volunteers. The patients were categorized into 2 groups; poor (Brunnstrom stage 3 or 4) and good (Brunnstrom stage 5 or 6) motor recovery. Both groups showed a reduction in range of hip extension during the stance phase of both the affected and unaffected leg when compared with the healthy. Significant side-to-side differences were shown among the poor group only. Decreased ankle plantarflexion during push-off of the hemiplegic leg was revealed in both groups when compared with the healthy, and significant side-to-side differences were also shown in both groups. For swing phase, both groups revealed decreased excursion of hip flexion, knee flexion, and ankle dorsiflexion on the hemiplegic sides. However, the good recovery group had less reduction in range of all joint kinematics than the poor recovery group (Figure 1.6) (Chen et al., 2003).

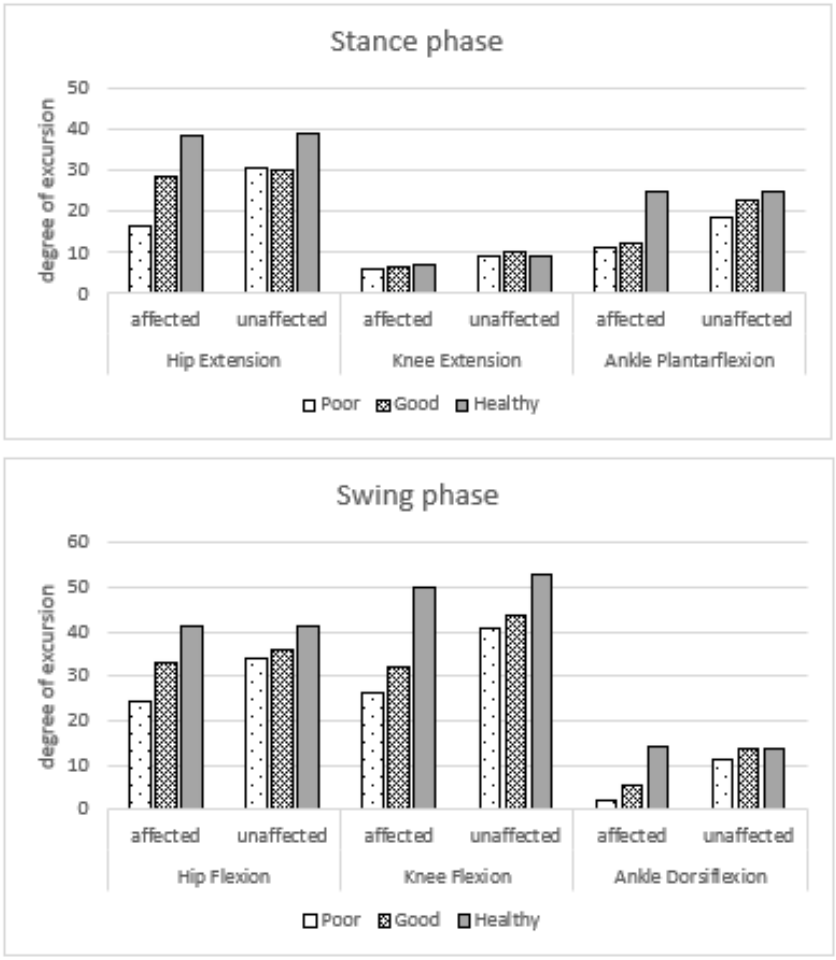


Figure 1.6: Excursion of hip, knee, and ankle for stance and swing phase among stroke patients with poor and good motor recovery. Adapted from Chen et al., (2003)

Changes in Kinetics

Stroke survivors normally have poor propulsion (push off) of the hemiplegic leg during the pre-swing phase. It causes the low excursion of hip flexion, knee flexion, and ankle dorsiflexion previously observed during the swing phase. Bowden et al (2006) measured the anterior-posterior ground reaction force during walking among 47 chronic strokes (> 12 month since

onset). The percentage of total propulsion generated by the paretic leg (% paretic propulsion) was calculated by dividing the propulsive impulse of the paretic leg by the sum of the paretic and non-paretic propulsive impulses. They found that the percentage of paretic propulsion of poor (Bronnstrom stage 3), moderate (stage 4 or 5), and good (stage 6) motor recovery subjects were 16%, 36%, 49%, respectively (Figure 1.7) (Bowden et al., 2006).Hence, it may be concluded that the degree of motor recovery is associated with amount of impulse generated by the paretic leg during the push-off phase.

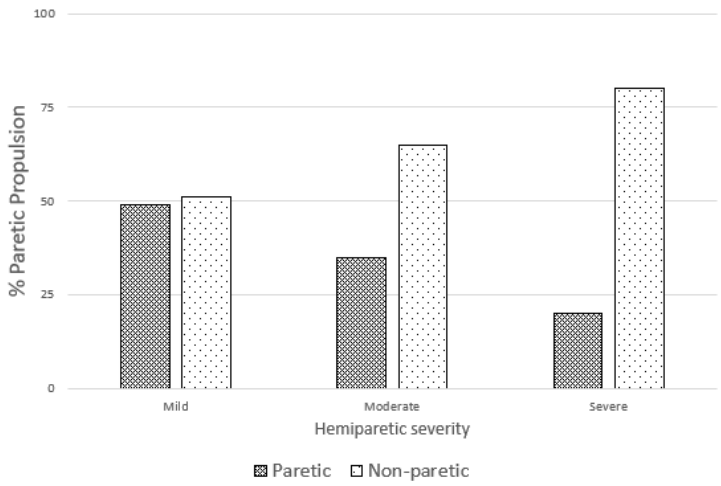


Figure 1.7: Percentage of propulsion categorized by hemiplegic severity. Adapted from Bowden et al.,(2006)

1.1.6. Gait rehabilitation after stroke

One of the primary goals of stroke survivors is to achieve independent walking. Thus, gait training is the main focus of many rehabilitation programs at least early after stroke. Gait training can be categorized into two groups: conventional physical training and technology-assisted training using for

example treadmills, functional electrical stimulation, virtual reality, and robotic technology.

For conventional physical training, there are two main concepts of gait rehabilitation techniques: neurophysiological and motor relearning.

- Neurophysiological concept

  This approach uses the knowledge of neurophysiology to restore gait function, and the physiotherapist supports the movement of the patients. For example, The Bobath technique which is widely used across European countries believes that muscle weakness is caused by the spasticity of their opposite muscles. Thus, inhibition of spasticity in these muscles by passive mobilization along with stimuli for touch and position senses is used in the Bobath method.

- Motor relearning concept

  This approach requires active participation from patients. It involves task-specific and context-specific training with related feedback. These are the key principles in the motor relearning approach (Langhammer and Stanghelle, 2000).

For technology-assisted gait training, some interventions have clinical evidence of gait improvement among patients with stroke. Treadmill gait training with or without body weight support (BWS) has been shown to have some benefits for stroke patients. Patients with balance problems who might not be safe with over-ground training can be given gait rehabilitation by using

a treadmill with BWS. In addition, treadmill training with BWS has been shown to eliminate the fear of falling, and to reduce cardiovascular demands (McCain et al., 2008). However, Duncan and colleagues (Duncan et al., 2011) conducted a large randomised controlled trial (RCT) among 408 patients with recent stroke to examine the effect of treadmill gait training with BWS on the achievement of community walking by 1 year post stroke. The results showed that early (2 months after the stroke) and late (6 months after the stroke) treadmill gait training with BWS were not superior to progressive exercise supervised by a physiotherapist. Put another way treadmill gait training with BWS was as good as progressive exercise supervised by a physiotherapist. Additionally, a Cochrane systematic review in 2017 concluded that treadmill training with or without BWS does not increase the probability of being able to walk independently but might improve speed and endurance of walking (Mehrholz et al., 2017).

Robotic devices for gait training were designed as end-effectors such as the Gait Trainer (Reha-Technology, Germany, G-EO, Figure 1.8), or as electromechanical exoskeletons such as the Lokomat (Belda-Lois et al., 2011). The systems support the patient's body weight by using a suspension with a hardness while the devices move or support the patient's lower extremities. Guidelines for adult stroke rehabilitation endorsed by AHA/ASA in 2016 stated that robot-assisted gait training combined with conventional physiotherapy may be considered especially for patients who had poor ambulatory level after a recent stroke (Class: IIb, level of Evidence: A) (Winstein et al., 2016). In 2017, Cochrane systematic reviews concluded that

patients who receive robotic gait training combined with physiotherapy are more likely to achieve independent walking than those who do not receive these methods.(Mehrholz et al., 2017)

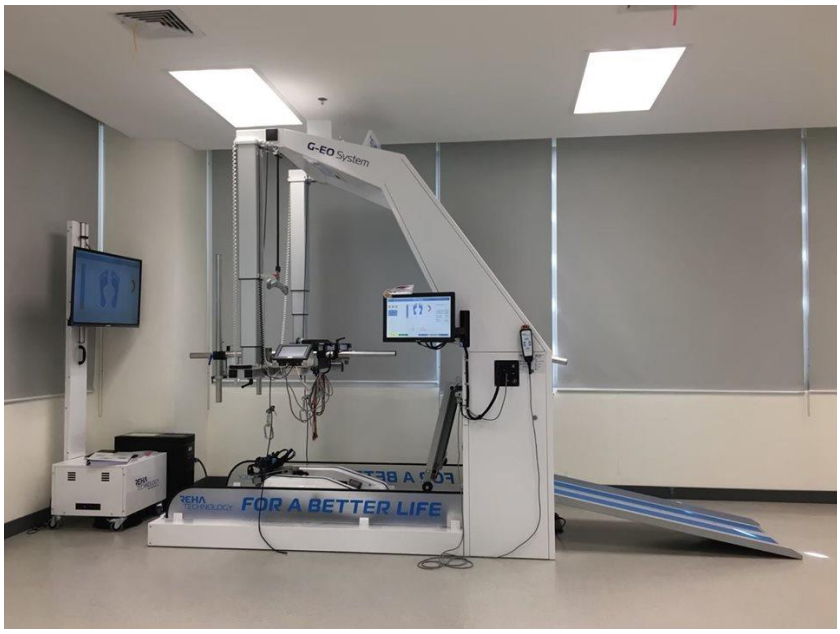


Figure 1.8: Gait training with Robotic G-EO system

Virtual reality is a realistic environment created by computerised technology. It can help provide engagement with specific task practice, interaction with an environment, and real-time visualisation feedback of motion to stroke patients. Nowadays, the virtual reality systems are often categorized into two groups: camera-based and sensor-based systems. An example for the first group is the Computer Assisted Rehabilitation Environment or CAREN system (Makssoud et al., 2009, Fung et al., 2004). It has a twelve-camera system tracking motion and 4 video projectors showing virtual environments on a large, semi-circular, immersive screen. Patients are trained on the treadmill with a first-person perspective. In addition, it can be

used for 3-dimentional motion analysis to report gait parameters and joint/segmental kinematics which are the most valid outcomes to determine gait performance of patients. This system is commercialized by Motek Medical company based in The Netherlands. A systematic review and meta-analysis in 2016 suggested that virtual reality training is more effective than balance or gait training without virtual reality (de Rooij et al., 2016).

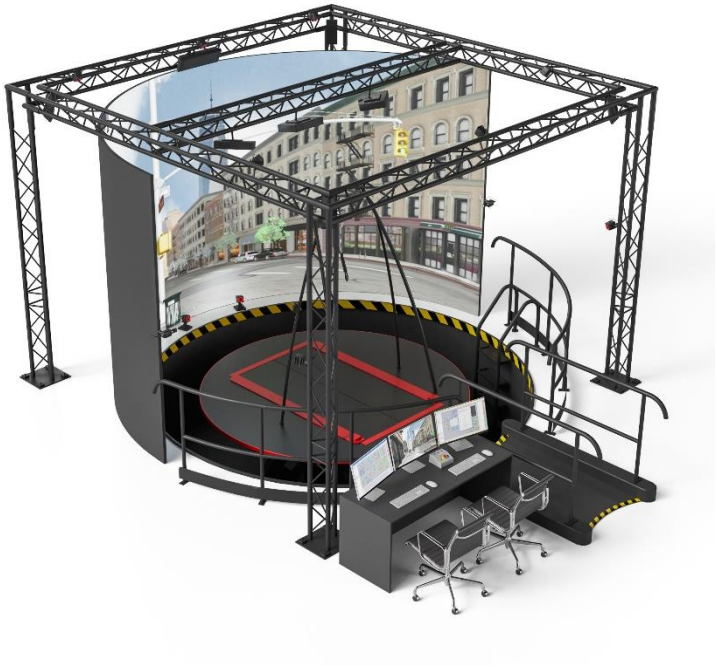


Figure 1.9: CAREN system (Credit: Motek Medical B.V.)

1.2. Functional electrical stimulation (FES)

FES is one of the oldest technologies used to assist gait training. It is the application of a low-level electrical current to elicit contraction in specific weak or paralyzed muscles due to upper motor neuron injuries/diseases such as stroke. It can be used while the user performs specific functions; for example, arm/hand control, standing, or walking. It can be used as an

assistive device, also known as a neuroprosthetic, to restore or to improve patient's movement such as foot drop during swing phase of stroke survivors. More recently, there has been clinical evidence that FES can encourage motor relearning and neuroplasticity by changing cortical excitability and stimulating cortical reorganization. This effect is called a therapeutic effect.

1.2.1. Neurophysiological principles of FES

FES uses a pair of the electrodes to create a localized electrical field by delivering an electrical current. The field can depolarize the motor nerves or nerve end plates which are nearest the electrode. If the degree of electrical stimulation is strong enough, nerve action potentials will be generated. The action potentials propagate along the axon to the terminal end, and release a neurotransmitter named Acetylcholine from synaptic vesicles into the neuromuscular junction. Finally, this Acetylcholine triggers the muscle action potentials that cause muscle fibre contraction.

The stimulus threshold for activating the nerve fibre is significantly lower than the threshold for stimulating muscle fibres directly so that the most common sites for FES are peripheral nerves and motor nerve endpoints of the target muscles. Nerves and motor points in the nearest area to the stimulating electrodes have more possibility to be activated than those farther away due to the higher density of electrical current in that area (Figure 1.10) (Wood and Swain, 2020). Hence, if the electrodes are placed in the nearest area to the neural tissue of the target muscles, the selectivity of stimulation will be increased, and the electrical intensity will be decreased.

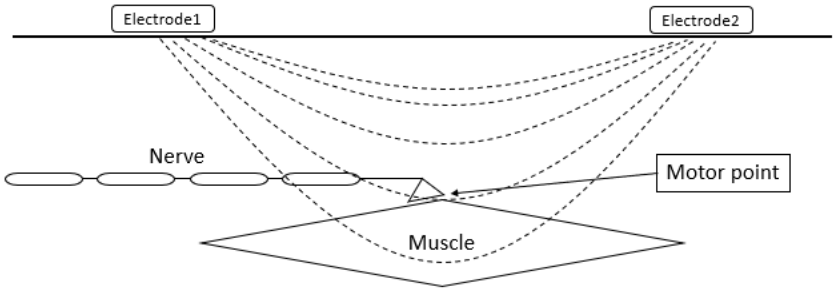


Figure 1.10: Electrical field between a pair of electrodes on the skin.

Adapted from Wood and Swain, (2020)

For physiologic muscle activation in normal people, neurons with smaller-diameter nerve fibre which innervate Type I muscle fibres are recruited first. In contrast, for the FES-induced muscle activation, neurons with larger-diameter nerve fibre which innervate Type II muscle fibres are recruit first due to a lower stimulus threshold. This phenomenon is called a “Reverse recruitment order” (Bickel et al., 2011). The characteristics of type II muscles fibres are that they are higher-force, fast-twitch, and less resistant to fatigue. Therefore, people using FES which requires sustained and repetitive muscle contraction for a long time may experience early muscle fatigue.

1.2.2. Waveform and Parameters of electrical stimulation

The electrical current waveform can be divided into 3 types including direct current (DC), alternating current (AC), and pulsed current (PC). DC and AC are a continuous monophasic and biphasic current flow, respectively. PC is an interval monophasic or biphasic current flow. Usually, biphasic PC, which can have symmetrical and asymmetrical waveforms, is the most commonly used method for FES (Figure 1.11). In addition, the key requirement for any

FES system is that the charge applied must be “Balance” in term of its polarity (no charge accumulation). This property is required to prevent complications from electrical burns.

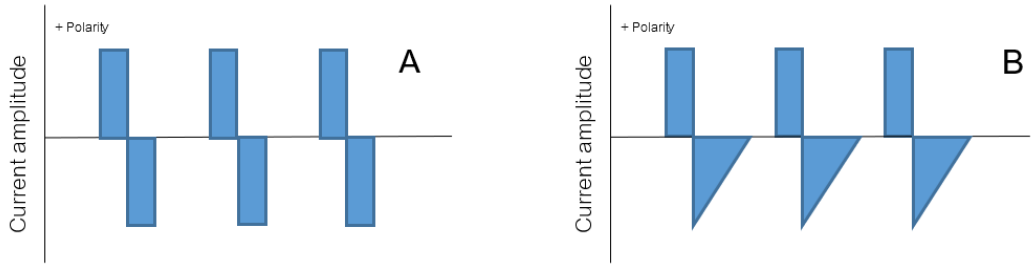


Figure 1.11: Balanced symmetrical (A) and Balance asymmetrical PC (B) waveform.

Stimulus intensity is regarded as the product of amplitude and pulse duration (Figure 1.12). The level of intensity that can generate muscle force is called the threshold of stimulation (T)

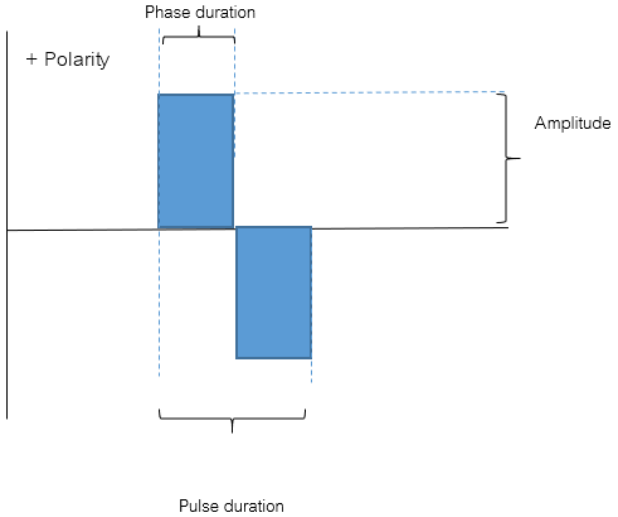


Figure 1.12: Amplitude and Pulsed duration of electrical stimulation

If the intensity rises above this threshold the muscle force will increase in a linear relationship (L) until reaching the plateau point (M) at which all muscle fibres are recruited (Figure 1.13) (Wood and Swain, 2020). Clinically, the typical pulse duration to produce muscle contraction is set between 150 to 350 microseconds. The amplitude can be increased to produce the maximal muscle contraction that patients can tolerate.

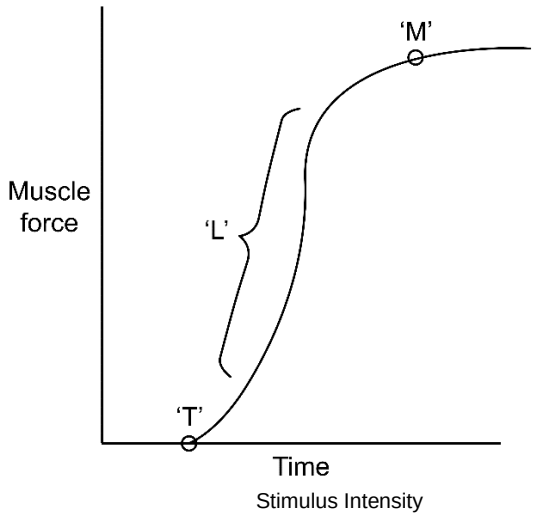


Figure 1.13: Muscle response in relation to stimulus intensity. Adapted from Wood and Swain, (2020) T = Threshold; L = Linear relationship, M = Plateau point

Frequency is the number of pulses per second (Hertz) and has an effect on the muscle force produced. Raising the frequency results in increasing muscle force due to the summation of muscle contractions (muscle tetany, Figure 1.14). However, the higher frequency reduces the rest time of muscle between stimuli, so that muscle fatigue occurs earlier in systems with high rates of stimulus and applied for a long time (Figure 1.15).

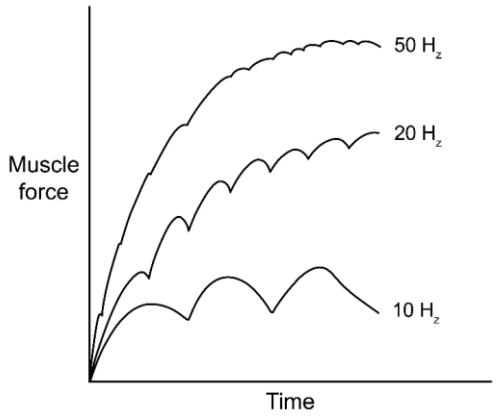


Figure 1.14: Summation of muscle contraction in relation to stimulus frequency. Adapted from Wood and Swain, (2020)

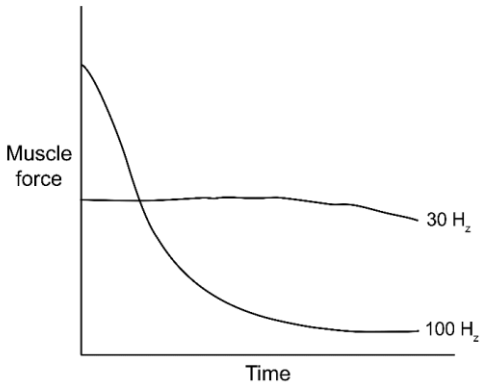


Figure 1.15: Effect of stimulus frequency on muscle fatigue. Adapted from Wood and Swain, (2020)

Ramping (Figure 1.16) is the amount of time to increase current amplitude from zero to its peak (ramp on), or to decrease current amplitude from its peak to zero (ramp down). It is used to avoid abrupt and jerky movement, and to reduce patient's discomfort.

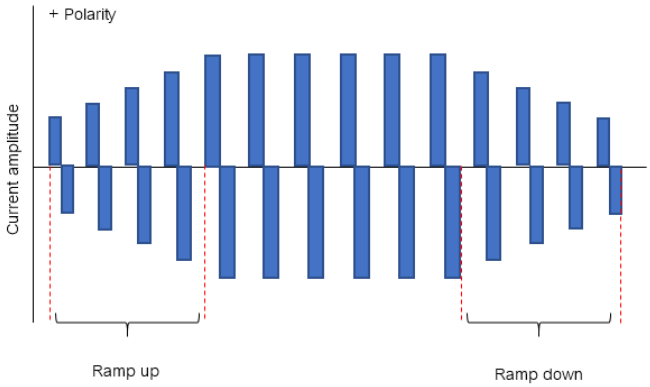


Figure 1.16: Ramping time

1.2.3. Components of a typical FES system

A typical FES system consists of a network of sensors, a control algorithm, and a stimulation unit with electrodes. The network of sensors is used to detect the phase of the gait cycle and send this information to the controller. The controller then processes and adjust inputs from sensors to the stimulation unit. The electrical stimulator should be portable, lightweight, and flexible in parameter setting (Melo et al., 2015).

Sensors

They can be divided into three categories: 1) Kinetic (Ground reaction force (GRF) assessment), 2) Kinematic (position and motion assessment), and 3) Muscle activity (Electromyography-EMG) sensors (Popovic, 2014).

The GRF is assessed by footswitches or force transducers located underneath the sole. They provide input in On/Off format to the controller. A single heel switch can be used to detect heel strike and heel off or a second

added at the toe to detect toe off and toe strike of the gait cycle. The footswitch technique is widely used in commercial FES systems to correct foot drop such as the Odstock Stimulator or the NESS L300 due to its high reliability (Melo et al., 2015). Nevertheless, this technique has some weaknesses including the fact that the sub-phases of the swing phase cannot be detected and that the accuracy and reliability of the system is dependent on the placement of sensors (Aminian et al., 2002, Taborri et al., 2016).

Kinematic sensors: for example, an accelerometer, gyroscope, or inertial measurement unit, have been used in both clinical and research settings (Melo et al., 2015, Sanchez Manchola et al., 2019). Some commercial FES systems designed to correct foot drop use this type of sensor such as the Walkaide system which uses a vertical axis accelerometer (Melo et al., 2015). There are many advantages of these sensors such as small size, low energy consumption, ability to be integrated with a microcomputer and wireless communication (Popovic, 2014). They can be used to measure kinematic parameters such as joint angle so that they can determine sub-phases of the swing phase which kinetic sensors cannot detect (Liu et al., 2009, Lopez-Meyer et al., 2011). However, the output signal is complex and depends on location of sensor placement requiring advanced control algorithm. Hence, there is an issue with reliability for these sensors (Taborri et al., 2016).

The assessment of muscle activity can be performed by measuring EMG signals from surface electrodes (Melo et al., 2015). The timing and intensity of muscle contraction is provided by this sensor. Because of the

pattern of coordinated muscle activity of lower extremity during walking, EMG can be used to determine phase of gait cycle. This sensor is less favoured in FES because the EMG signal is rather difficult to obtain in the presence of electrical stimulation, especially if many stimulation electrodes are placed close to each other. Reduction of the stimulation artefact is feasible, but this process has not been perfected yet (Popovic, 2014).

Control systems

They are normally classified into two groups depending on the configuration of the system elements. The first is a feedforward or “open-loop” control system where the output signal all proceed in one direction (figure 1.17 A). The second is a feedback or “close-loop” control system where the output signal is transduced by a sensor into a feedback signal that can be added to or subtracted from the reference signal (figure 1.17 B) (Phillips, 1991).

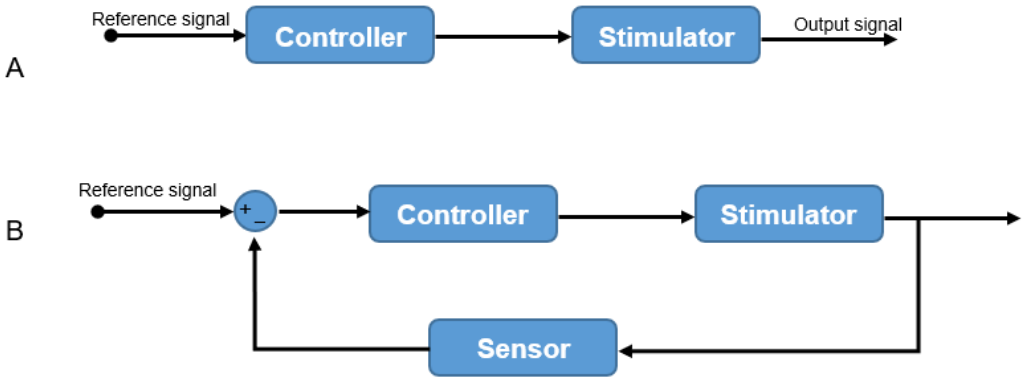


Figure 1.17: Open-loop (A) and closed-loop (B) system of FES

Nowadays, most of the FES systems that are used outside a research setting are controlled by open-loop system. Open-loop system need continuous user input meaning that the users must pay full attention during operating the device (Lynch and Popovic, 2008). Open-loop systems execute a pre-set stimulation sequence when a specific condition is met. Many commercial FES devices to correct foot drop among stroke patients; for example, the Odstock (Salisbury FES), the WalkAide (NeuroMotion, Inc.), and the L300 (BIONESS, Inc.), are operated by an open-loop system that uses a sensor to detect heel lifting of patients and then stimulates the dorsiflexor muscles to prevent the dragging foot during the swing phase. FES systems that use open-loop control do not correct for model errors or disturbance (Lynch and Popovic, 2008).

Although open-loop control is simple and reliable for controlling the stimulation, this system cannot provide performance levels equivalent to healthy people. To mimic biological control of the musculoskeletal system requires more sophisticated real-time control as well as compensation for modelling error and disturbance in other words a closed loop system. However, there are significant challenges to controlling paralyzed muscles with FES such as the coupled, non-linear, time vary behaviour and fatigue of stimulated muscles (Lynch and Popovic, 2005). There are several strategies that are used for closed-loop control; for example, Proportional-integral differential controller which use feedback to adjust stimulus intensity (amplitude or pulse duration) to keep the actual output as near to the target output as possible (Lynch and Popovic, 2008).

Electrodes

There are three categories of electrodes for FES including surface, percutaneous, and implanted.

Surface electrodes are placed on the skin and are connected with flexible lead wires to a stimulator. The advantages of surface electrode are non-invasive, relatively technologically simple, and relatively inexpensive so that they are mostly used in clinical applications. However, they have some disadvantages. The placement of electrodes in the proper locations requires skill and patience of the users. Skin problem may be developed after prolong usage and the stimulation may generate unpleasant sensation due to cutaneous pain receptor activation. Additionally, it could be difficult to provide isolated contraction in small muscles or activation of deep muscles (Peckham and Knutson, 2005).

Percutaneous (Intramuscular) electrodes use a hypodermic needle for delivering electrical current into target muscles (Peckham and Knutson, 2005). The needle is inserted through the skin and implanted in the muscle. Hence, they can activate deep muscles, and can provide isolated muscle contraction. Also, they are less likely to generate pain because they bypass cutaneous pain receptors and require less electrical intensity than surface systems. However, skin infections at the electrode site must be considered. For this reason, the skin must be cleaned, properly inspected and maintained to reduce the risk of infections. For clinical application, they can be used to investigate the feasibility of using surgically implanted system.

Implanted FES systems are designed for long-term use because a stimulator with electrodes is implanted by surgical operation. The stimulator receives power and commands via a radio-frequency telemetry link to an external control unit. The implantable electrodes may be placed on the muscle surface, within the muscle, close to a nerve, or around a nerve. Although these systems are more invasive and expensive, they can eliminate the disadvantages of surface and percutaneous systems (Peckham and Knutson, 2005).

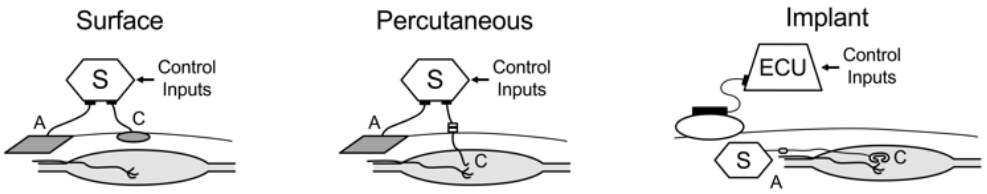


Figure 1.18: Three types of electrode system. S = stimulator, A = anode (reference electrode), C = cathode (active electrode), ECU = external control unit. Adapted from Peckham and Knutson, (2005)

1.2.4. FES used to restore gait performance after stroke

FES to correct foot drop

According to guidelines for adult stroke rehabilitation and recovery endorsed by the American Academy of Physical Medicine and Rehabilitation and the American Society of Neurorehabilitation in 2016 (Winstein et al., 2016), an Ankle-foot orthosis (AFO) is recommended for stroke patients with gait abnormalities such as foot drop to improve mobility, and ankle and knee kinematics of the paretic leg as well as energy expenditure of walking (Class

I, Level of evidence A). However, most AFOs are passive assistive devices with little or no neuro-stimulatory effect and hence no ability to effect neuroplasticity. They also restrict normal movement of the ankle foot complex. Hence, another option to correct foot drop that is also recommended as a reasonably alternative to an AFO is a FES-based system (Class IIa, Level of evidence A).

There is clinical evidence in patients with chronic stroke to support the conclusion that the benefits of FES to correct foot drop when walking were comparable with those produced by an AFO. For example, a multi-centre RCT in 2014 (Bethoux et al., 2014) enrolled 495 chronic strokes who had foot drop to compare the effect of AFO and FES (the WalkAide system) on gait speed (10-Meter walk test), a composite of the Mobility, Activities of Daily Living, and Social participation subscores on the Stroke Impact Scale, and device-related serious adverse event rate as primary endpoints. The results indicated that FES was not inferior to AFO for all primary endpoints. Another large multi-centre RCT (overall 197 participants) (Kluding et al., 2013) compared the effect of the NESS L300 Foot Drop stimulator and an AFO device on gait speed (10-Meter walk test in comfortable and fast speed) as primary endpoints. After 30 weeks of follow up, the results revealed that both groups had significant improvement in gait speed but there were no significant differences between-group comparison. Nowadays, there have been many commercial FES stimulators launched into the markets (Table 1.3).

Table 1.3: Commercial FES stimulators to correct foot drop (Melo et al., 2015).

Model	Type	Channels	Pulse type	Simulation parameters		
				Amplitude (mA)	Pulse width (µs)	Frequency (Hz)
Actigait	Implant	4	Balanced symmetrical	Up to 1.2	Up to 300	5 to 50
STIMuSTEP	Implant	2	Balanced asymmetrical	Up to 1.6	300	30
Ness L300	Surface	1	Balanced symmetrical	Up to 80	250/450/650	20 to 45
Odstock Pace	Surface	1	Balanced symmetrical	10 to 100	Up to 360	20 to 60
WalkAide	Surface	1	Biphasic asymmetrical	Up to 200	25 to 300	16.7 to 33

Multi-channel FES for gait rehabilitation

FES is not only used to correct or compensate for foot drop as an assistive devices, but also used for gait rehabilitation. Motor weaknesses caused by stroke normally affect gait performance during both stance and swing phases particularly in early stroke recovery. Thus, multi-site or multi-channel FES (MFES) has potential capability for assisting gait training among stroke patients.

MFES has been studied since the 1970's. In 1971, Kralj and colleagues developed the first 3-channel stimulator for the control of swing phase among patients with hemiplegia (Vodovnik and Grobelnik, 1977, Kralj

and Vodovnik, 1977a). Also, the same group of researchers conducted a study which used a programmed, six-channel surface FES system triggered by a foot switch (Strojnik et al., 1979, Kralj and Vodovnik, 1977b). During the swing phase, three muscles groups were stimulated: the ankle dorsiflexors for correcting foot drop; the knee flexors for initiating knee flexion; and the rectus femoris for knee extension and partial hip flexion. During the stance phase, at least four muscle groups had to be stimulated; the gluteus maximus, the quadriceps, the gastro-soleus, and tensor fasciae latae or gluteus medius. The preliminary results showed that this approach was successful in correction of the hemiplegic gait in both the swing and stance phases.

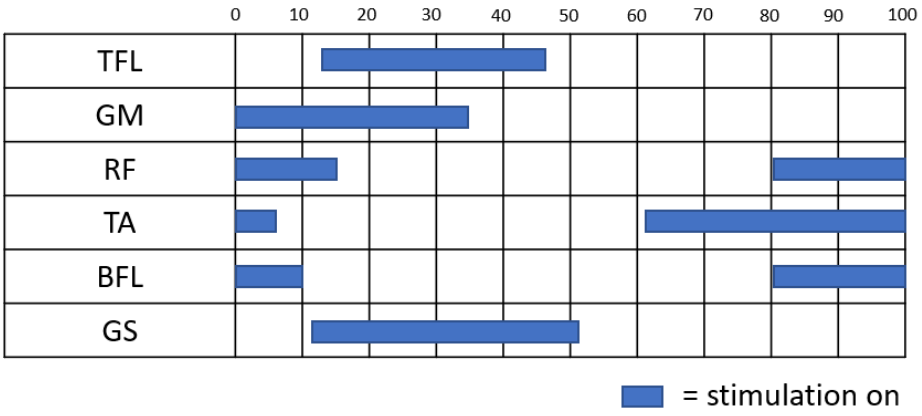


Figure 1.19: Sequence of the muscle groups that were stimulated by multichannel FES of Kralj et al (TFL = Tensor fascia latae; GM = Gluteus medius/maximus; RF = Rectus Femoris; TA = Tibialis Anterior; BFL = Biceps femoris long head; GS = Gastrosoleus) (Kralj and Vodovnik, 1977b).

Bogataj et al investigated six-channel FES applied to the common peroneal nerve, the soleus muscle, the quadriceps femoris muscle, the hamstring muscle, the gluteus maximus and the triceps brachii muscle to improve gait performance among twenty chronic hemiplegic patients (sixteen participants were stroke patients). A one group pre-test/post-test study was conducted. After receiving two- to three-week therapy (five days per week), The results demonstrated that MFES provided potential beneficial effects for severe hemiplegic patients on gait parameters and ground reaction force as well as visual assessment (Bogataj et al., 1989). To explore the effectiveness of this multichannel FES, they also conducted a two-group comparison study (cross-over design). In this study, twenty patients with severe hemiplegic stroke received MFES therapy added to conventional therapy. The study divided subjects into two groups: 3 weeks of MFES followed by 3 weeks of conventional therapy alone and 3 weeks of conventional therapy alone followed by 3 weeks of MFES. The evidence form this study showed that MFES therapy had a positive effect on temporal-distance variables (stride length, gait cadence, and speed), ground reaction force, and Fugl-Meyer scores (Bogataj et al., 1995).

MFES combined with treadmill training with BWS

There is some evidence that MFES can improve gait kinematics for stroke patients with a gait impairment. MFES system can help provide more normal kinematics of hip, knee, and ankle during the swing phase. However, pelvic control, knee control, ankle stability during stance phase could not be efficiently supported by MFES. Additionally, patients with FES alone may not

achieve the target dosage in terms of gait training time and repetitions with an MFES system alone due to the high cardiovascular demands from abnormal gait, and the muscle fatigue caused by electrical stimulation. As mentioned before, treadmill training with BWS has been shown to have some benefits for gait training in stroke; for example, by reducing cardiovascular demand, eliminating fear of falling, and preventing adverse event from falling. As such it can help patients to better control the pelvis and lower extremity during the stance phase. However, some weaknesses of traditional treadmill training with BWS should be noted. Multiple therapists are required to progress the hemiplegic limb of patients during the swing phase manually which may create a repetitively abnormal swing phase pattern and is labour intensive.

Hence, the combination of MFES and treadmill training with BWS may have a greater positive effect on walking recovery after stroke than either treatment alone by making use of the advantages of one treatment to help with the disadvantages of the other (Postans et al., 2004, Daly and Ruff, 2004). Daly et al carried out a feasibility study of the combination of these two treatments. Eight chronic stroke patients (>12 months post stroke) were enrolled into this study. All participants were treated with the same protocol for 12 weeks, 90 minutes per session, 4 sessions per week. Each session included 30 minutes exercise, 30 minutes over-ground gait training, and 30 minutes combination of MFES (open-loop eight-channel stimulator based on force sensing resistors) and treadmill training with BWS. They found that the combined treatments were safe and feasible and there were significant

improvements in motor impairment and function outcomes (Daly and Ruff, 2004). They also conducted two randomized controlled trials of MFES in 2006 and 2011 among chronic stroke patients (32 subjects with >1 year after stroke for 2006, and 53 subjects with > 6 months after stroke for 2011) to examine the effect of MFES support combined with exercise, over-ground gait training, and treadmill training with BWS compared with the control group who did not receive MFES support (Daly et al., 2006, Daly et al., 2011). The MFES system and treatment protocol was the same as the pilot study. The MFES target was to restore ankle dorsiflexion during swing phase, knee flexion at toe-off, knee flexion during swing, knee extension before heel strike, and knee and pelvic control during stance. They found that added MFES support could significantly improve walking ability compared with the control treatment at the end of the programme (Daly et al., 2006, Daly et al., 2011) and the improved gait function was also seen at the 6-month follow-up (Daly et al., 2011).

1.3. Biofeedback feedback

1.3.1. Background

Physiologic sensory feedback is an essential function in the modulation of our motor control (Friesen, 2009). Patients after stroke often have impaired sensory feedback, thus making it difficult for them to recognise and to control their body movements (Bolognini et al., 2016). Biofeedback is a technique to provide patients (or clinicians) with biological information measured by the use of instruments of their body movement and sometimes it is known as augmented or extrinsic feedback (Huang et al., 2006). It can provide

physiological and biomechanical information during training and is typically shown in the form of a visual display and/or sound (Giggins et al., 2013). Physiological feedback of muscle activation measured using electromyography has been used to improve muscle control while biomechanical biofeedback which can be measured by inertia sensors, electrogoniometers, force plates, or camera systems has been used for training in balance, posture control, and whole body movement (Giggins et al., 2013).

1.3.2. Principle and concept

The effect of biofeedback in stroke rehabilitation on the neurological system remains unclear at this time. One possible mechanism is that unused or underused neural pathways for motor commands are activated due to new sensory engrams (Huang et al., 2006). In the past, biofeedback was used to re-educate single muscle activity in static positions or simple movements unrelated to a desired function which this old concept of biofeedback might not benefit motor and functional recovery in patients with stroke due to the no task specific nature of the practice (Huang et al., 2006). The concept of task-specific repetitive training is widely accepted and used in stroke rehabilitation (Winstein et al., 2016). This concept suggests that biofeedback for stroke should be provided in real time during dynamic movement of task-specific training to enhance neuroplasticity (Huang et al., 2006).

1.3.3. Visual feedback of gait performance for gait rehabilitation after stroke

Stanton et al (2011) conducted a systematic review and meta-analysis of the effect of any type of biofeedback on motor activities of the lower limb such as sitting, sit to stand, standing, and walking after stroke (Stanton et al., 2011). Ten high-quality studies (241 participants) were included in the final analysis and the results showed that there were significant improvements in lower limb activities in the biofeedback group compared with usual care/placebo group (SMD 0.49, 95%CI 0.22 to 0.75) (Stanton et al., 2011). The updated version of the systematic review (Stanton et al., 2017) included eighteen moderate-to-high quality studies (429 participants): 11 studies for weight distribution (force plate/sensor); 3 studies for muscle activity (EMG); 3 studies for step length/width (foot sensor); and 1 study for joint angle (goniometer). Visual feedback (8 studies), auditory feedback (8 studies) and a combination of both (4 studies) were used. The results continued to show that biofeedback had a moderate beneficial effect on standing/walking when compared to usual care (SMD 0.50, 95%CI 0.30 to 0.70) (Stanton et al., 2017). Hence, based on the positive treatment effect that was found in the systematic review (Stanton et al., 2017) and the principles of motor relearning concept that require training-related feedback (Belda-Lois et al., 2011), providing patients with stroke with biofeedback in gait rehabilitation appears a reasonable intervention.

Biofeedback can be augmented with treadmill training with BWS. For example, Gait trainer ^{TM} (Biodex) is a treadmill with BWS system which can

provide patients with visual real-time biomechanical feedback. The treadmill is equipped with force sensors and software to determine the location on the treadmill at which each foot is placed. This information was shown in real-time to patients in the form of a graphic visualisation of the foot contour on the screen in order to try to improve the symmetry of step lengths. The visual display on the screen also included time spent, distance covered, walking speed, step length. Drużbicki and colleagues conducted two efficacy studies of this treadmill training with and without visual feedback in 50 patients with chronic stroke (at least 6 months after onset) and 30 patients with subacute stroke (up to 1 month after onset) in 2015 and 2018, respectively (Druzbicki et al., 2015, Druzbicki et al., 2018). In both studies, participants were randomly allocated into 2 groups equally: biofeedback group or control group (no visual feedback). In chronic stroke study, participants received 10 sessions of gait training (5 day a week for 2 consecutive weeks) whereas participants in subacute stroke study received 15 sessions of gait training (5 day a week for 3 consecutive weeks) (Druzbicki et al., 2015, Druzbicki et al., 2018). The results in the chronic stroke study showed an insignificant difference of improvement on over-ground walking speed (10-MWT) (mean changes in Biofeedback group = 0.18 m/s vs Control group = 0.12 m/s; p = 0.131) and distance (2MWT) (mean changes in Biofeedback group = 18.6 m vs Control group = 16.6 m; p = 0.577) between 2 groups (Druzbicki et al., 2015). However, significant difference of improvement on 10-MWT (mean changes in Biofeedback group = 0.27 m/s vs Control group = 0.20 m/s; p = 0.003) and 2MWT (mean changes in Biofeedback group = 25.73 m vs

Control group = 14.0 m; p = 0.012) were found in subacute stroke study (Druzbicki et al., 2018).

Also, rather than showing the positions of the feet, step length asymmetry can be calculated and fed back visually to the user in a virtual environment during treadmill training. This system named “the integrated virtual environment rehabilitation treadmill” (IVERT) consisted of a split-belt treadmill with a front-screen. Force sensors were mounted under the treadmill to measure kinetic data in order to control treadmill speed and the virtual scene. The step length asymmetry was presented visually by showing a curved walking path in the virtual environment, and proprioceptively by increasing the difference in speed between the left and right treadmill belt (Feasel et al., 2011). A case series of using the IVERT system was reported in 2012. Two participants with chronic stroke received 6-week gait training programme (18 sessions) using the IVERT system followed with over-ground training and some positive results such as improved asymmetry of step-length or stance time were reported (Lewek et al., 2012). However, to date, no RCTs to determine the effect of IVERT system on walking recovery after stroke have been conducted and its efficacy remain unclear.

Interestingly, lower-limb movement during gait training could be presented to patients as a real-time visual feedback. Thikey and colleagues (Thikey et al., 2012) used a 3D motion capture system and software package to create a virtual Avatar to facilitate gait re-education after stroke. In this system lower-limb movement of the patient was displayed by dynamic visualisation of a stick figure on the screen (Thikey et al., 2012). With this

kind of feedback, patients and their therapists were able to review and understand easily about their gait kinematics information. However, the publication of Thikey was a study protocol for a pilot RCT and its results have not been reported yet. Visual feedback of gait biomechanics such as temporo-spatial parameters or lower-limb kinematics seems to be a useful modality for stroke survivors who need gait re-education.

In conclusion, there is good evidence of a moderate effect on gait of MFES and Treadmill training with BWS and it is reasonable to conclude that the addition of visual feedback of gait biomechanics into gait rehabilitation after stroke may also have positive benefit .Pilot studies have been conducted involving 2 of these modalities in combination but following an extensive literature review no study was found that combined MFES, Treadmill training with BWS and visual feedback of gait biomechanics. Further the majority of these technology assisted stroke gait retraining studies were carried out in chronic patients where the capacity for neuro-plasticity has diminished compared to the acute or sub-acute patient.

There is a need to establish a method for combining MFES, treadmill training with BWS and visual feedback of gait biomechanics into one intensive intervention and piloting this with stroke patients including acute patients. If the technique proves feasible it should then be tested in a phase II trial.

Chapter 2: Thesis Aims

2. Thesis aims

According to guidelines for adult stroke rehabilitation and recovery from the American Heart Association/American Stroke Association (AHA/ASA) published in 2016, gait rehabilitation with intensive, repetitive and task-specific training has treatment benefits and is recommended for stroke survivors with gait impairment (Winstein et al., 2016). They also indicate that treadmill training with or without body weight support (BWS) which can provide progressive, intensive, walking-specific practice when used alongside conventional physiotherapy might be a reasonable approach to produce gait recovery after stroke (Winstein et al., 2016).

FES has shown a therapeutic effect on motor recovery after stroke (Lee and van Donkelaar, 1995). The AHA/ASA guideline in 2016 stated that FES for persistent foot drop is a reasonable treatment for improving mobility and biomechanics on the hemiplegic side, and reducing the energy consumption of walking (Winstein et al., 2016). Although, the guideline does not mention about Multi-channel FES (MFES), MFES-assisted gait training has been shown to give improvement in gait performance after stroke (Daly et al., 2006, Daly et al., 2011, Tan et al., 2014, Yan et al., 2005). Combining treadmill training with BWS and MFES has been shown to be feasible and safe in patients with stroke (Daly and Ruff, 2004, Daly et al., 2000).

Task-oriented biofeedback in which the user is provided with feedback during dynamic movement is another treatment that might benefit motor recovery (Huang et al., 2006). This approach has been widely used in sports biomechanics to improve task performance (Mullineaux et al., 2012,

Kiefer et al., 2015, Christie et al., 2020, Steinberg et al., 2016, Neptune et al., 2009). To be effective the biofeedback must involve both the perceptive and cognitive learning processes (Huang et al., 2006). Also, it should be attractive, motivating, and easy-to-understand for patients. Thus, visual displays of computerised graphics/animations such as virtual reality or an avatar can be used as biofeedback and might be a useful therapy for motor recovery after stroke (Huang et al., 2006, Giggins et al., 2013).

3D motion capture is the current gold standard for clinical gait analysis, but it could also be used for neurorehabilitation therapies (Subramanian et al., 2007, Ustinova et al., 2011). Using advanced computer technology, the 3D motion capture information can be used to display the real-time movement of patients' as an avatar and/or display gait parameters as dynamic biofeedback of the kinematics of the lower-extremities (Millar et al., 2019). Moreover, marker trajectories and gait kinematics data can be used to determine the phases of the gait cycle and so might be used as the sensor to trigger the MFES system.

Treadmill training with or without BWS, MFES, and dynamic biofeedback of lower-extremities kinematics have each shown treatment benefit for motor recovery after stroke. Currently, there are no studies of these 3 treatments in combination for stroke rehabilitation. It may be that when combined these three modalities have a beneficial synergistic effect on motor recovery after stroke (Belda-Lois et al., 2011). It is the hypothesis of this study that the most effective therapy will be delivered using these three modalities in combination. Current technology would seem to allow the

augmentation of treadmill training with MFES, and real-time visualisation feedback for gait rehabilitation after stroke.

Therefore, the present study aims to

1. design and develop a computerised MFES system which uses motion capture data to trigger the MFES.
2. integrate this system with a self-paced treadmill with a weight support system and with a motion capture system giving biomechanical feedback in real time during gait.
3. conduct a feasibility study of this combination of augmented treadmill training using a series of case studies.
4. examine whether the developed system can be used in clinical context and the effect of augmented treadmill training on gait performance in these individuals.
5. Discuss the possible benefits and limitations of augmented treadmill training and its future implementation in clinical practice.

Based on Medical Research Council framework for the development and evaluation of complex interventions, this study is at the stage of developing a complex intervention and assessing feasibility and piloting methods.

Chapter 3: The Development of Motion Capture-based MFES

3. The development of motion capture-based FES

This chapter will provide information about the development of the research MFES system which is triggered based on the phases of the gait cycle determined by a 3D motion capture system. This chapter will describe, the components of the MFES system, why those components were chosen and how the present study determined the phase of the gait cycle. It will then examine the method used to determine the phase of the gait cycle to ensure it works well. Next a control algorithm will be developed and programmed on an Arduino board to trigger the MFES devices. Lastly, the chapter will report experimental checks to ensure the electrical stimulation can be provided at the targeted time.

3.1. Components of the developed FES system

The MFES systems consist of a network of sensors, a control algorithm, and multiple stimulation units with electrodes. In the present study, the sensors for the MFES system were markers attached to the body recorded by a 3D motion capture system. A control algorithm was developed based on the phases of the gait cycle (Finite state control) determined from these marker trajectories. The stimulators were four, commercial, dual-channel surface electrical stimulation devices with a remote hand switch trigger. They were connected using an Arduino Board as shown schematically in figure 3.1.

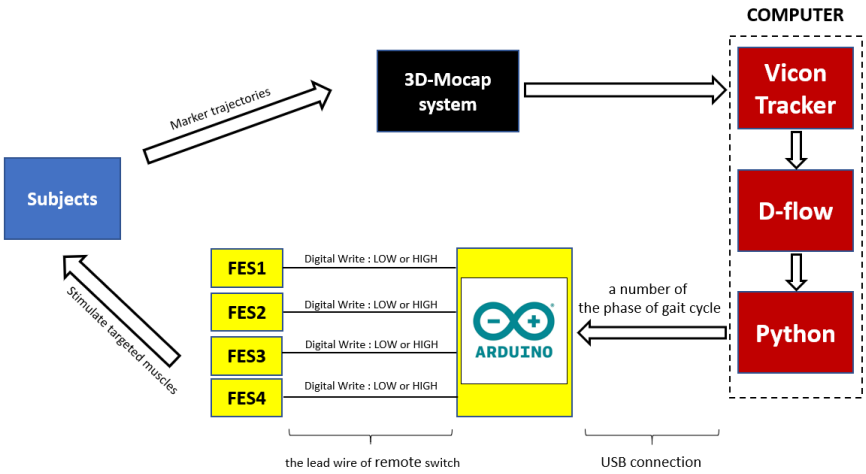


Figure 3.1: The schematic of the motion capture system triggering FES.

The 3D motion capture system as a sensor of FES system

The present study used a 6-camera Vicon motion capture system installed around the treadmill (3 cameras in front of and 3 cameras behind the treadmill). A cluster marker model with pointer anatomical calibration was used for lower-limb kinematics (Millar et al., 2019). Seven sets of cluster markers, each with an individualised, asymmetric, and unique configuration of 4 markers on a plastic plate, were used to track the pelvis, both thighs, both shanks, and both feet. Vicon Tracker Software was used to identify each cluster as an independent object and to stream marker trajectories at a frame rate of 60 Hz into the D-Flow software (Motekforce Link, Netherlands). The purpose written D-Flow application was able to manipulate the marker data and calculate the required information from the 3D motion capture data using computer scripts written in Lua language or using modules provided by D-Flow. Hence, the D-Flow application allowed calibration of key anatomical landmarks of the lower limb and pelvis using a pointer, the calculation of joint

kinematics, and the determination of the phase of the gait cycle at 60 Hz in real time.

For the present study, the toe marker trajectory in the anterior-posterior (AP) direction of both feet was used to determine the phases of gait cycle in real time (Pham et al., 2017, Supakkul, 2017) and this method can divide the phase of the gait cycle into five phases: 1. First double support (1DS), 2. Single support (SS), 3. Second double support (2DS), 4. Early swing (ESw), and 5. Late swing (LSw).

For treadmill walking, the stance phase was determined when the toe marker moved backward (as the treadmill on which the foot is resting is moving backwards) whereas the swing phase was determined when the marker moved forward (Supakkul, 2017). The present study needed to determine the phase of the gait cycle in real time for triggering the MFES. It was determined that this signal contained some noise and could therefore be falsely triggered. Some noise reduction techniques such as filtering can be used but may cause latency in the system. Hence, the summation of toe marker X-position over the last 5 frames (5-sum X) was used to determine the movement direction of toe marker and this prevented the problem from the noise affecting the reliability of this method.

Simple algorithm to determine stance and swing phase was shown below.

If 5-sum X of previous frame **>** 5-sum X of current frame,

then Stance = 1 **else** Stance = 0.

Table 3.1: Stance and swing phases determined by toe marker trajectory in AP direction

Time	X-position of toe	Last 5-frame summation		Stance
		Current frame	Previous frame	
4144.269	0.159173	0.58156	0.451127	0
4144.285	0.169711	0.688123	0.58156	0
4144.299	0.175835	0.769427	0.688123	0
4144.316	0.177304	0.825613	0.769427	0
4144.332	0.174459	0.856483	0.825613	0
4144.349	0.168463	0.865772	0.856483	0
4144.365	0.160885	0.856946	0.865772	1
4144.381	0.15348	0.834592	0.856946	1
4144.397	0.146283	0.803571	0.834592	1
4144.414	0.139139	0.76825	0.803571	1
4144.429	0.131054	0.730842	0.76825	1

For the example given in Table 3.1, at frame time 4144.365, the stance phase was identified (stance = 1) because the summation of marker positions in the last 5 frames of the current frame (0.856946) was lower than that of the previous frame (0.865772). In this way, the script was designed to track the toe marker moving backwards as its positional values decreased. The first frame determined to occur during stance phase was defined as the initial contact (IC) event. Conversely, rising positions were used to detect the swing phase (stance = 0). The first frame determined to occur during swing phase was defined as the toe off (TO) event.

After establishing the stance and swing phases of both feet, the gait cycle on the plegic side was divided into 5 phases: 1DS, SS, 2DS, ESW, and LSW, denoted by numbers 1, 2, 3, 4, and 5, respectively, in Figure 3.2. The frame time at IC of each foot was required to classify 1DS and 2DS phases.

When stance phase was identified on both feet, 1DS was determined if the frame time of IC on the plegic side was greater than that of the non-plegic side; whereas 2DS was determined if the frame time of IC on the non-plegic side was greater than that of the plegic side. Lastly, LSW was determined when the x-position of the toe marker on the plegic foot moved beyond the non-plegic foot.

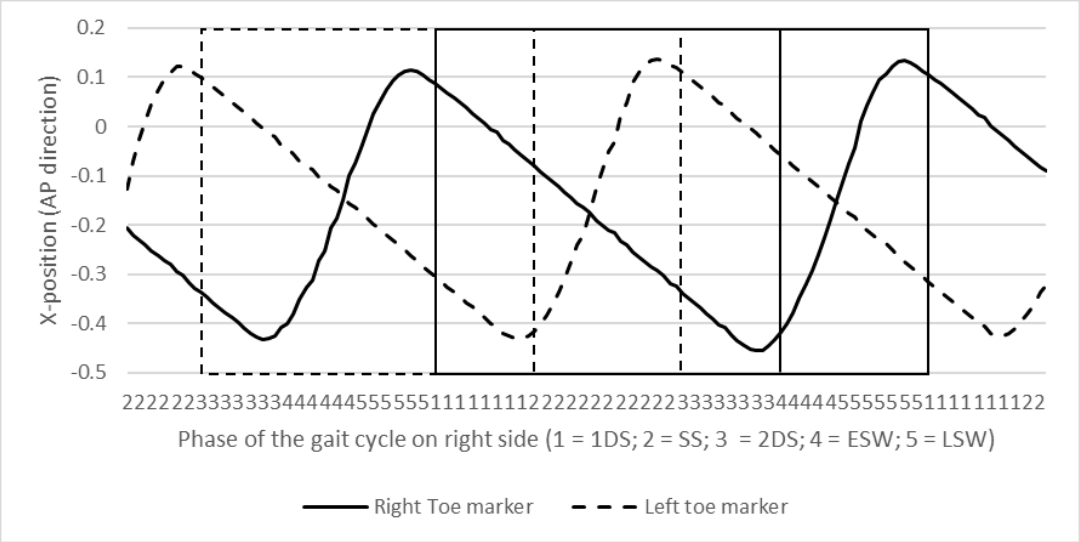


Figure 3.2. The 5 phases of the gait cycle calculated compared to the toe marker trajectories for both feet.

The details of algorithm used to determine the 5 phases of the gait cycle is shown below.

If Stance on plegic side = 1 **AND** Stance on non-plegic side = 1 **AND** frame time of IC on plegic side **> or =** that on non-plegic side

Then Phase = 1 (1DS)

If Stance on plegic side = 1 **AND** Stance on non-plegic side = 0

Then Phase = 2 (SS)

If Stance on plegic side = 1 **AND** Stance on non-plegic side = 1 **AND** frame time of IC on non-plegic side **> or =** that on plegic side

Then Phase = 3 (2DS)

If Stance on plegic side = 0 **AND** Stance on non-plegic side = 1 **AND** Toe marker x-position on plegic side **< or =** that on non-plegic side

Then Phase = 4 (ESW)

If Stance on plegic side = 0 **AND** Stance on non-plegic side = 1 **AND** Toe marker x-position on plegic side **>** that on non-plegic side

Then Phase = 5 (LSW)

After the phase of the gait cycle was determined, D-Flow sent this information as a single number (0 = No determination, 1 = 1DS, 2 = SS, 3 = 2DS, 4 = ESw, 5 = LSw) to the Arduino board (Controller of FES) at a rate of 60Hz via its network module and Python software. The connection between the computer and Arduino board was achieved using a USB cable rather than by WiFi or Bluetooth so as to achieve good reliability.

As explained in the rationale chapter patients were to receive real-time visualisation feedback from the motion capture system during their gait training sessions. The present study made use of this sensor network to also trigger our MFES system. Hence, no more sensors were needed to provide MFES to our patients. The advantage of the determination of gait phases in

the present study was that it can determine subphases of both stance and swing phases whereas all MFES system for gait training in the previous studies used foot switch or force-sensitive resistors as sensors of their MFES system which has no capability to determine subphases of the swing (Bogataj et al., 1989, Daly et al., 2011, Stanic et al., 1978, Strojnik et al., 1979). So, the previous studies had to rely on a timer-based stimulator for triggering FES devices during swing phase. If required more of the sensor data from the motion capture system could be used for the MFES system trigger for example knee or hip angle but for this feasibility study were used a simple foot contact based model of MFES.

Arduino board as a controller of the FES system

The Arduino board is a small electronics board containing all the components required to produce a microcontroller. Also, it can communicate with a computer, and can be connected to sensors or actuators. The board is programmed using the Arduino software called the Integrated Development Environment (IDE). The IDE is a special programme running on a computer that can write sketches (Arduino's scripts) and then upload to the board through a USB connection. Once, the sketch is uploaded onto the board, it is stored even if the board is turned off or reset and is only replaced when a new script is uploaded via the USB cable. The Arduino can be powered using a small lithium battery and hence is inherently safe for patient use as there is no mains connection once it has been programmed.

The Arduino board has digital pins that can be either inputs used to read information from sensors or outputs used to control actuators. These pins can read or output one of two values (HIGH or LOW). The electrical stimulators were set as actuators of the Arduino board. The HIGH and LOW output are similar to pressing and un-pressing the remote switch, respectively. Hence, the pushbutton of the switch was removed and replaced with Arduino output via a 3.5 mm Jack plug. The Arduino board was contained in a 3D printed plastic box (Figure 3.3) and the lead wire of remote switches of the electrical stimulators was connected to the Arduino board via 3.5 mm jack plug and socket.

Figure 3.3: The controller box containing the Arduino board with jack sockets.

As the present study used the commercial electrical stimulation devices, all stimulation parameters required pre-setting and were not able to be adjusted during gait training under computer control (Open-loop control). After using the stimulator to find out the suitable amplitude of stimulation for the targeted muscle, the jack plug of the remote switch was inserted into the

socket assigned for each muscle on Arduino control box (Figure 3.3) resulting in stimulation being stopped. Once the connection between the stimulator and Arduino had been made, stimulation could be started and stopped under computer control, but the level of stimulation was set by the researcher manually so preventing the computer from accidently over stimulating the subject. As stated previously the stimulation control algorithm was based on the phase of the gait cycle (Finite state control).

The script in Arduino was written to output HIGH or LOW to all four electrical stimulators depend on the state of the devices (0 = stimulation being stopped and 1 = stimulation being started) and the phases of the gait cycle (0, 1, 2, 3, 4 and 5). The state of the devices was changed; “0” to “1” or “1” to “0” if the output from the Arduino board changed from LOW to HIGH which is similar to pressing the pushbutton of the remote switch. For instance, pre-tibial muscle needed to be stimulated during 2DS and the whole of the swing phase. Therefore, the digital pin for FES of the pre-tibial muscle was set to output LOW most of the time. As shown in Figure 3.4, the Arduino sent an output HIGH pulse to start stimulation when the first frame of 2DS was detected. It output a second HIGH pulse to stop stimulation when the first frame of 1DS was detected. Hence the stimulation was on during 2DS and the whole of the swing phase.

Figure 3.4. Software-controlled FES for pre-tibial muscle

The details of algorithm used to trigger FES for the pre-tibial msucle are shown below.

```
If phase ≠ 0 then
    If phase ≠ previous_phase then
        If phase = 1 and previous_phase = 5 then
            If fes_state = 1 then output = HIGH else output = LOW
        If phase = 2 and previous_phase = 1 then
            output = LOW
        If phase = 3 and previous_phase = 2 then
            If fes_state = 0 then output = HIGH else output = LOW
        If phase = 4 and previous_phase = 3 then
            output = LOW
        If phase = 5 and previous_phase = 4 then
            output = LOW
    If phase = previous_phase then
        output = LOW
If phase = 0 then
    If fes_state = 1 then output = HIGH else output = LOW
If output = HIGH and previous_output = LOW then
    fes_state = 1 - fes_state
```

FES Stimulation unit and electrodes

Four, NeuroTrac® Rehab (Model number: ECS305A), dual-channel surface transcutaneous electrical nerve stimulation (TENS) and neuromuscular electrical stimulation (NMES) devices with remote switch control manufactured from Verity Medical Ltd, the UK, were used in the present study. Their technical data are shown in Table 3.2.

Table 3.2**:** Technical information of NeuroTrac® Rehab device

Output current	0-90 mA (with 500Ω load)
Waveform	Asymmetrical, rectangular, biphasic
Pulse Frequency	2- 200 Hz [5% accuracy]
Pulse Width	50-450 μs [10% accuracy]
Weight	90 g
Power supply	9V battery

The device provides 10 pre-set TENS programmes and 10 pre-set NMES programmes. However, this study used the customisable programme (P 15) with 300 μs of pulse duration, 30 Hz of pulse frequency based on the previous studies (Bogataj et al., 1989, Yan et al., 2005). Amplitude (mA) was maximised to reach appropriate muscle function without pain or discomfort. The customised stimulation protocol could be started and stopped with the remote switch (Figure 3.5). The stimulation can be stopped and then re-started by briefly pressing the pushbutton of the remote switch. Self-adhesive reusable skin electrodes of size 50 x 50 mm were used. Each subject had

their own set of electrodes for hygiene safety. The electrodes were placed at the motor point of the targeted muscles.

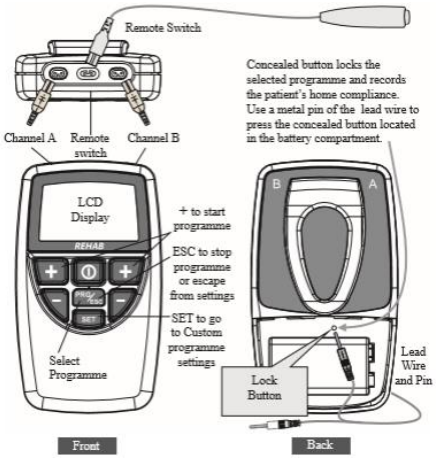


Figure 3.5: NeuroTrac® Rehab

The present study used surface electrical stimulation because it is non-invasive, and easy to don and doff in an outpatient clinic. Up to four dual-channel stimulators could be triggered using the developed software controller (Arduino). This number of FES devices should be enough to support patients during gait training. The present study decided to use commercial electrical stimulation devices to avoid difficulties of ethical approval for clinical trials using non-CE marking products. NeuroTrac® Rehab device was chosen because it is a certified medical device in the UK with CE marking and manufactured in the UK. It also has the remote switch facility which allow the user to stop and start electrical stimulation manually or by computer. The present study did not do any modification to the electrical stimulation machine other than replacing the manual triggering from the pushbutton switch with software triggering from Arduino's digital output.

3.2. Validation of the phase of the gait cycle as determined in this study and when compared with previous studies

A number of other studies reported in the literature have used kinematic data to determine the phases of the gait cycle (Bruening and Ridge, 2014). The study of Zeni and colleagues (2008) produced one of the most widely used algorithms to detect gait events using the peak values of foot marker position to locate initial contact (IC) and the minima to detect toe off (TO) for treadmill walking (Zeni et al., 2008). They collected marker kinematics at 60 Hz with a six-camera motion capture system. The kinematic-based gait events were compared to force-plate data which was defined as a gold standard test. Among healthy subjects, Zeni reported that maximal error of the event detection was 3 frames (~ 50 ms), and accuracy rate to determine gait events within 1 frame (16.67 ms) of the ground-reaction force event were 83.24% to 87.43% for IC and 94.76% to 95.28% for TO. The most common offset was -1 frame (71.2% to 73.3% of the events) for IC and zero frames (56.02% to 60.73%) for TO. In conclusion, the Zeni's method was a simple and accurate. In addition, it was based on the position of foot marker in the AP direction during treadmill walking and kinematic data was collected at 60Hz using a 6-camera motion capture system both of which were similar to the present study. Hence, the Zeni's method was used to compare with the present study's method.

To compare the present study's method with that from the Zeni's method, the kinematic data of a healthy subject walking on a treadmill were used. Walking speed of the subject was 0.7 m/s, and the motion capture

system was the same as that to be used for the gait training of the stroke patients. Figure 3.6 shows a line graph of toe marker position in the AP direction (Y-axis) for both feet over time (X-axis) and trajectory maxima and minima used to define the IC and TO events respectively using the Zeni's method. Below the graph, the phases of the gait cycle based on the present study's method are shown. This figure shows that the present study's method determined 1DS phase slightly after the maxima of the toe marker trajectory (the IC of the Zeni), and also determined ESw phase slightly after the minima of the toe marker trajectory (the TO of the Zeni). This information shows that the present study's method had a slightly delayed detection for the IC and TO events due to the averaging of 5 frames needed in the algorithm to reduce noise.

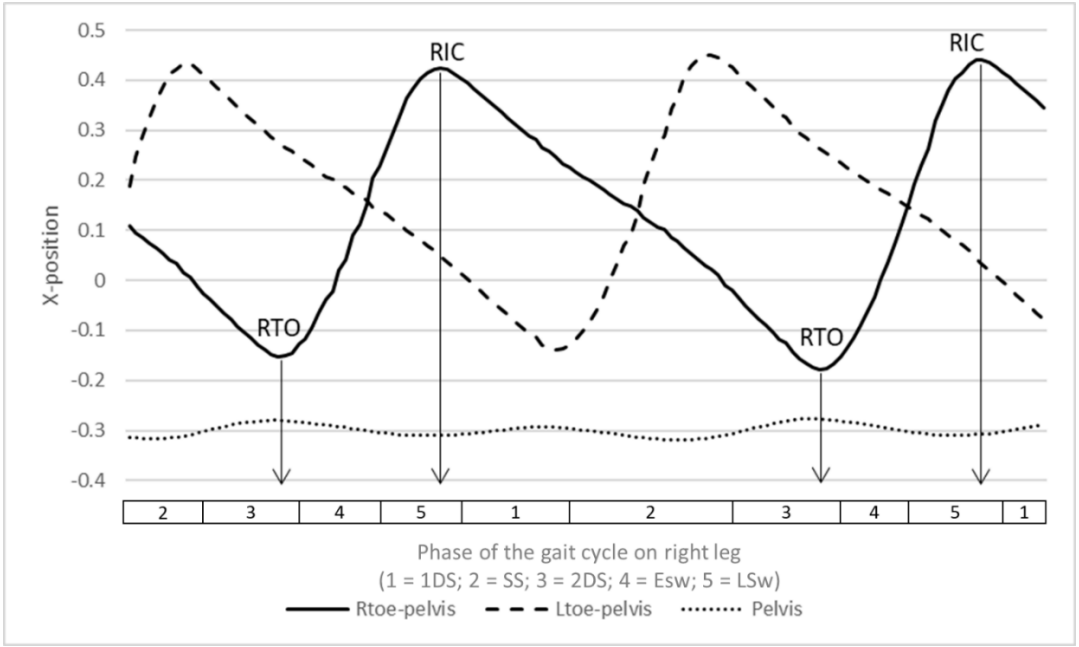


Figure 3.6: Initial contact and toe off determined by the Zeni's method compared with the phase of the gait cycle determined by this study's method.

Further, twenty-eight gait cycles (14 cycles on each side) were recorded and collected. The IC and TO event of the present study were defined as the first frame of 1DS and the first frame of ESw, respectively. Then, the time in frames between IC and TO using both methods were compared. The frame difference between IC and TO of the present study's method compared to the Zeni's method is shown in Table 3.3. This result showed that of the median offset for the IC was 3 frames (Min – Max: 3 – 4 frames) and the median offset for the TO was 3 frames (Min – Max: 2 – 4 frames).

Table 3.3: The frame offset of the present study's method compared with the Zeni's method.

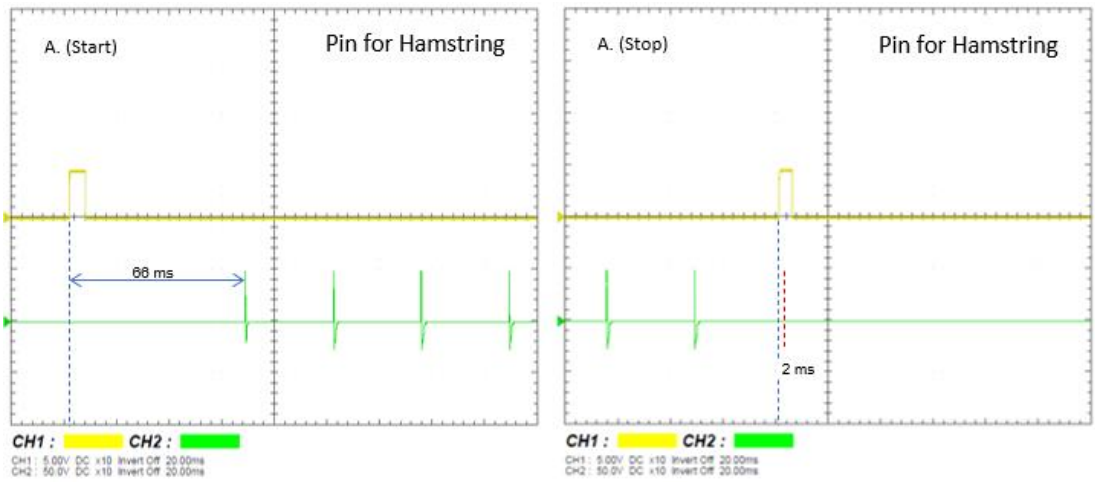
Cycle	Offset for IC: frame (ms)		Offset for TO: frame (ms)	
	Right side	Left side	Right side	Left side
1	3 (49.93)	3 (53.82)	3 (42.59)	3 (51.92)
2	3 (51.36)	3 (46.06)	3 (47.13)	4 (64.81)
3	4 (65.12)	4 (59.09)	3 (48.04)	3 (52.58)
4	3 (51.89)	3 (44.35)	3 (49.23)	3 (47.17)
5	4 (63.56)	3 (45.35)	3 (47.01)	3 (49.54)
6	4 (64.01)	3 (48.16)	3 (44.80)	3 (49.27)
7	3 (49.36)	3 (48.07)	3 (49.52)	3 (49.60)
8	3 (49.37)	3 (46.88)	3 (47.61)	3 (47.94)
9	3 (48.98)	3 (47.79)	3 (50.47)	3 (47.17)
10	4 (62.08)	4 (67.74)	3 (48.75)	3 (43.94)
11	3 (48.33)	3 (48.12)	3 (49.50)	2 (29.52)
12	3 (50.44)	4 (58.69)	2 (32.31)	4 (64.00)
13	4 (62.66)	3 (49.66)	3 (49.46)	3 (46.59)
14	3 (48.86)	4 (64.36)	3 (46.64)	3 (49.79)
Median	3 (49.93)	3 (53.82)	3 (47.82)	3 (49.40)
Maximum	4 (65.12)	4 (67.74)	3 (50.47)	4 (64.81)

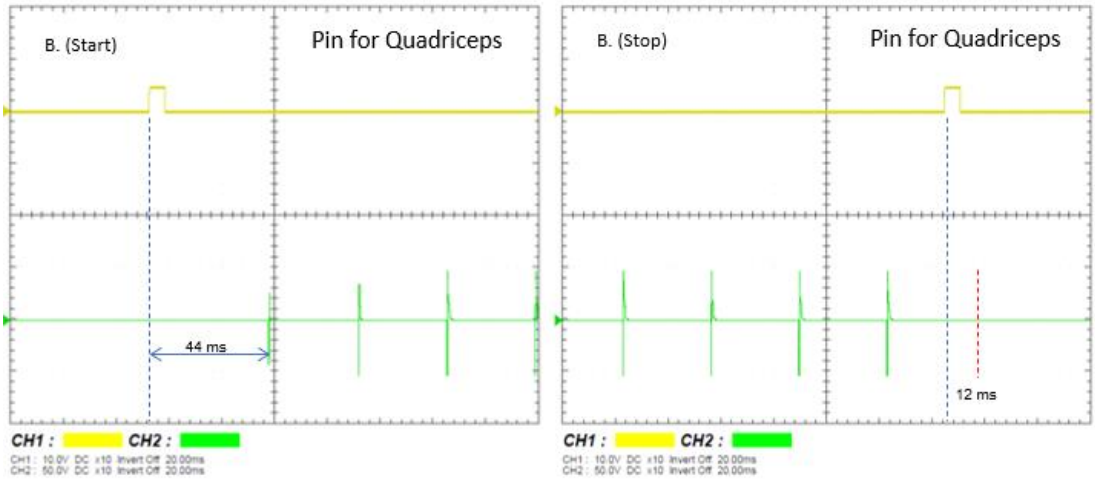
It can be seen that both IC and TO consistently occurred 3-4 frames later in this study's method than that of Zeni, again showing the effect of the moving average of 5 frames. As mentioned previously Zeni et al (2009) showed that with their method 84.29% to 87.95% of the IC frames were determined 1 or 2 frames before the force plate detection (offset frame of -2 to -1). Therefore, one can conclude that the method deployed in the present study detects IC and FC 2 or 3 frames after the force-plate detections of IC and FC in other words 30 to 50 milliseconds into stance or into swing, respectively.

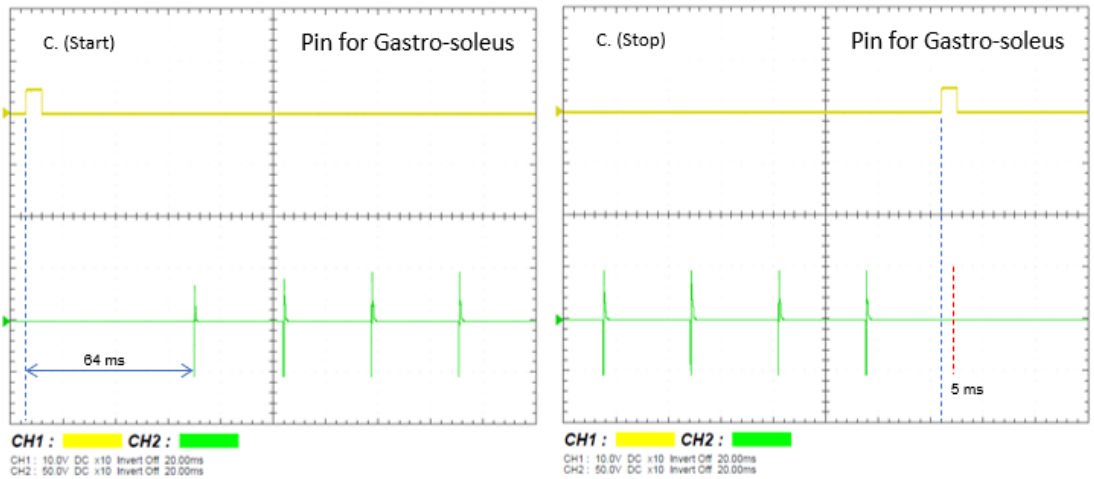
3.3. Arduino-controlled FES and its system latency

To determine whether the MFES device was consistently triggered using Arduino digital output or not and to determine the latency between Arduino output and electrical stimulation, an oscilloscope (Hantek 6022BE) was used to detect the digital signal from Arduino and the electrical waveform from the MFES devices simultaneously. In the experiment the D-Flow software determined the phase of the gait cycle from a recording file of a walking trial, and then sent those phases to the Arduino board. On the monitor of the oscilloscope (Figure 3.7), the first channel detected the digital signals from the Arduino whereas the second channel detected the electrical waveform from a stimulator (300 μs of pulse duration, 30 Hz of pulse frequency). The results showed that all four output pins of Arduino board were able to start and stop the stimulation of the MFES device. In addition, the latency in the stimulator to start stimulation ranged from 44 to 66 ms (from triggering to the

first observable waveform) and there was a latency of 2 ms to stop stimulation (from triggering to the observable loss of the waveform).







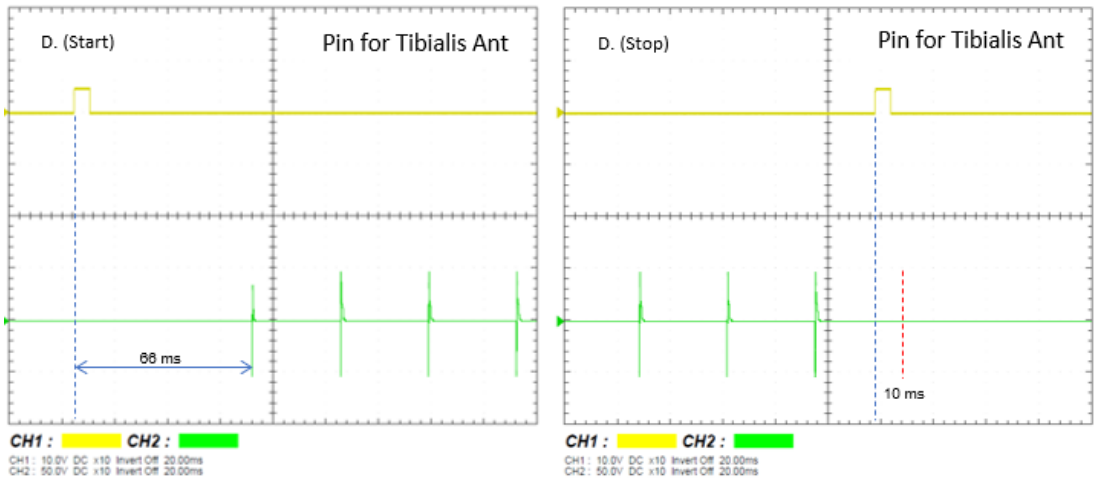


Figure 3.7: The system latency between the Arduino's output and electrical stimulation. The red dashed line is the upcoming waveform.

3.4. Pattern of FES Stimulation

Normal gait pattern relies on muscle function and coordination of leg muscles. Some stroke patients have significant loss of motor control of their leg muscles which contribute to loss of walking ability. The present study used FES stimulation to support four muscle groups during the gait training:

1. Hamstring (Semitendinosus and Long-head Biceps femoris)

Hip extensor muscles function to decelerate the limb at terminal swing to restrain the forward momentum at the initial foot contact and provide hip/knee stability during 1DS. Gluteus maximus and hamstring muscles - semimembranosus; semitendinosus; biceps femoris (long head) - are responsible for this task (Webster and Darter, 2019).

The present study intended to stimulate the hamstring muscles because they are easy to access for electrode placement when patients wear shorts whereas the buttock area needed to be exposed

for the gluteus muscle. However, hamstring can also provide knee flexion. Therefore, if more knee flexion during 1DS was found when using FES stimulation, Gluteus maximus could be selected instead.

2. Quadriceps (Vastus medialis/lateralis)

They are the key muscles for knee extension. During terminal swing, these muscles cooperate with the hamstring muscles to prepare the swinging limb for stance and are also the main muscles to provide knee stability and relieve the shock of the ground reaction force during 1DS (Webster and Darter, 2019).

3. Tibialis Anterior

It is the key muscle for ankle dorsiflexion. Its main function is to keep the ankle in slight dorsiflexion or a neutral foot position to allow foot clearance during the swing phase and to decelerate ankle plantarflexion during 1DS (Webster and Darter, 2019).

4. Gastro-soleus

This muscle is the primary ankle plantar-flexor. Tibial advancement after midstance is decelerated by eccentric contraction of these muscles, so the femur moves more rapidly than the tibia (Webster and Darter, 2019). This results in passive hip and knee extension and weight-bearing stability. In other words, hip and knee stability is dependent on the gastro-soleus muscle. Heel rise during 2DS phase requires a slightly dorsiflexed ankle but further dorsiflexion is restrained by the gastro-soleus muscle (Webster and Darter, 2019).

The Arduino board controlled four FES devices simultaneously. The time point used to trigger the start and stop of FES stimulation for each muscle channel is shown in Table 3.4.

Table 3.4: Time of Arduino's triggering

Muscle	To start stimulation	To stop stimulation
Hamstring or Gluteus	At the first frame of Late swing	At the first frame of Single support
Quadriceps	At the first frame of Late swing	At the first frame of Single support
Tibialis Anterior (pretibial)	At the first frame of Second double support	At the first frame of First double support
Gastro-soleus (calf)	At the first frame of Single support	At the first frame of Early swing

To observe if the stimulation was provided at the targeted time or not, the timing of the FES stimulation was compared with the gait cycle based on Zeni's algorithm and is shown in Figure 3.8. For gait temporal parameters in the Figure 3.8, Stride time was 1.33 s. and 1DS, SS, 2DS and Sw were 21.25%, 27.75%, 20%, and 30% of gait cycle. The time delay to start electrical impulses was about 50 ms (or 3 frames) and stimulation ceased rapidly once the Arduino's output indicated it was to be stopped as indicated by the oscilloscope. Electrical impulses in Figure 3.8 are represented as the thick coloured line.

For the hamstring and quadriceps muscles (Figure 3.8a), electrical impulses were started at 70% of swing phase and were stopped at the early SS which is similar to these two muscle's activities during normal gait cycle. For tibialis anterior (Figure 3.8b), electrical impulses were started at the early 2DS and was stopped at the early 1DS. Hence, we can be sure that the FES support offered in this study was suitable to correct foot drop during the swing phase. Normal activity of tibialis anterior can be observed from the late 2DS but the foot is still in contact with the ground at this point and hence stimulation for foot drop is not required at this time. For gastro-soleus (Figure 3.8c), electrical impulses were started at the early SS and were stopped at the very early Sw. Although the stimulation went beyond 2DS, it should not be difficult for patients to lift their foot off the ground if they had normal activity of pre-tibial muscle or received the FES to correct for foot drop.

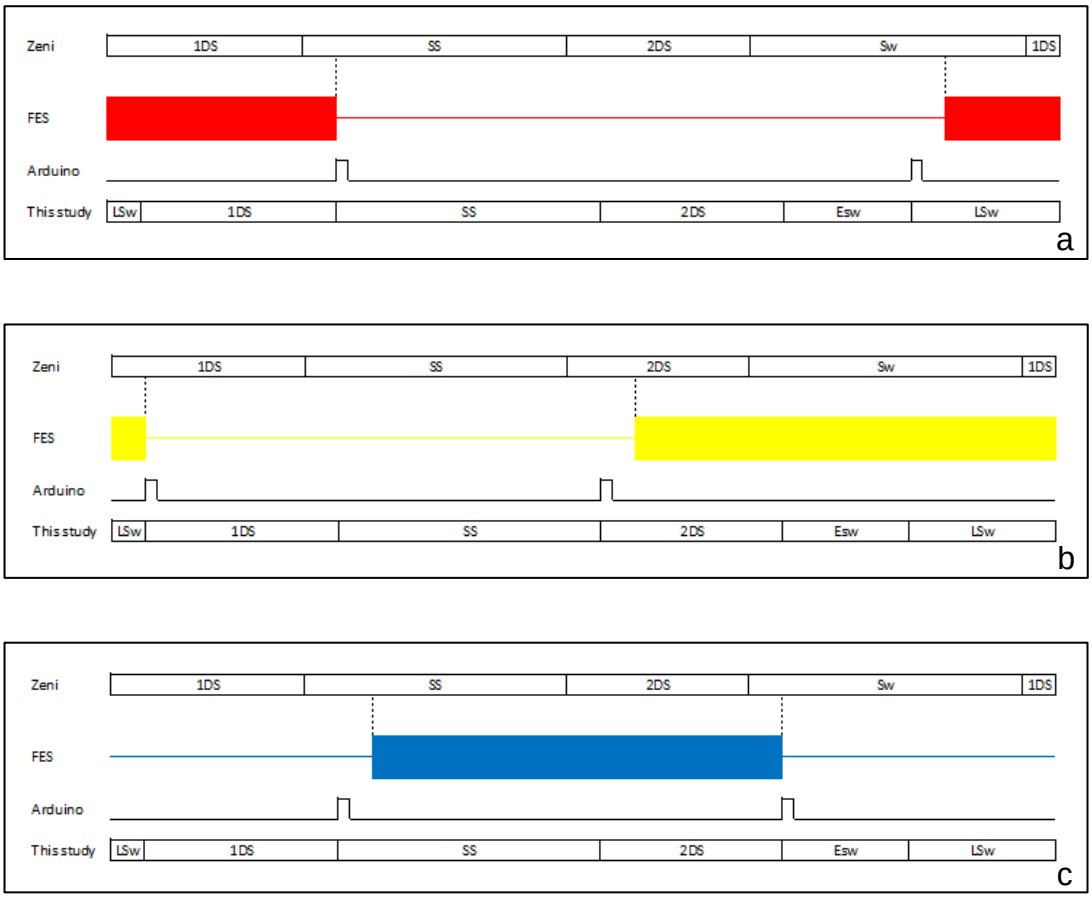


Figure 3.8: Stimulation periods for hamstring(a), quadriceps(a), pre-tibial(b), and calf (c) of the present study compared with the gait cycle determined by Zeni's method.

From this data it was concluded that the stimulation pattern produced by the system was fit for purpose despite the small latencies involved in the hardware and software. Indeed when stroke patients walk they walk considerably slower than normal meaning that the stride time is prolonged occupying many more frames than during normal gait which in turn implies that these latencies will be of significantly less import for stroke subjects than would appear to be the case from this normal data.

In conclusion, this chapter has introduced the components of the research MFES system. The FES stimulators were triggered using Arduino digital output. A control algorithm using motion capture was developed to give the phase of the gait cycle determined using the toe marker trajectories. The evidence from this chapter suggests that the research MFES system based on the 3D motion capture system could be used reliably and validly used for treadmill gait training in stroke. However, its feasibility and efficacy in clinical practice remains unknown and needs to be explored. The next phase of development was to incorporate this MFES system into a self-paced treadmill system with weight support and visual feedback which is the focus of the next chapter.

Chapter 4: Enhanced Treadmill Gait Training

4. Enhanced treadmill gait training

The enhanced treadmill-based gait training of the present study consisted of a treadmill augmented with

1 a 3D motion capture gait analysis system installed around the treadmill,

2 a real-time visual feedback system producing a stick-man avatar and some gait parameters on a TV screen at the head of the treadmill

3 a multi-channel function electrical stimulation (MFES) system to elicit contraction in targeted weak muscles of the hemiplegic leg.

4 In addition, the treadmill had a self-paced mode to allow patients to walk at their own preferred speed and

5 a body weight support (BWS) system which was used to prevent falling and to unweigh the patients if required.

4.1. 3D motion capture gait analysis

4.1.1. Hardware

3D motion capture systems have become the gold-standard for measurement and assessment of human movement because they have been shown to have excellent validity and reliability. Multiple charged-couple device (CCD) cameras are used for tracking the position of points or markers in 3D-space. The markers could be categorized into two group: 1) active or light-emitting diode markers; and 2) passive or retro-reflective markers. Although the passive markers are thought to be less accurate than active

ones, they are more widely used due to their important advantages such as the absence of wire, battery, and pulsing circuit on the subjects. The placement of the markers can be divided into two categories: individual markers or cluster placement. In the individual system, the markers are placed on the anatomical landmarks of interest for processing and calculating kinematic data with biomechanical models. Plug-in-gait (PIG) marker placement which is one of the worldwide-used protocol from Vicon is an example of an individual marker system. However, the validity of gait protocols using individual marker has been questioned due to soft tissue artefact (Leardini et al., 2005); for example, movement of the skin stretch over the femoral epicondyle during walking or running. Additionally, it might be difficult to place ASIS markers among patients with obesity or who are wearing a safety harness. Importantly, the PIG method is not very practical to use for gait rehabilitation in a clinical setting because patients need to wear tights and many markers need to be attached to the pelvis and lower extremities during before training can begin. Therefore, a clustered marker system, which uses a group of at least three markers on a fixed plate on each segment of the lower limb, was chosen for the present study so that there was no need for markers on the anatomical landmarks during dynamic activities or training.

The 3D motion capture system used in the present study consisted of six Vicon cameras fixed on a framework of aluminium alloy struts installed around treadmill as shown in Figure 4.1. Before each session, camera calibration and volume/origin set-up were conducted with the Vicon active

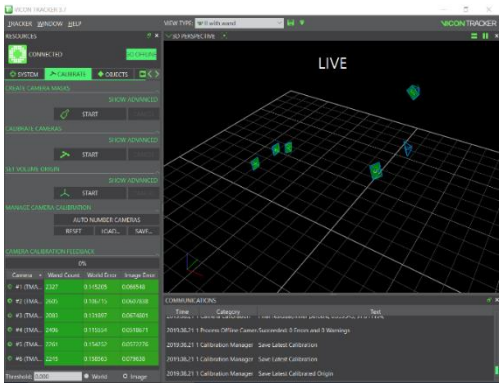
wand. A Strathclyde Cluster Model (SCM) with pointer anatomical calibration was used and found to be more suitable in clinical practice than the Plug-in-Gait model (Millar et al., 2019). It could provide visual feedback and in this study was used for lower limb kinematics (Millar et al., 2019). Active clusters consisting of 4 LED markers mounted into a flat plastic box with a rechargeable battery inside the box were used in the present study (Figure 4.2).

Figure 4.1: six cameras were installed around treadmill.

Figure 4.2: Active cluster maker

4.1.2. Software

As mentioned in the previous chapter, the present study used Vicon Tracker (Figure 4.3a) (Vicon Motion Systems, Oxford, UK) to identify each clusters set as an independent object, and to stream marker trajectory data at a rate 60 Hz into the visualisation program D-Flow (Figure 4.3b) (Motekforce Link, Netherlands). As shown in the figure 4.4, The D-Flow program was able to manipulate and calculate the input from the 3D motion capture system using scripts written in the Lua language or using the provided D-Flow modules. Hence, the anatomical calibration, the calculation of joint kinematics, and the determination of phase of gait cycle were carried out by D-Flow at 60 Hz in real time. Also, D-Flow was used to create an avatar of the subject's lower limbs and pelvis on the DRS visualisation window during gait training as real-time visual feedback to encourage motor relearning and the D-Flow package also had a module for controlling the self-paced mode of the treadmill system.

a 

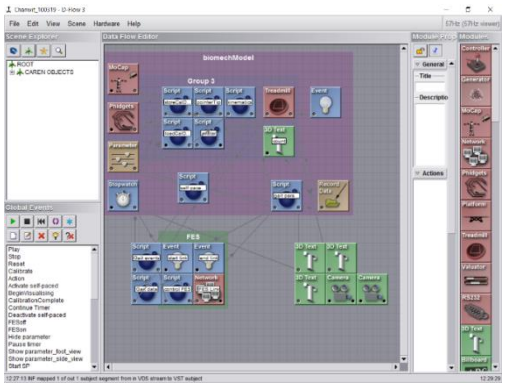
b. 

Figure 4.3: Vicon Tracker (a) and D-Flow (b).

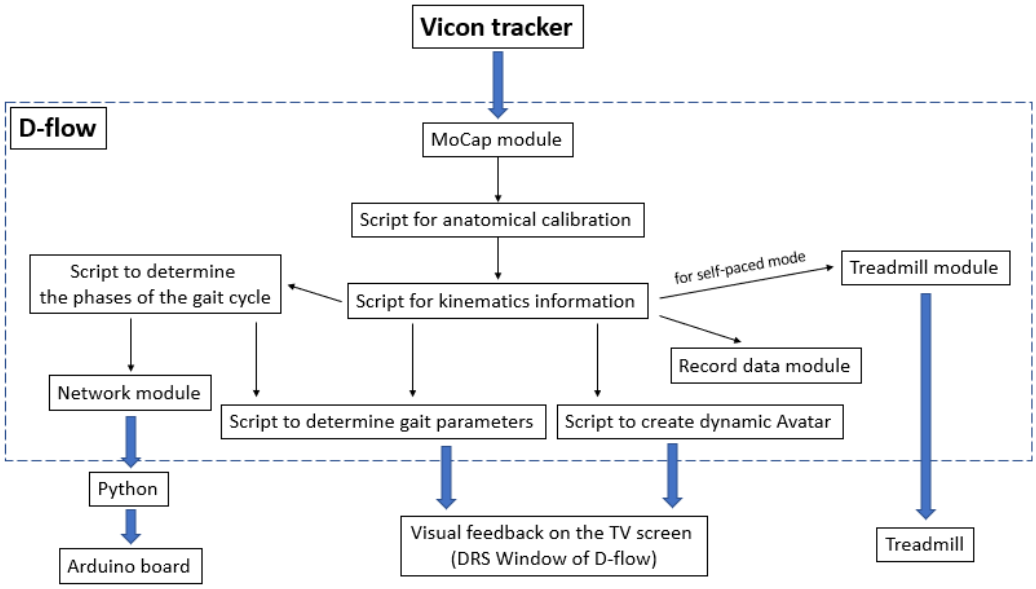


Figure 4.4: Schematic diagram of D-Flow operated enhanced treadmill training.

4.1.3. Reference frame

3D motion capture provides a position of the tracked objects relative to a reference frame for the system. This reference frame is defined during the system calibration and is called the global frame (GF). In addition, rigid objects or body segment can be assigned a local frame. The local frame is fixed in the objects, and its axes can translate or rotate in the space when the objects move. The present study has two local frames: the marker cluster technical frame (TF) and anatomical frame (AF). The TF is used to describe the movement of the clusters. During subject calibration prior to using the system a pointer is used to locate key anatomical landmarks and to describe them in the TF of the cluster. Assuming a fixed relationship between these key anatomical landmarks and the cluster, i.e that they are on the same rigid

body. allows their position to be reconstructed in the global frame during dynamic movements without a physical marker in place. These are known as virtual markers. Finally using these virtual anatomical markers an Anatomical Frame (AF) is created which aligns with the anatomical axes of that segment as defined by the anatomical landmarks of that bony segment. The AF is used to describe bony movement and the relative movement between AFs to describe joint kinematics. The transformation of the position vector between these three frames can be conducted using a 3x3 rotational matrix (Figure 4.5).

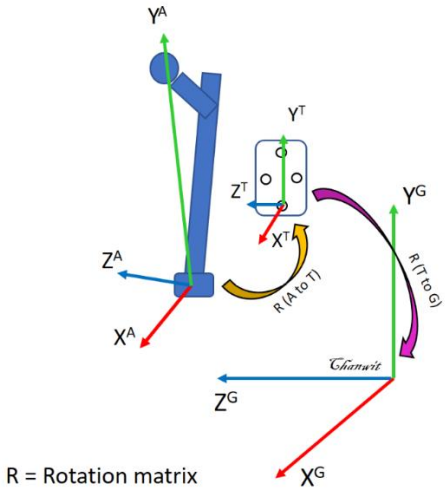


Figure 4.5: Global frame (X^G, Y^G, Z^G), marker cluster technical frame (X^T, Y^T, Z^T), anatomical frame (X^A, Y^A, Z^A).

4.1.4. Biomechanical model

This study used the SCM model for gait analysis, determination of the phase of the gait cycle, and real-time visual feedback. In a previous study the SCM model showed excellent inter/intra reliability for hip flexion/extension (ICC = 0.99/0.99), knee flexion/extension (ICC = 0.99/0.99) and ankle dorsiflexion/plantarflexion (ICC = 0.98/0.92), and kinematic results in sagittal plane were comparable to the PiG model (Millar et al., 2019). Table 4.1 and Figure 4.6 show the D-Flow coordination system used in the present study. This definition of the global coordination system followed that mostly used in biomechanics laboratories and recommended by the International Society of Biomechanics (ISB) (Cappozzo et al., 2005, Wu et al., 2002).

Table 4.1: D-Flow coordination system in this study

	Axis colour in DRS window	Default positive direction
X	Red	Forward
Y	Green	Upward
Z	Blue	Right hand side

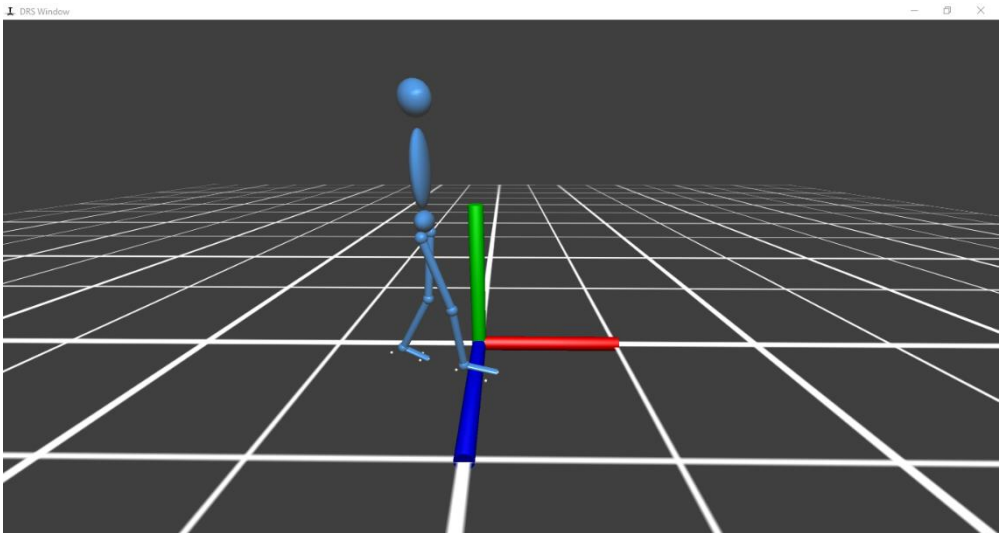


Figure 4.6: D-Flow coordination system in this study

Seven active clusters were used and attached to the posterior pelvis, both anterior thighs, both anterior shanks, and both dorsum of the feet and these were used to recreate lower limb kinematics for analysis. (Figure 4.7)

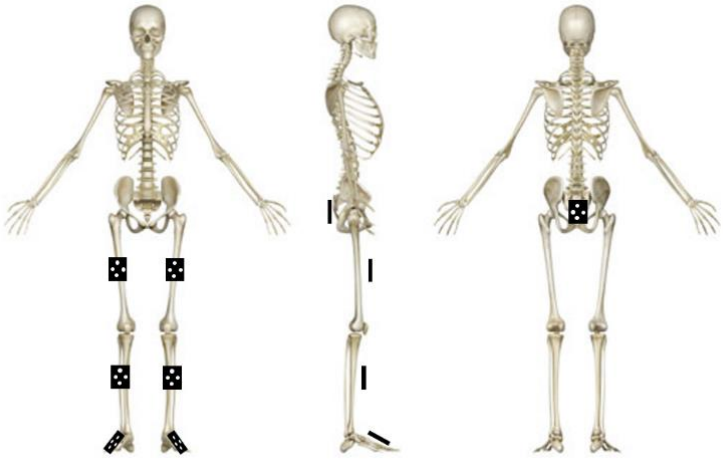


Figure 4.7: The location of cluster markers

Anatomical calibration included the left and right anterior superior iliac spines, left and right posterior superior iliac spines, left and right medial and lateral epicondyles, left and right medial and lateral malleoli, the left and right calcaneus, the left and right head of the first and fifth metatarsals and the left

and right apex of the big toe (Millar et al., 2019). The position of the anatomical landmarks relative to the TF of the relevant cluster was determined using the tip of a pointer that also carried an active cluster and where the location of the tip of the short arm of the pointer had been previously determined (Figure 4.8). The information from anatomical calibration was used to establish hip, knee, and ankle joint centre and to define the relevant AFs.

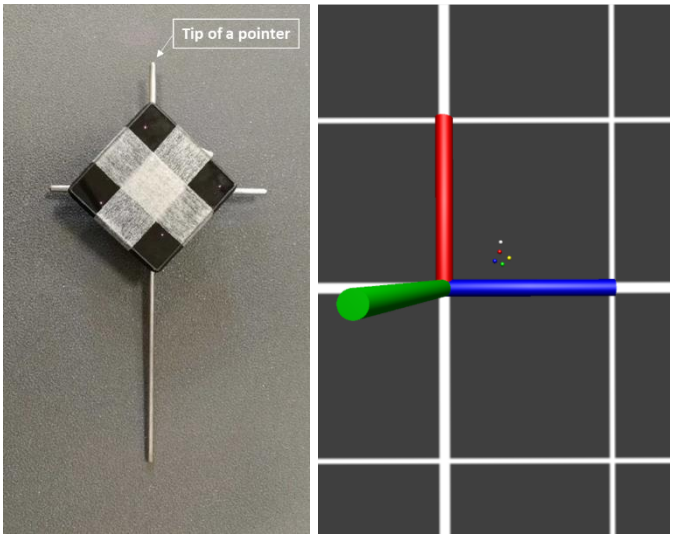


Figure 4.8: The position of the tip of the wand was determined by D-Flow.

The calculations of joint kinematics were based on generalised algorithm proposed by Cole et al (1993). They proposed the labelling of the segment axes as follows. The F-axis is the axis of flexion chosen as the axis of the segment that is oriented predominantly in the mediolateral direction with unit vector f. Next, L-axis is the longitudinal axis chosen as the axis that is oriented longitudinally along the segment with unit vector l. Lastly, T-axis is the third axis of the segment calculated as the cross product of the L axis and the F axis, and oriented in the direction l X f = t.

In clinical term, flex-extension is defined as motion of the segment in a sagittal plane. The ad-abduction is defined as motion of the segment in a frontal plane (away from or toward the midline). The external-internal rotation is defined as movement of the segment in a horizontal plane (rotate about its longitudinal axis). For calculation of the three angles of rotation, the unit vectors describing the attitude of the axes between the reference (proximal) segment (i) and the target (distal) segment (j) relative to an inertial system can now be defined according to the ISB standardization proposal as $e^1 = f_i$, $e^3 = l_j$, and $e^2 = e^1 \times e^3$.

The angle of flex-extension (σ) is calculated as follows (Figure 4.9):

$$\sigma = \arccos (e^2 \cdot t_i) \times B$$

where $B = 1$ if $(e^2 \cdot l_i) > 0$ else $B = -1$

The angle of ab-adduction (β) is calculated as follows:

$$\beta = \arccos (r \cdot l_j) \times C$$

where $C = 1$ if $(f_i \cdot l_j) > 0$ else $C = -1$

and $r = (f_i \cdot e^2) \div | f_i \cdot e^2|$

The angle of external-internal rotation (γ) is calculated as follows:

$$\gamma = \arccos (e^2 \cdot t_j) \times D$$

where $D = 1$ if $(e^2 \cdot f_j) > 0$ else $D = -1$

The positive results mean the counter-clockwise rotation about each axis. Hence, flexion, abduction, and external rotation are positive values.

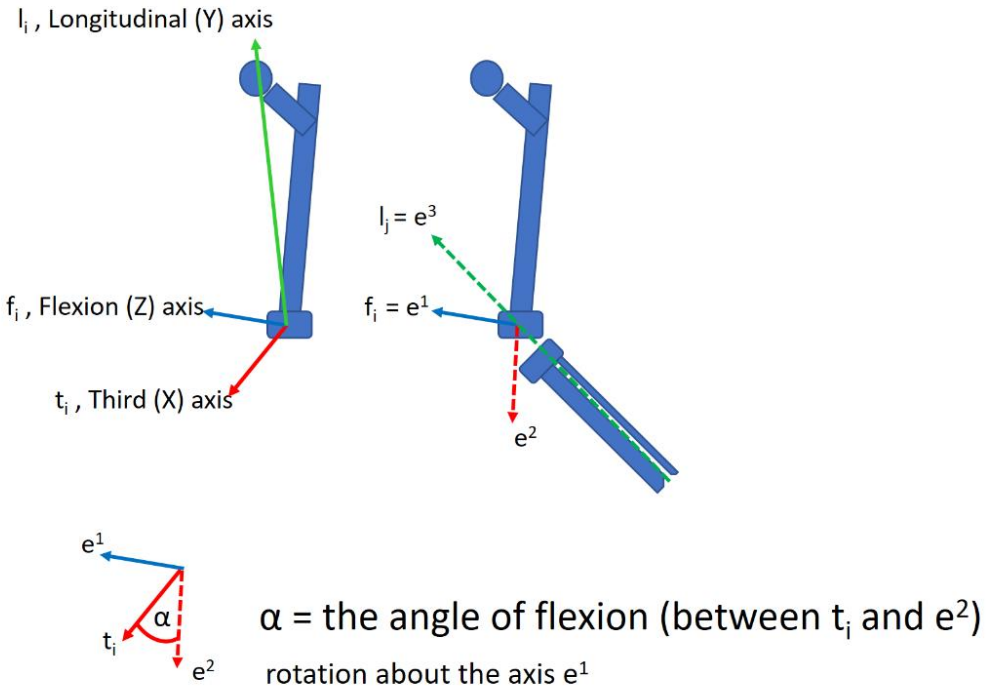
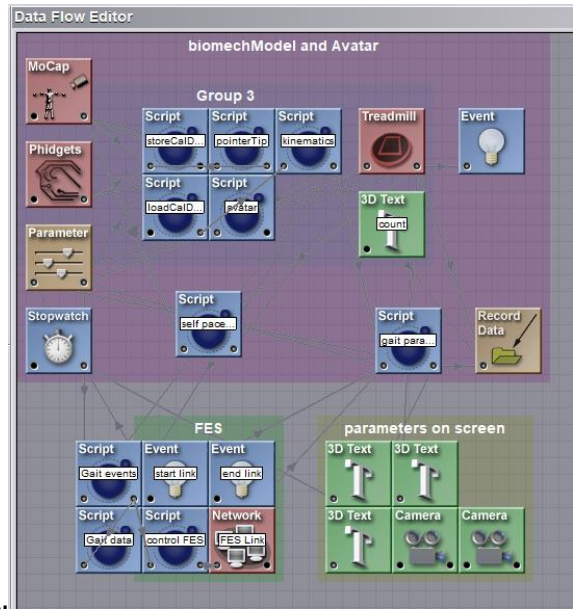


Figure 4.9: The calculation of the angle of flexion proposed by Cole et al.

To run the SCM model in D-Flow, patients with cluster markers on posterior pelvis, both anterior thighs, both anterior shanks, and both dorsum of feet were required to stand on the treadmill. Vicon tracker and MoCap module of D-Flow (Figure 4.10a) were run in Live mode. D-Flow runtime console which is the D-Flow operator's window was used to control application and needed to be open. In the runtime console the "Calibrate" tab was selected (Figure 4.10b). The operator then had to select "All" to input all the anatomical landmarks in a pre-defined order and then click the play button (right green arrow) which ran all modules in D-Flow except the script module to determine the phase of the gait cycle. Next, operators needed to identify each anatomical landmark using the tip of the pointer and then press

a hand switch linked to the system using a Phidgets board and the in-built "phidgets" module.

a.



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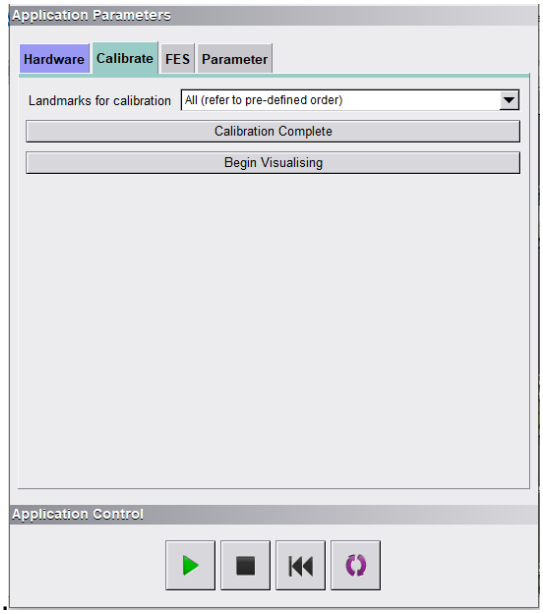


Figure 4.10: a. D-Flow application in the present study and b. Calibrate tab on runtime console.

The order of identification of anatomical landmarks must be

1. Right anterior superior iliac spine
2. Left anterior superior iliac spine
3. Right posterior superior iliac spine
4. Left posterior superior iliac spine
5. Right medial epicondyle
6. Right lateral epicondyle
7. Left medial epicondyle
8. Left lateral epicondyle
9. Right medial malleolus
10. Right lateral malleolus
11. Left medial malleolus
12. Left lateral malleolus
13. Right calcaneus
14. Right first metatarsal
15. Right fifth metatarsals
16. Right apex of the big toe
17. Left calcaneus
18. Left first metatarsal
19. Left fifth metatarsals
20. Left apex of the big toe

Lastly, operators clicked the button “Calibration Complete” and “Begin Visualising” on Calibrate tab, respectively to finish anatomical calibration and to start Kinematic calculation and Avatar modules. If a mistake was made

during subject calibration individual points could be re-recorded the whole set repeated. Having calibrated the subject, the program then began automatically to calculate the lower limb kinematics. Moreover, kinematic results could be recorded, or output to other modules such as the treadmill or other purpose written script modules.

4.2. Real-time visual feedback

Real-time visual feedback was provided to participants due to the concept of visuomotor control of gait which uses visual inputs to modify the gait patterns (Higuchi, 2013). The present study used real-time dynamic visualisation of lower extremities movement using the methods developed by Millar, L.J (Millar et al., 2019). The avatar was constructed using Lua scripts in D-Flow and displayed in the DSR window and shown on a TV screen in front of the treadmill. The lower extremities of the avatar were developed by linking segments between joint centres. Cylindrical objects were used to create graphically each segment, and spherical objects were placed at each joint centre to link them togetter.

This study wrote additional Lua scripts in D-Flow to calculate step length of both sides of the body and the step length ratio in real time and showed this information on the screen. Step length was the distance in the antero-posterior direction between both toe markers at initial foot contact and step length ratio was the hemiplegic step length divided by the non-hemiplegic one. This feedback was used to reduce step length asymmetry which was commonly found among stroke survivors. The distance covered (in yards)

and time spent walking (in minutes) were also shown on the screen to motivate patients to keep training.

To show the step lengths, the step length ratio and the avatar on the TV screen for real-time visual feedback, the operator needed to open the “Parameter” tab of the D-Flow runtime console (Figure 4.11) and click “Show on the screen1” button to show the side view of the avatar (Figure 4.12a) and to provide participants with sagittal hip, knee, and ankle kinematics of their walking (as the primary view) as stroke survivors usually had kinematic changes in the sagittal plane. However, if patients had the problem of mental rotation of 3D objects (Shepard and Metzler, 1971), the view of looking-down on feet (Figure 4.12b) could be shown as the alternative view by clicking “Show on the screen2” button. “Hide from the screen” button was used to make step length/ratio disappear from the screen and unlock the camera view to be able to show the avatar from any point of view. Moreover, operators were able to know the percentage of the phase of the gait cycle using the “Parameter” tab and turning on the script to determine the phase of the gait cycle.

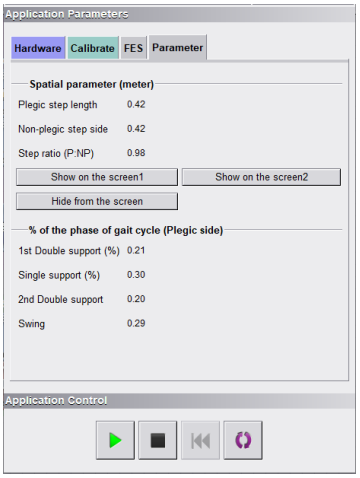


Figure 4.11: Parameter tab of D-Flow runtime console.

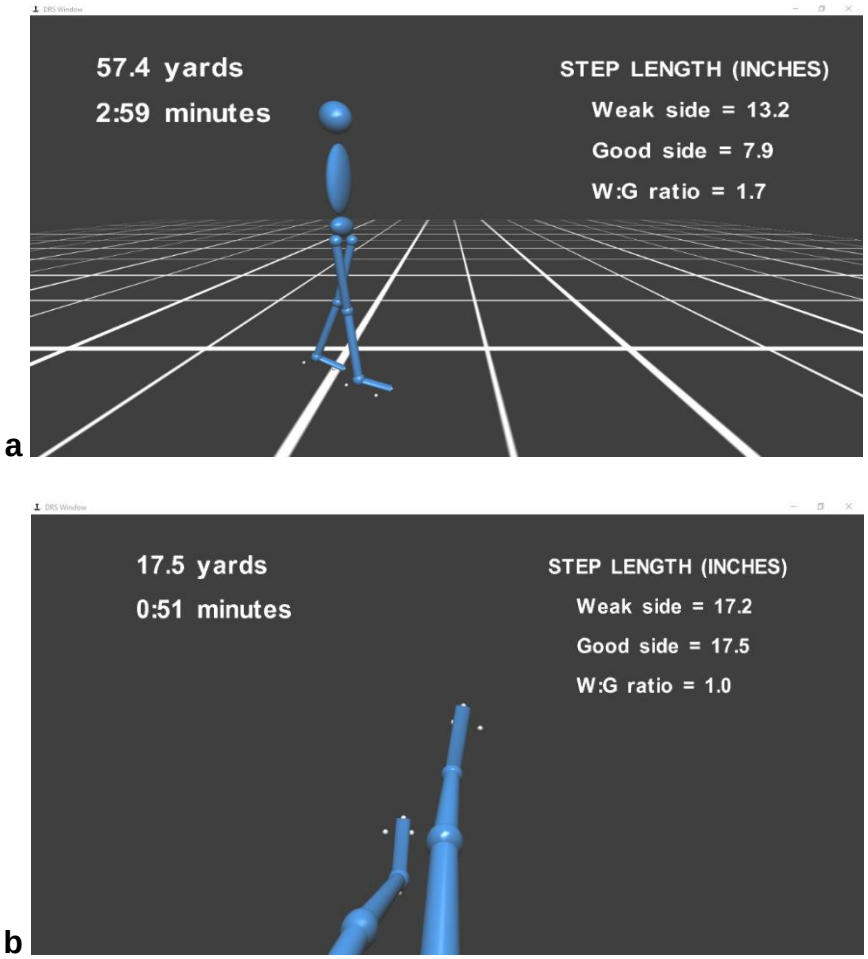


Figure 4.12: Human avatar for real-time visual feedback;
the side view (a) and the looking-down on feet view (b)

4.3. Multi-channel FES (MFES)

The previous chapter provide the details of the development of the research MFES system including the components of the system and its control algorithms, this chapter will provide how the system operator controlled the MFES device using D-Flow software during the treadmill gait training.

To control the MFES system the individual FES devices attached to the MFES system were set up and the USB cable of Arduino board in the MFES system was plugged into the computer. Next, the operator ran a

Python program that was written provided a connection between the network module of D-Flow and the Arduino board in the MFES system. When the connection succeeded, D-Flow sent the number “0” to the Arduino board to show that the script to determine the phases of the gait cycle was not yet running.

Initially, the hemiplegic side in the FES tab of the D-Flow runtime console (Figure 4.13) needed to be chosen (left side was the default) to determine the phase of the gait cycle in treadmill walking correctly. After patients settled into treadmill walking, operators clicked the “FES On” button to run the script of the gait phase determination to start MFES support. The number 1, 2, 3, 4, or 5 could be seen in the “Phase of Gait Cycle” indicator of the FES tab once the script was played. These codes for the phases of gait were sent to the Arduino board automatically if the D-Flow network module and the Python file were running properly. To stop FES support, the operator needed to click the “FES Off” button to stop the script of the gait phase determination and then the number 0 which mean no output from the script of the gait phase determination was sent to the Arduino board to stop FES support.

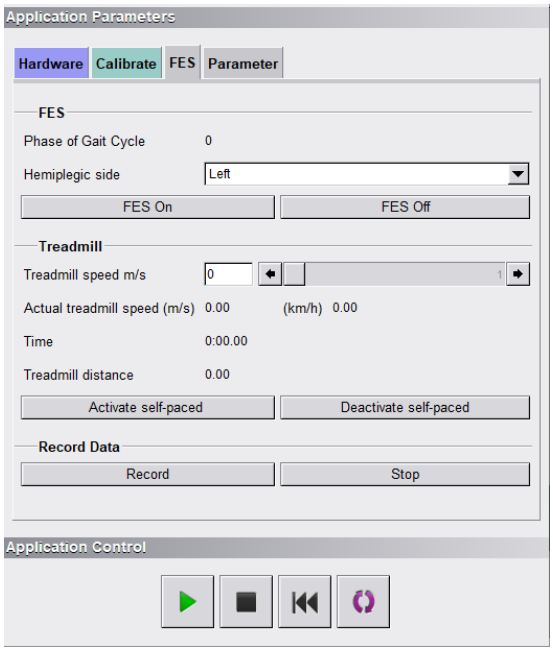


Figure 4.13: FES tab in D-Flow runtime console.

4.4. Treadmill and Body weight support (BWS) system

A single-belt treadmill (Model: N-Mill 1N75, ForceLink B.V., Culemborg, Netherlands) was used in the study. The treadmill can be controlled either by its in built console or by computer. It was connected to the computer using a USB port and was controlled using the treadmill module of D-Flow. The module can adjust treadmill speed (m/s) and set a maximum speed and acceleration/deceleration (m/s^2) limits of the treadmill. Importantly, when self-paced mode of the module is activated, it will adjust the treadmill speed to the walking speed of the user using the motion capture data (Figure 4.14). In this case the self-paced mode used the pelvic marker information in the antero-posterior direction to pace the treadmill and to maintain the subject in their initial position on the treadmill (i.e. halfway along its length).

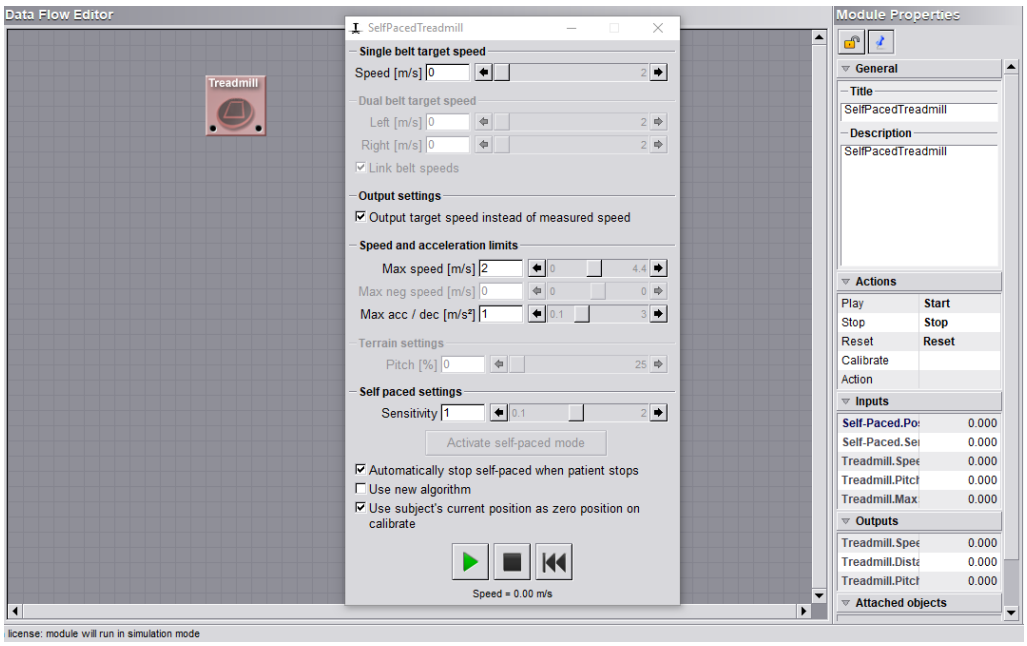


Figure 4.14: Treadmill module in D-Flow.

To control the treadmill using D-Flow the runtime console was again used. The operator needed to open the “FES” tab (Figure 4.13). The section for controlling treadmill was under the section for controlling the FES system. It had a “slider” to control treadmill speed and two buttons to activate and deactivate self-paced mode of treadmill. The operator could increase or decrease the treadmill speed using the slider and using interaction with the user on the treadmill. The present study did not primarily aim to operate in self-paced mode. Therefore, the fixed paced mode was used in all sessions of the gait training, but patients could try to use self-paced mode if they wanted and if their motor power/control and walking ability were good enough to use it.

This study also used a Body Weight Support (BWS) system manufactured by PneuMex Inc. The system used pneumatic power and a specialized vest attached to an overhead cable assembly. The primary aim of

using the BWS system in the present study was to prevent falling during treadmill training. However, patients could receive unweighting support if needed. Its unweighted capacity is up to 136 kg (300 lb). Amount of unweighting was dependent on the participants' walking ability and a judgement by the physiotherapist in charge of the patient. Additionally, the BWS system could be operated into 2 modes: exercise and balance mode. The exercise mode allowed patients to perform exercises with up to 30 inches vertical movements such as jumping or climbing, whereas the balance mode allowed them to perform activities with less than 6 inches vertical movement such as walking, running, or balance exercises. Hence, the balance mode which can prevent the falling was chosen for gait training.

Having reported the development and implementation of the MFES and Treadmill Training with Visualisation systems the following chapter will set out the methods for the feasibility study conducted to assess this health technology.

Chapter 5: Clinical Feasibility Trial

5. Clinical feasibility trial

5.1. Introduction

The present study developed a novel treadmill gait training system for patients after stroke. This enhanced treadmill training used a treadmill and BWS system augmented with MFES and real-time visual feedback. Chapter 3 reported the developed MFES system to be used with 3D motion capture with multiple FES channels and an Arduino board as a controller which could trigger the FES stimulators at the targeted time to support gait training. Chapter 4 described the enhanced treadmill training systems developed and operated using the D-Flow software. However, the feasibility in routine clinical practice of this “research” intervention remain unknown. This chapter will provide the details of the clinical trial that was used to determine if this enhanced treadmill training is feasible in a clinical or hospital setting or not.

5.2. Subjects

This study was a part of the study titled Enhanced Treadmill Gait Training with Lower Limb Support after Stroke (ENTRES) (ClinicalTrials.gov Identifier: NCT03348215). The study was granted ethical approved by the NHS Ethics Committee, West of Scotland REC5, Western Infirmary, Glasgow (REC reference: 17/WS/0245). R&D approval was granted by NHS Lanarkshire (R&D ID: L16008). This study was conducted at Coathill Hospital, Coatbridge, Lanarkshire, United Kingdom. Because this is a feasibility study, a formal sample size calculation based on power of detection and alpha error was not required. However, based on the capacity of the research facility and recruitment rate, a sample size of 10 – 20 cases were targeted to fulfil the

objectives of the study (Billingham et al., 2013). The inclusion and exclusion criteria are shown in Table 5.1.

Table 5.1: Participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Over 18 years old. 2. Have had a diagnosed stroke. 3. Onset of stroke between 1 week and 12 months ago. 4. Attending Coathill Hospital (NHS Lanarkshire) for stroke rehabilitation which includes gait training. 5. Have Hemiplegia. 6. Medically Stable. 7. Able to follow simple, verbal instructions in English, or in another language if an appropriate translator is available. 8. Able to provide informed consent.	1. Considered by the GP or NHS clinicians to be unsafe to do mild exercise for the duration of time required (about 20 minutes). 2. Have contracture of the hip, knee or ankle which prevents walking. 3. Have any lower limb metal implants. 4. Have any skin irritation on the shank. 5. Have a cardiac pacemaker. 6. A body mass that exceeds the capacity of the equipment (>100Kg). 7. Cognitive impairment severe enough to prevent adherence with the protocol (assessed using the Montreal Cognitive Assessment and the clinicians responsible for the participant). 8. Walking difficulty before stroke (for example, patients who had history of severe spinal stenosis or peripheral vascular diseases)

5.3. Study design

This study used a case series design because it is easy to conduct in a hospital setting and can provide information on new interventions. Eligibility for participating in the study was determined by the researchers screening stroke patients attending the outpatient service for stroke survivors at Coathill hospital. Suitable potential participants were approached with the treating physiotherapist and the study explained in detail. Those interested were provided with a written participant information sheet. They were allowed at least 24 hours, and at most 5 days, for consideration before being asked for their consent. The percentage of eligible subjects asked who chose to agree to participate was noted. Participants had the opportunity to withdraw from the study at any time.

Coathill hospital was a community hospital providing several outpatient clinic services including physiotherapy for stroke. The standard physiotherapy for stroke survivors at Coathill hospital depended on premorbid status, stroke severity, and neurological recovery. It might include strengthening and coordination exercise, range-of-motion and stretching exercises, gait training on the ground, and stair climbing. The patients normally received training up to 20 minutes per session, merely once or twice a week because of physiotherapist or caregiver availability. Hence, the present study provided all participants with up to 20-minute treadmill gait training with BWS augmented with real-time visual feedback and FES instead of their over-ground gait training once or twice a week for 6 weeks although a frequency of 3 sessions a week was recommended in general.

During training sessions, any ankle foot orthosis they were prescribed was removed. Participants could request pauses in the training session as needed. The treadmill was equipped with front and side bars from which support could be taken at any time. All adverse events were monitored and recorded throughout the study. A comprehensive mobility assessment was performed before and after the treatment programme. Additionally, a 1-month follow-up assessment was provided if participants and their physiotherapists were available to attend. The timeline of the present study is shown in Table 5.2.

Table 5.2: The schedule of the study.

	E	B	Tx						A	F/U
		W0	W1	W2	W3	W4	W5	W6	W7	W12
Screening eligibility criteria	x									
Providing study information	x									
Obtaining informed consent	x									
Demographic data		x								
3D-Gait analysis		x							x	x
10-MWT		x							x	x
RMI questionnaire		x							x	x
Feedback from participants and clinicians									x	
Monitoring adverse events		x	x	x	x	x	x	x	x	x

E = Enrolment; B = Before treatment; A = After treatment; F/U = follow-up.

5.4. Research outcomes

The number and percentage of attendance at training sessions and training duration were used to assess the feasibility of enhanced treadmill training as the primary outcome of the present study (El-Kotob and Giangregorio, 2018). Also, participants' feedback and occurrence of adverse events about gait training using the new system were collected (El-Kotob and Giangregorio, 2018). Moreover, walking and mobility outcomes including 1) Gait variables of treadmill walking; 2) 10-meter walk test (10mWT); 3) Rivermead mobility index (RMI) questionnaire were measured before and after treatment, and at 1-month follow-up if possible. As a feasibility trial, the study evaluated only these 3 clinical outcomes so that assessment sessions were not too long.

Gait parameters on treadmill

Gait analysis was conducted at 60 Hz sampling rate using the SCM protocol and using the same equipment and software as for the enhanced treadmill training. Up to 6-minutes of walking on the treadmill was carried out for the gait analysis. Five gait cycles for both sides were analysed. All kinematic data were normalized to 100% of the gait cycle and was reported as the mean plus or minus 1SD. Also, some gait analysis parameters such as stride length, step length ratio were compared.

Rivermead mobility index (RMI)

The RMI has been shown to be a reliable and desirable instrument to quantify mobility performance in patients after stroke and to be responsive to changes over time (Forlander and Bohannon, 1999, Franchignoni et al., 2003, Green et al., 2001, Roorda et al., 2008, Chen et al., 2007). It consisted

of 15 questions: 14 self-reported and 1 direct observation (standing unsupported).

- Turning over in bed: Do you turn over from your back to your side without help?
- Lying to sitting: From lying in bed, do you get up to sit on the edge of the bed on your own?
- Sitting balance: Do you sit on the edge of the bed without holding on for 10 seconds?
- Sitting to standing: Do you stand up from any chair in less than 15 seconds and stand there for 15 seconds, using hands and/or an aid, if necessary?
- Standing unsupported: ask client to stand without aid and observe standing for 10 seconds without any aid.
- Transfer: Do you manage to move from bed to chair and back without any help?
- Walking inside (with an aid if necessary): Do you walk 10 meters, with an aid if necessary, but with no standby help?
- Stairs: Do you manage a flight of stairs without help?
- Walking outside (even ground): Do you walk around outside, on pavements, without help?
- Walking inside, with no aid: Do you walk 10 meters inside, with no calliper, splint, or other aid (including furniture or walls) without help?

- Picking up off floor: Do you manage to walk five meters, pick something up from the floor, and then walk back without help?
- Walking outside (uneven ground): Do you walk over uneven ground (grass, gravel, snow, ice, etc) without help?
- Bathing: Do you get into/out of a bath or shower to wash yourself unsupervised and without help?
- Up and down four steps: Do you manage to go up and down four steps with no rail, but using an aid if necessary?
- Running: Do you run 10 meters without limping in four seconds (fast walk, not limping, is acceptable)?

A total score is the number of questions that patients gives a YES response. A maximum score of 15 is possible: higher scores reflect better mobility performance. A minimum score improvement that indicates a real clinical improvement for an individual case has been reported as 2.2 points (Chen et al., 2007).

10-Meter Walk test (10mWT)

The 10mWT was used to evaluate walking speed over ground for assessing functional mobility. Patients walked 10 meters without assistance but could use individual gait aids or an AFO if needed. They were timed for the middle 6 meters (Figure 5.1). Participants were asked to walk at their comfortable speed. Two or three trials were conducted, and the time was averaged to calculate walking speed in meter/second. The test was not carried out among patients who need a helper for walking. As a research outcome in the stroke population, this walking test was highly recommended

by the American Physical Therapy Association Neurology Section due to its excellent psychometric properties and clinical utility (Sullivan et al., 2013). A meaningful change was reported as 0.14 m/s (Perera et al., 2006).

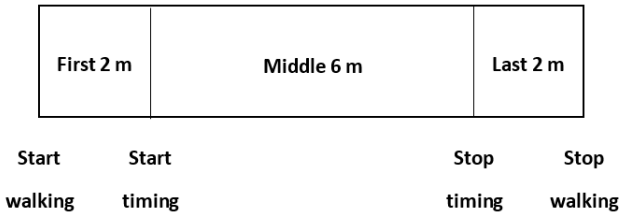


Figure 5.1: Ten-meter walk test

Feedback from participants and physiotherapists

Patients' and therapists' feedback based on the structured questionnaire was collected after each individual training programme finished. The self-administered questionnaire provided statements that needed the agreement or disagreement (Strongly Agree; Agree; Neutral; Disagree; Strongly Disagree) from patients or therapists (for patients, their caregiver could help them complete questionnaire if needed). The questions were based on the factors that might affect the acceptability of research training. This study decided to use the questionnaire because it is easy to conduct and to analyse. However, it has some weaknesses such as difficulty to fully convey feelings of respondents and misunderstanding in the questionnaire. The statements in the questionnaire are shown below.

For patients

1. The amount of set up time before each session was acceptable.
2. Walking with all of the equipment set up was not too cumbersome.
3. The treadmill is comfortable to walk on, and easy to get used to.
4. Walking with the harness was comfortable and made me feel safe.

5. The sessions as a whole were enjoyable.
6. The instructions given during the sessions were easy to understand and carry out.
7. I still feel motivated to continue with this training program.
8. I would recommend treadmill training such as this to other stroke survivors.

For therapists

1. The amount of set up time before each session was acceptable.
2. Walking with all of the equipment set up was not too cumbersome for this participant.
3. The enhanced treadmill system was user friendly.
4. Any inconvenience during the training sessions was unimportant.
5. This enhanced treadmill training program increases motivation in participants.
6. I would like to continue using the enhanced treadmill system after the study ends.
7. I would recommend treadmill training such as this to other therapists working in gait rehabilitation

Occurrence of adverse events.

All adverse events were recorded regardless of if they were related to the research intervention or not. Importantly, serious adverse events that causes 1) death; 2) life-threatening; 3) hospitalization or prolonged of existing hospitalization; 4) persistent or significant disability or incapacity were reported.

5.5. Statistical analysis

Due to a case series design, descriptive statistics was mainly used. However, analytical statistics was used for explorative purposes only. Moreover, because of the small sample size in a feasibility study, caution was needed to interpret the results of statistical tests.

Data Collection	Descriptive statistics	Analytical statistics
Recruitment rate	Number and fraction	-
Retention rate	Number and fraction	-
Attention rate at training	Number and fraction	-
Time spent on training	Median (Min – Max)	-
Distance covered on the treadmill	Median (Min – Max)	-
Gait parameters before/after gait training or with/without FES	Mean (SD) or Median (Min – Max)	Paired t-test or Wilcoxon signed-rank test
Relationship between time spent on training and increased walking speed		Spearman's rank correlation
Association between clinical factors and clinically improved walking speed		Fisher's exact test

Chapter 6: Results of a Feasibility Trial

6. Results of a feasibility trial

This chapter reports the results from data collected during a feasibility trial of enhanced treadmill training in clinical practice. Initially, demographic and baseline data of all participants will be provided. Subsequently training programme, clinical outcomes, gait outcomes, and adverse events of each participant will be reported case-by-case. The overall feasibility and acceptability of enhanced treadmill training will then be addressed. Lastly, although the present study contained only a modest sample size, any signs of clinically relevant improvement in gait parameters from the novel treatment will be evaluated. Nevertheless, caution was needed to interpret the results due to inadequately power statistical testing. Missing data was only reported but not replaced with any values because this study mainly employed descriptive statistics. Analytical statistics was used only for explorative purposes.

6.1. Participants' characteristics and performance

This study was conducted from June 2018 to October 2019 at the physiotherapy service, Coathill hospital. Twelve patients with stroke initially met the inclusion criteria, but two were excluded; one for severe sciatic pain, and the other for thrombophlebitis of the hemiplegic leg. Ten patients were therefore invited to participate in the study and were given the participant information sheet. All ten eligible cases consented to participate in the study (100% consent rate). Of the ten participants, the majority of whom were male (8/10), most had suffered a brain infarction (9/10), with resulting left hemiplegia (6/10). The cohort had a median age of 51 (30 – 84) years, and a

median time since stroke of 5 (2 – 12) months. For walking speed and ambulation performance at baseline assessment, 2/10 and 7/10 patients had very slow (<0.4 m/s) and slow (0.4 – 0.8 m/s) walking speed, respectively, with a median RMI score of 11 (4 – 14). The characteristics and baseline performance of all the study participants are shown in Table 6.1.

Table 6.1: Participants' characteristics and performance

Case	Sex	Age (yr)	Type of stroke	Location of stroke	Affected side	Time since stroke (m)	Walking speed (m/s)	RMI
1	M	61	I	MCA	Left	6	0.12	4
2	M	84	I	PC	Left	3	0.44	9
3	F	30	I	MCA	Right	12	0.82	13
4	M	40	I	BG	Left	4	0.44	12
5	M	55	I	MCA	Right	10	0.19	10
6	M	47	I	MCA	Left	12	0.67	10
7	M	43	H	BG	Right	2	0.58	14
8	M	45	I	PC	Right	5	0.73	13
9	M	64	I	MCA	Left	4	0.48	12
10	F	56	I	MCA	Left	4	0.57	9

M/F = Male/Female; I/H = Infarction/haemorrhage; MCA/PC/BG = Middle cerebral artery/Posterior circulation/Basal ganglion; RMI = Rivermead Mobility Index

6.2. Series of case reports

6.2.1. Case 1

Case 1 was a 61-year-old male who suffered from left spastic hemiplegia due to right middle cerebral artery (MCA) infarction within 6 months. Before having a stroke, he could perform self-care and ambulation independently. At the time of enrolment, he was considered to have poor motor recovery. Some

motor control was found in the hip and knee on his plegic side. There was no observable motor control of the pretibial muscle, and moderate spasticity was found in the calf muscle. Additionally, his upper extremity on plegic side had no motor recovery. He was able to ambulate on level surfaces very slowly using a solid ankle-foot orthosis (AFO) and a tripod walking stick. He did not need physical support from another person, but supervision from his carer was required for safety reasons. During the pre-training assessment, his walking speed and RMI score were 0.12 m/s and 4, respectively.

Training programme

Due to the availability of the patients' carer, case 1 received enhanced treadmill training twice a week, which was the same physiotherapy schedule he followed before participating in the present study. He attended 11/12 training sessions of the present study and did not receive other training sessions of physiotherapy at the hospital during this period. Treadmill speed ranged from 0.07 to 0.17 m/s in fixed pace mode. He needed interval training and support from a side bar while walking on the treadmill. Functional electrical stimulation was applied to the pretibial muscle for the first 7 sessions. However, the patient reported increased spasticity of his toe flexors in week 4 of the treatment programme. It was determined that FES did not cause this problem, but could potentially exacerbate the patient's discomfort. Hence, an AFO was used instead of FES for the last 4 sessions. The time spent and distance covered on the treadmill ranged from 8 to 20 min and 52 to 149 m (Figure 6.1).

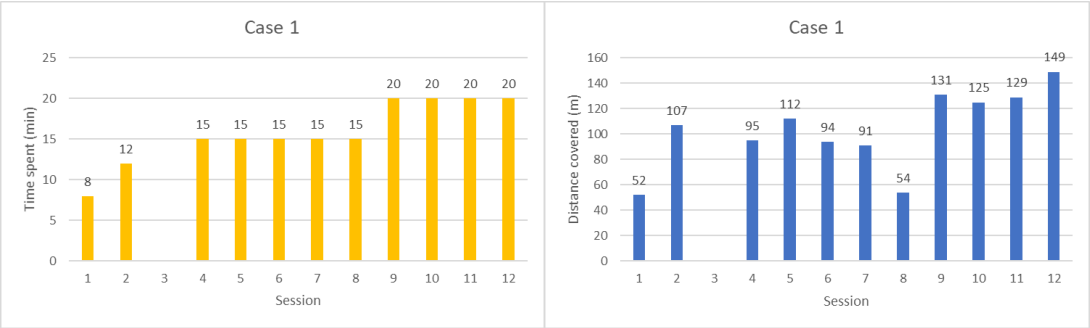


Figure 6.1: The time spent and distance on the treadmill of case 1.

Immediate effect of FES

The effect of FES to the pretibial muscle on foot drop during the swing phase is shown in Figure 6.2. From the graph it can be seen that FES during walking produced a lower plantarflexion angle than walking without FES during swing phase. At 90% of the gait cycle, there was statistically significant difference between the two conditions, with mean difference of 7.3 degrees (95% CI: 6.5 to 8.1).

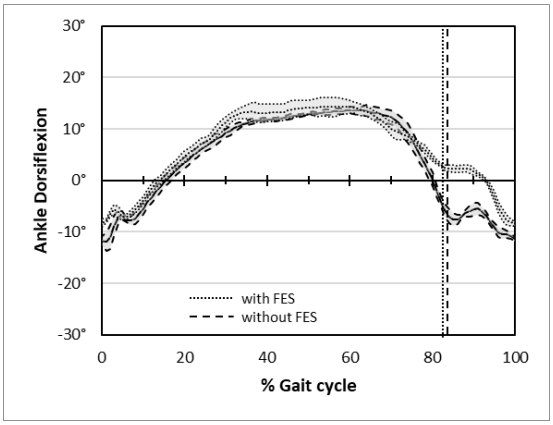


Figure 6.2: Sagittal ankle kinematics on plegic (left) side (Mean ± SD) of case 1, walking with and without FES to the pretibial muscle (N = 5 cycles for both conditions).

Therapeutic effect of enhanced treadmill training

Case 1 over-ground walking speed, RMI score, stride length, and step length ratio measured in pre- and post-training assessments are shown in Table 6.2. It may be noted that only RMI score demonstrated significant improvement, changing from 4 at pre-training to 9 at post-training assessment. This indicates that the patient had improved bed mobility and transfer, but not necessarily walking ability.

Table 6.2: Walking speed, RMI score, stride length, and step length ratio of case 1 at pre- and post-training assessments

Outcomes	Pre-training	Post-training	P-value
walking speed (m/s)	0.13	0.14	-
RMI score	4	9	-
Stride length* (m)	0.42 (0.02)	0.32 (0.02)	<0.001
Step length (P/NP) ratio *	1.71 (0.12)	1.07 (0.08)	<0.001

* Mean (SD) of 5 cycles; P-value of paired t-test (pre vs post).

The sagittal kinematics of the hip, knee, and ankle joints at pre and post- training assessments are plotted in Figure 6.3. In both assessments, the patient wore his own solid AFO. It can be seen that the gait patterns in the two assessments show a high degree of similarity. The patient consistently had poor hip excursion, knee buckling in stance phase, reduced knee flexion in swing phase, and required solid AFO to ambulate safely in the post-training assessment.

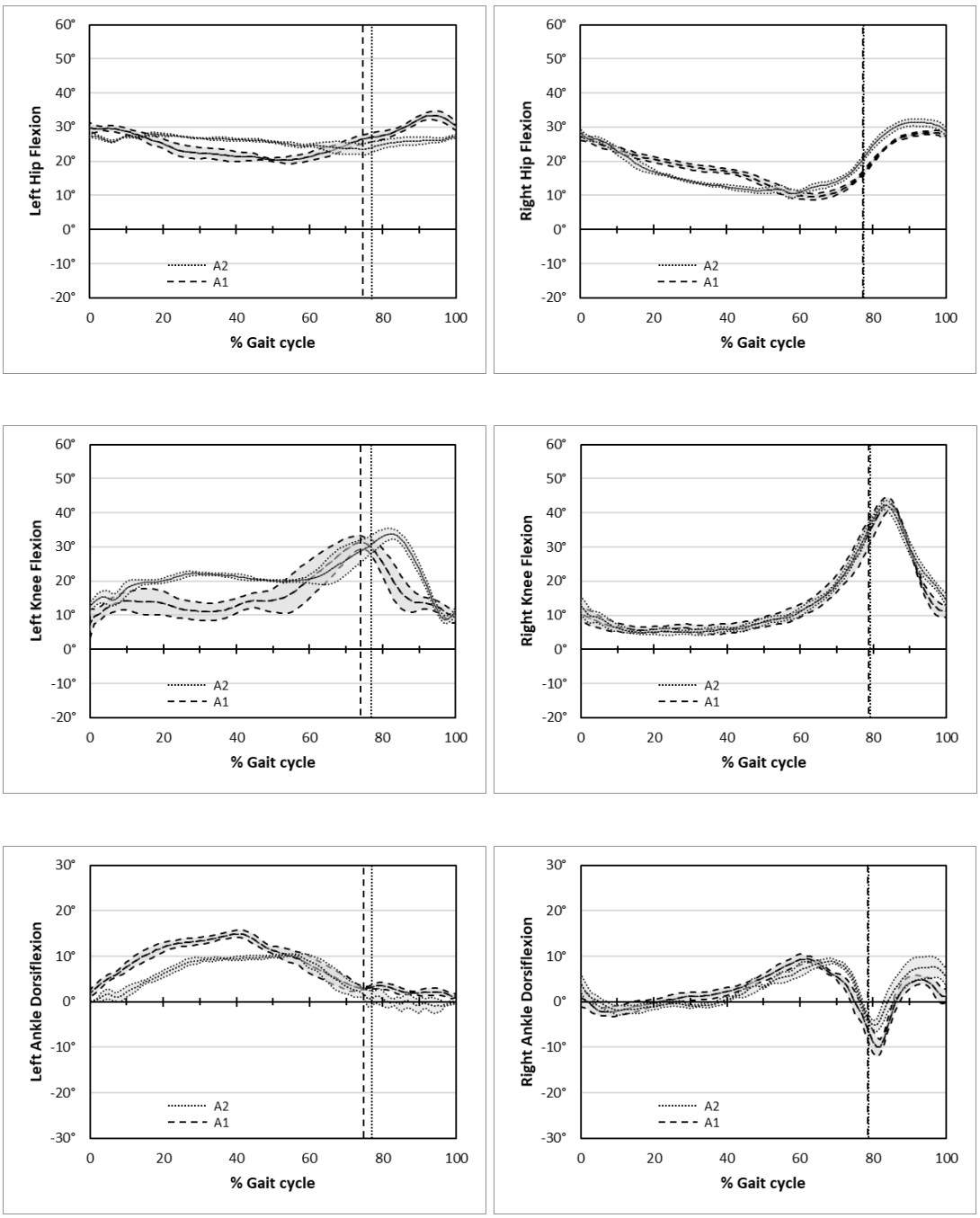


Figure 6.3: Joint kinematics (Mean ± SD) of case 1 at pre-treatment (A1) and post-treatment (A2) assessment (N = 5 cycles for both assessments).

6.2.2. Case 2

Case 2 was an 86-year-old male who was diagnosed with left posterior circulation infarction within 3 months. His stroke predominately caused ataxia (lack of coordination), rather than weakness, on the left side. At enrolment, he was able to ambulate on a level surface using a 3-wheeled walker, which was similar to his ambulation status before having a stroke. He did not need a physical support, although supervision from his carer was required for safety reasons. During the pre-training assessment, his walking speed and RMI score were 0.44 m/s and 9, respectively.

Training programme

Before case 2 participated in the present study, he received physiotherapy once a week to maintain his physical function. Hence, he and his carer chose to receive the research training once a week, maintaining consistency with his pervious rehabilitation schedule. He attended all (6/6) training sessions and did not receive other training sessions of physiotherapy in the hospital during this time. His treadmill speed ranged from 0.08 to 0.16 m/s on fixed-pace mode. He required interval training and support from the front bar of the treadmill during training. FES to the pretibial muscle was applied during all training sessions. No adverse events were reported throughout the study period. The time spent and distance covered on the treadmill ranged from 9 to 13 min and 42 to 112 m, respectively (Figure 6.4).

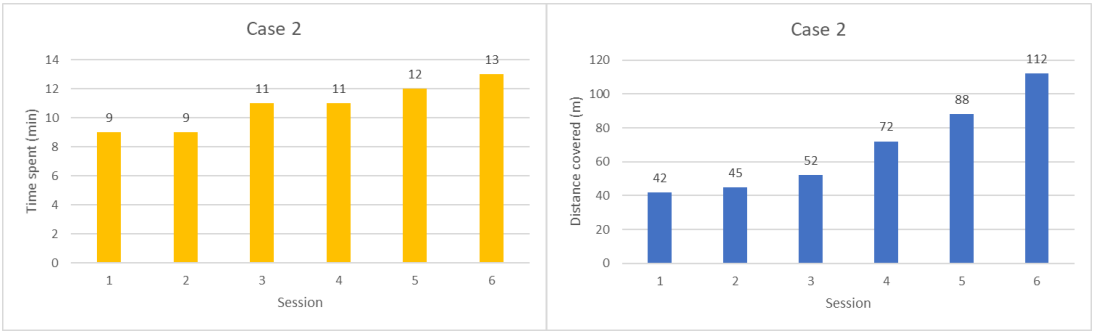


Figure 6.4: The time spent and distance on the treadmill of case 2.

Immediate effect of FES

The effects of FES to the pretibial muscle on foot drop during swing phase are illustrated in Figure 6.5. From this graph, it can be seen that application of FES while walking reduced the plantarflexion angle compared with no FES. At 95% of the gait cycle a statistically significant difference was measured between the two conditions, with a mean difference of 6.0 degrees (95% CI: 4.9 to 7.0).

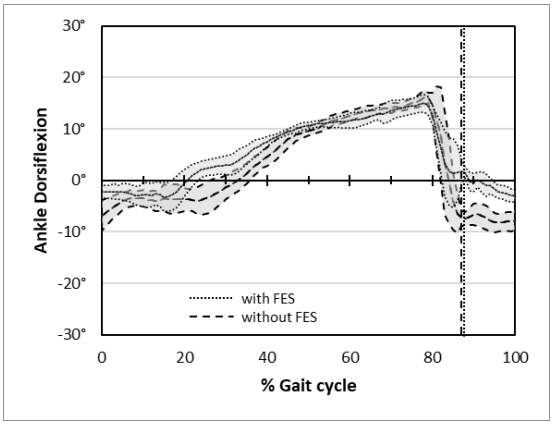


Figure 6.5: Sagittal ankle kinematics on plegic (left) side (Mean ± SD) of case 2, walking with and without FES to pretibial muscle (N = 5 cycles for both conditions).

Therapeutic effect of enhanced treadmill training

His over-ground walking speed, RMI score, stride length, and step length ratio measured in pre- and post-training assessments are shown in Table 6.3. Although over-ground walking speed and step length ratio were not improved at the end of the programme, the patient had a better stride length, which had increased by 0.25 m (95% CI: 0.19 to 0.31).

Table 6.3: Walking speed, RMI score, stride length, and step length ratio of case 2 at pre- and post-training assessments

Outcomes	Pre-training	Post-training	P-value
walking speed (m/s)	0.44	0.35	-
RMI score	9	-	-
Stride length* (m)	0.38 (0.04)	0.63 (0.05)	<0.001
Step length (P/NP) ratio *	0.80 (0.14)	0.82 (0.10)	0.66

* Mean (SD) of 5 cycles; P-value of paired t-test (pre vs post).

The sagittal kinematics of the hip, knee, and ankle joints at pre- and post-training assessments are shown in Figure 6.6. It may be noted that lower limb kinematic patterns observed from the plegic (left) side were fairly similar to those of the non-plegic side in both assessments.

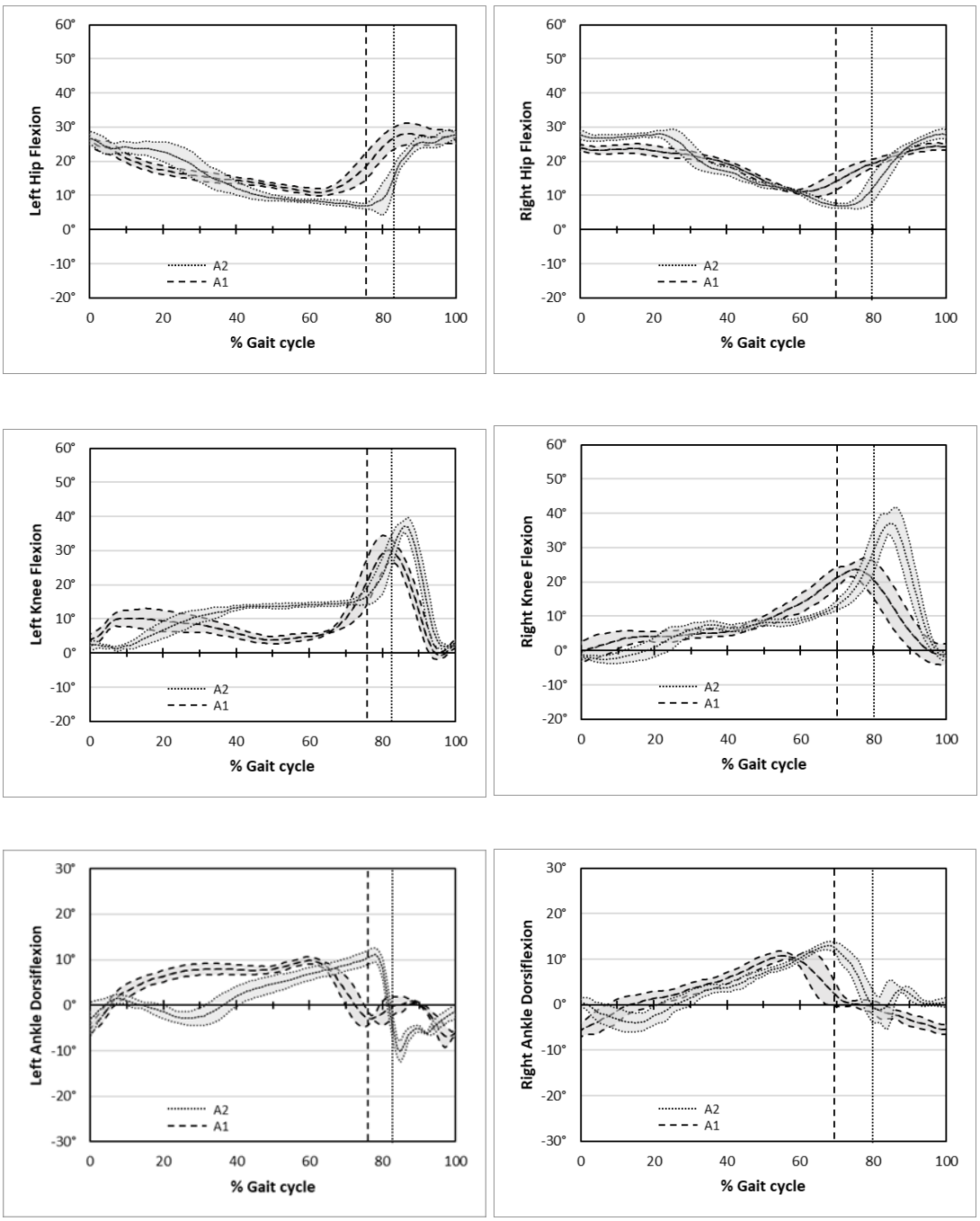


Figure 6.6: Joint kinematics (Mean ± SD) of case 2 at pre-treatment (A1) and post-treatment (A2) assessments (N = 5 cycles for both assessments).

6.2.3. Case 3

Case 3 was a 30-year-old female who had suffered from right spastic hemiplegia for 12 months due to a left MCA infarction. Her pre-stroke functional abilities allowed her to perform self-care and ambulation independently. At enrolment, some motor control with mild spasticity was found on her plegic leg, and she had a demonstrable foot drop problem. There was no apparent motor recovery in her upper extremity. She was able to ambulate on a level surface independently without using an AFO or walking aids, and could also manage a flight of stairs without help. At the pre-training assessment, her walking speed and RMI score were 0.82 m/s and 13, respectively.

Training programme

Case 3 received enhanced treadmill training twice a week upon her physiotherapist's request. She attended 11/12 training sessions and did not receive any other sessions of physiotherapy in the hospital during the study. Treadmill speed ranged from 0.25 to 0.30 m/s at fixed-pace mode, which was much slower than her over-ground walking speed, due to the physiotherapist's desire to modify her compensated gait pattern. She needed interval training and support from the front bar of the treadmill during training. Functional electric stimulation was applied to her pretibial muscle during all 11 training sessions. She had hemiplegic arm pain and requested to terminate one session (session 10) after 14 minutes of training. The time spent and distance covered on the treadmill ranged from 10 to 20 min and 149 to 343 m, respectively (Figure 6.7).

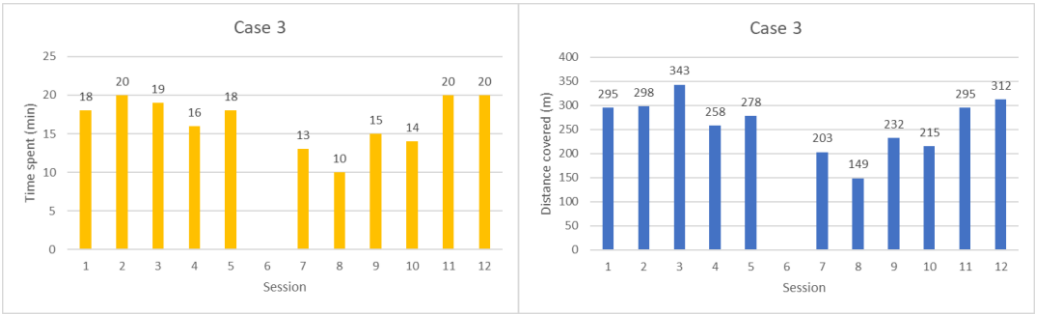


Figure 6.7: The time spent and distance on the treadmill of case 3.

Immediate effect of FES

The effect of FES applied to the pretibial muscle on foot drop during swing phase is shown in Figure 6.8. This graph shows that walking with FES resulted in a reduced plantarflexion angle in comparison to walking without FES. At 95%of the gait cycle, there was statistically significant difference between these two conditions, with mean difference of 6.6 degrees (95% CI: 6.4 to 6.8).

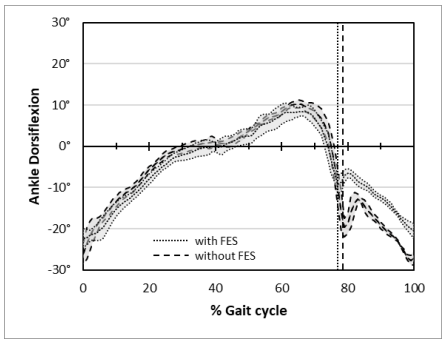


Figure 6.8: Sagittal ankle kinematics on plegic (right) side (Mean ± SD) of case 3, walking with and without FES to pretibial muscle

(N = 5 cycles for both conditions).

Therapeutic effect of enhanced treadmill training

Her over-ground walking speed, RMI score, stride length, and step length ratio measured during pre- and post-training assessments are shown in Table 6.4. Although her walking speed was not improved at the end of the programme, she had a better stride length that increased by 0.19 m (95% CI: 0.14 to 0.23), and no step-length asymmetry; this reflects the physiotherapist's intention of correcting the patient's gait compensated pattern.

Table 6.4: Walking speed, RMI score, stride length, and step length ratio of case 3 at pre- and post-training assessments.

Outcomes	Pre-training	Post-training	P-value
walking speed (m/s)	0.82	0.74	-
RMI score	13	14	-
Stride length* (m)	0.52 (0.04)	0.71 (0.01)	<0.001
Step length (P/NP) ratio *	2.12 (0.47)	1.03 (0.09)	0.007

* Mean (SD) of 5 cycles; P-value of paired t-test (pre vs post).

The sagittal kinematics of the hip, knee, and ankle joints at pre- and post-training assessments are shown in Figure 6.9. In both assessments, although she had a substantial foot drop problem on her plegic (right) side, she was able to walk without any assistive device. At the end of training programme, she still exhibited a foot drop problem during swing phase, and knee hyperextension during midstance phase on her plegic (right) side.

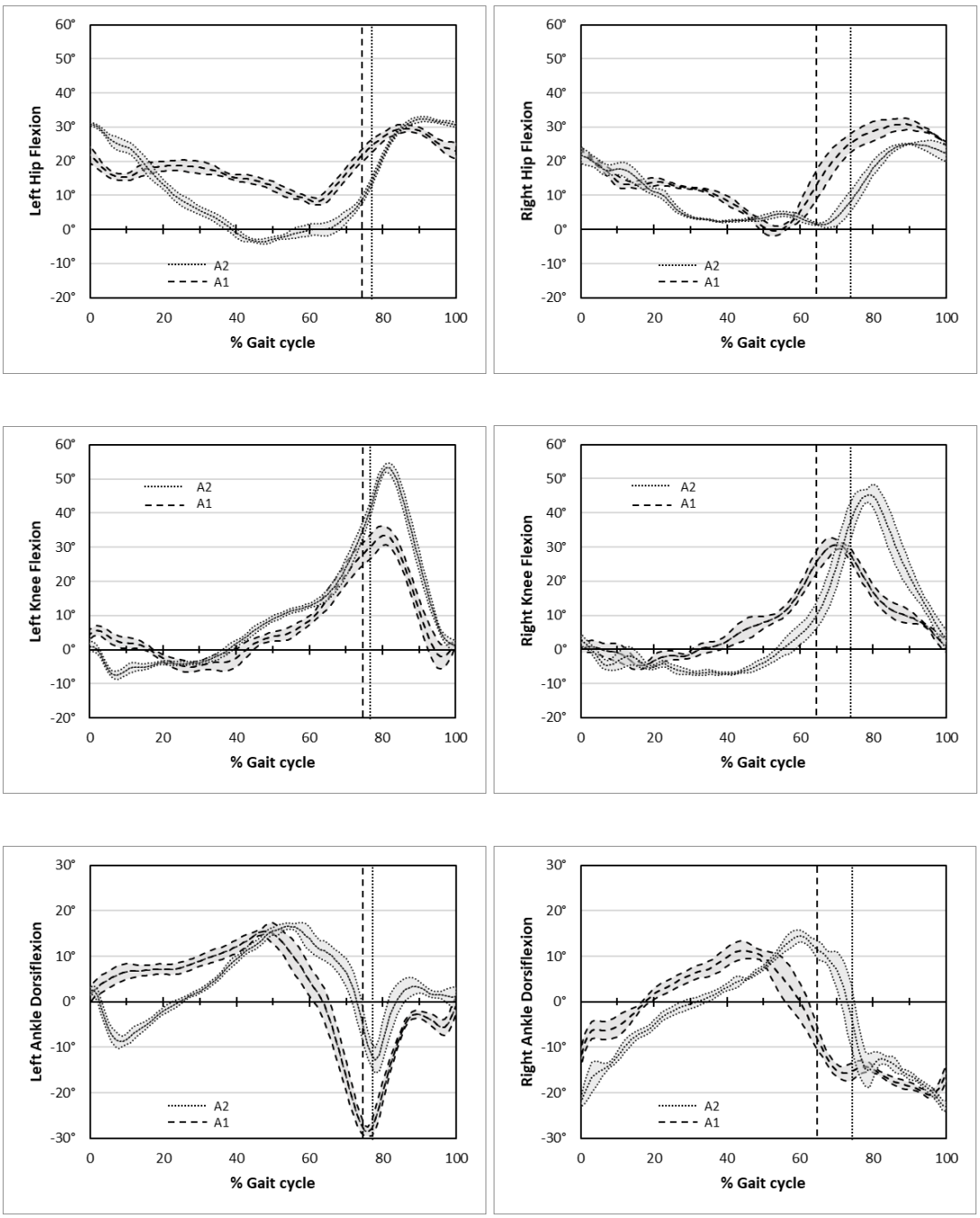


Figure 6.9: Joint kinematics (Mean ± SD) of case 3 at pre-treatment (A1) and post-treatment (A2) assessment (N = 5 cycles for both assessments).

6.2.4. Case 4

Case 4 was a 40-year-old male who had left spastic hemiplegia for 4 months due to right internal capsule and basal ganglion infarction. Before having a stroke, he could perform self-care and ambulation independently. At the enrolment, he had some motor control of the hip, knee, and ankle on his plegic side. He was able to ambulate on a level surface and walk up and down stairs independently using a single leg walking stick. Although he had voluntary motor control of the pretibial muscle, he still used a solid AFO for ambulation. He also had some recovery of hand movement, and received intensive training for improving hand function from occupational therapists. During the pre-training assessment, his walking speed and RMI score were 0.44 m/s and 12, respectively.

Training programme

Due to caregiver availability, case 4 received enhanced treadmill training twice a week, which was the same as before he participated in the present study. He attended all (12/12) training sessions and did not receive other sessions of physiotherapy in the hospital within the duration of the study. His treadmill speed ranged from 0.25 to 0.30 m/s on fixed-pace mode. He required interval training and support from the front bar during treadmill walking. There were 5 training sessions with FES applied only to the pretibial muscle, and 7 training sessions with FES applied to both pretibial and quadriceps muscles. The patient reported an event of falling at home due to leg spasticity which resulted in non-significant left shoulder pain. The time

spent and distance covered on the treadmill ranged from 10 to 20 min and 178 to 330 m, respectively (Figure 6.10).

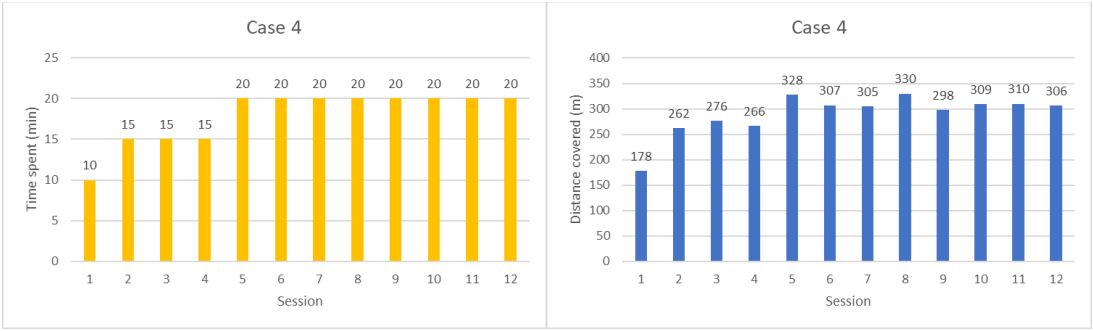


Figure 6.10: The time spent and distance on the treadmill of case 4.

Immediate effect of FES

The effects of FES applied to the pretibial muscle on foot drop during swing phase, and the quadriceps muscle on knee stability during early stance phase, are both shown in Figure 6.11. According to the figure, it can be seen that walking with FES applied to the pretibial muscle produced less plantarflexion than walking without FES during swing phase. Statistically significant differences in plantarflexion angle between the two conditions were observed at the 70% and at the 90% of the gait cycle, with mean differences of 9.6 (95% CI: 7.5 to 11.6) and 4.8 degrees (95% CI: 3.4 to 6.1), respectively. Moreover, walking with FES applied to the quadriceps muscle appeared to reduce knee hyperextension during early stance phase in comparison to walking without FES. There was a statistically significant difference in knee flexion angle between two conditions with mean difference of 6.4 degree (95% CI: 4.6 to 8.2) at the 10% of the gait cycle.

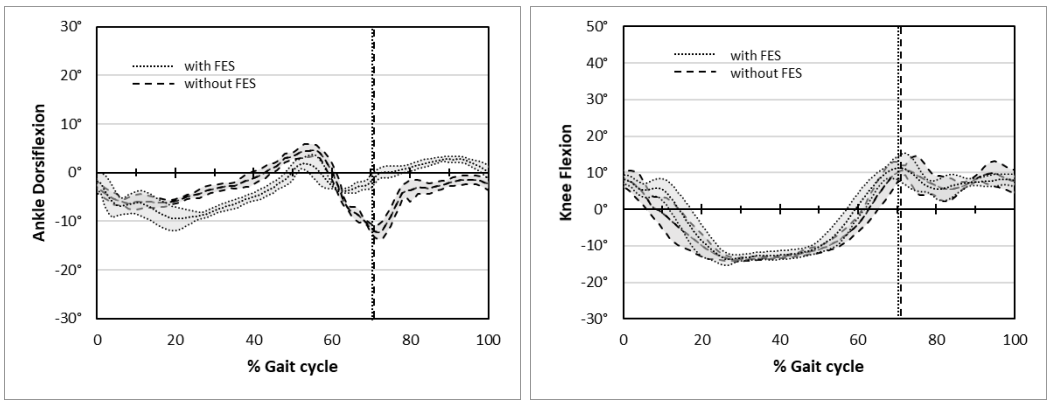


Figure 6.11: Sagittal kinematics of ankle and knee on plegic (left) side (Mean ± SD) of case 4, walking with and without FES to pretibial and quadriceps muscles (N = 5 cycles for both conditions).

Therapeutic effect of enhanced treadmill training

The over-ground walking speed, RMI score, stride length, and step length ratio of case 4 during pre- and post-training assessments are given in Table 6.5. The patient had clinically significant improvement in walking speed that increased by 0.15 m/s and in stride length that increased by 0.29 m (95% CI: 0.25 to 0.34).

Table 6.5: Walking speed, RMI score, stride length, and step length ratio of case 4 at pre- and post-training assessments

Outcomes	Pre-training	Post-training	P-value
walking speed (m/s)	0.44	0.59	-
RMI score	12	13	-
Stride length* (m)	0.50 (0.03)	0.79 (0.02)	0.001
Step length (P/NP) ratio *	0.89 (0.09)	1.09 (0.06)	0.04

* Mean (SD) of 5 cycles; P-value of paired t-test (pre vs post).

The sagittal kinematics of the hip, knee, and ankle joints at pre- and post-training assessments are shown in Figure 6.12. The patient wore his own solid AFO for both assessments. Post-training assessment showed increased hip excursion on both sides compared with pre-training. Improvements were also observed from knee flexion during swing phase and ankle plantarflexion during push-off on his non-plegic side. However, knee hyperextension during midstance, and poor knee flexion during swing phase were still apparent on the patient's plegic (left) side in the post-training assessment.

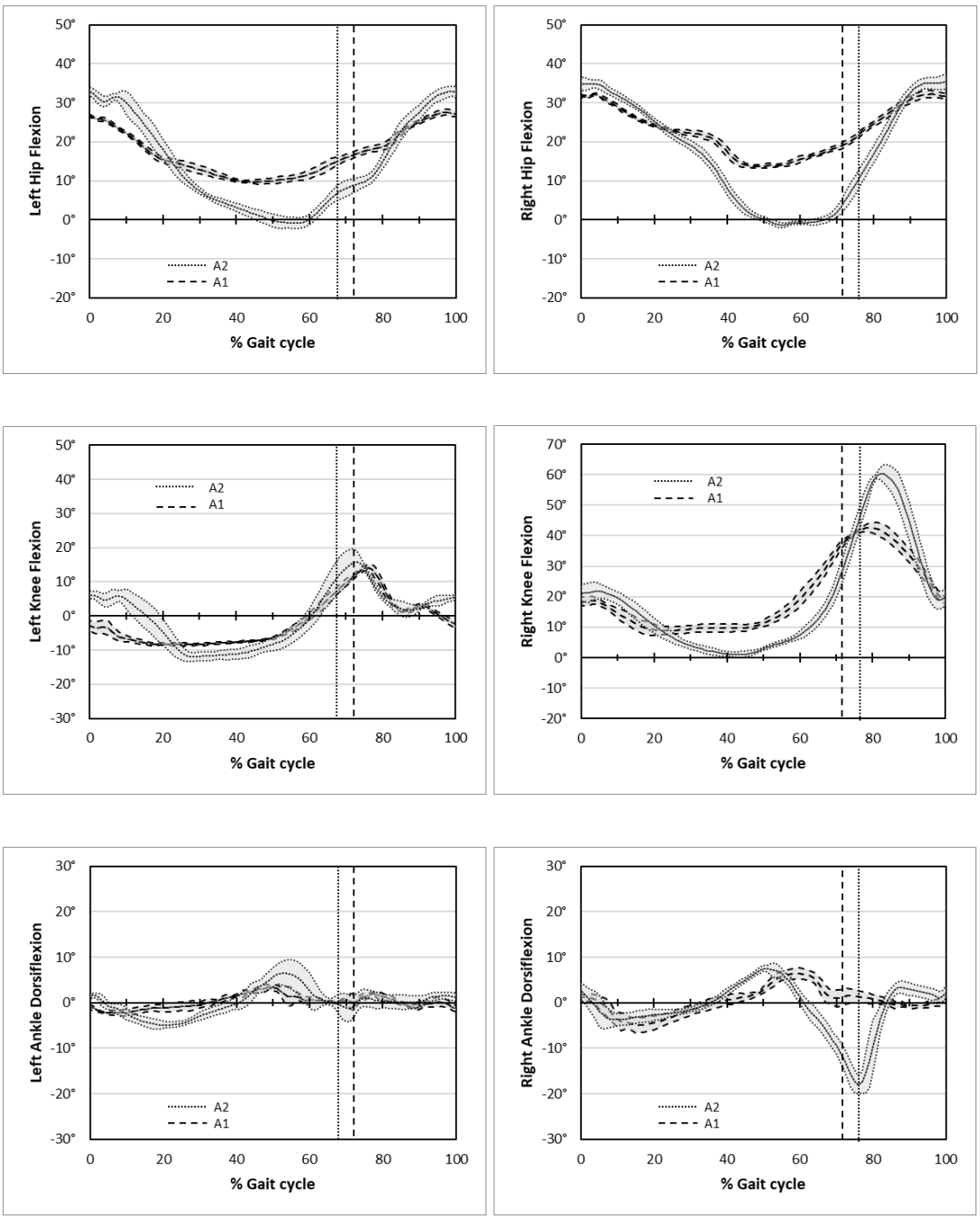


Figure 6.12: Joint kinematics (Mean ± SD) of case 4 at pre-treatment (A1) and post-treatment (A2) assessment (N = 5 cycles for both assessments).

6.2.5. Case 5

Case 5 was a 55-year-old male suffering from right hemiplegia with motor aphasia (an inability to speak), and severe right shoulder subluxation, due to having a left MCA infarction within 10 months. Before having a stroke he was able to perform self-care and ambulation independently. At the enrolment stage, the extent of his motor recovery was deemed to be poor. On the plegic side, he was unable to move his arm or hand, although a small amount of motor power remained in his leg. When using a solid AFO and a tetrapod walking stick, he was able to ambulate at a very slow speed without physical support but under supervision. He also needed to wear an arm sling to support his shoulder subluxation. At the pre-training assessment, his walking speed and RMI score were 0.19 m/s and 10, respectively.

Training programme

Due to availability of ambulance service, case 5 received enhanced treadmill training once per week, mirroring his schedule before participating in the present study. He attended 5/6 training sessions and did not receive any additional sessions of physiotherapy in the hospital during the study. Treadmill speed ranged from 0.20 to 0.22 m/s in fixed-pace mode. He needed interval training and used support from the front bar of the treadmill during while walking. There were 2 training sessions using FES only to the pretibial muscle, and 3 training sessions using FES to pretibial and quadriceps muscles. He did not report any adverse events throughout the study period. The time spent and distance covered on the treadmill ranged from 15 to 20 min and 178 to 230 m, respectively (Figure 6.13).

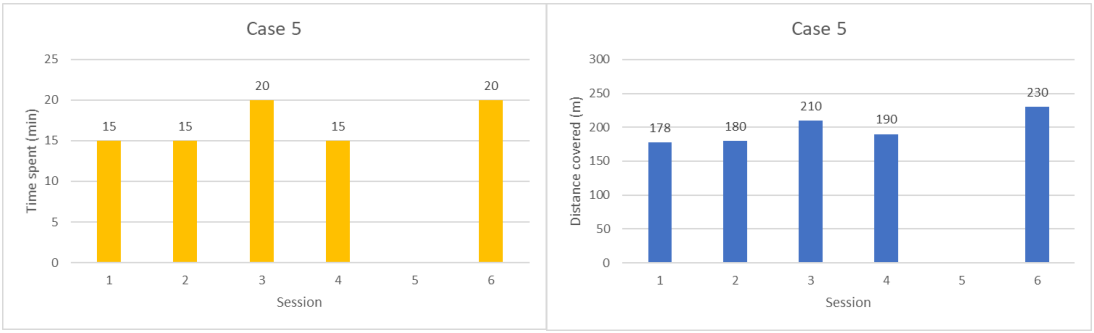


Figure 6.13: The time spent and distance on the treadmill of case 5.

Immediate effect of FES

The effects of FES applied to the pretibial muscle on foot drop during swing phase, and to the quadriceps muscle on knee stability during early stance phase, are shown in Figure 6.14. From the graph, it can be seen that walking with FES applied to the pretibial muscle produced less plantarflexion during the swing phase than walking without FES. There was statistically significant difference in plantarflexion angle between the two conditions at 90% of the gait cycle, with a mean difference of 7.09 degrees (95% CI: 5.99 to 8.18). Concerning the effects of FES applied to the quadriceps muscle, there were no statistically significant differences between the knee flexion patterns during the two assessments.

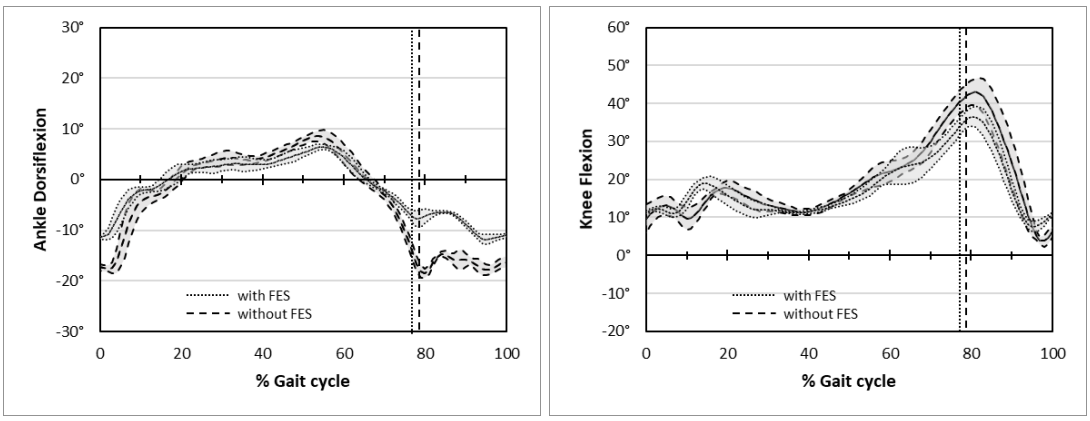


Figure 6.14: Sagittal kinematics of ankle and knee on plegic (right) side (Mean ± SD) of case 5, walking with and without FES to pretibial and quadriceps muscles (N = 5 cycles for both conditions).

Therapeutic effect of enhanced treadmill training

The over-ground walking speed, RMI score, stride length, and step length ratio from pre- and post-training assessments are reported in Table 6.6. It can be seen that there were no significant improvements in walking speed, RMI score, or stride length. However, a statistically significant difference in step-length asymmetry was found in the post-training assessment.

Table 6.6: Walking speed, RMI score, stride length, and step length ratio of case 5 at pre- and post-training assessments

Outcomes	Pre-training	Post-training	P-value
walking speed (m/s)	0.19	0.17	-
RMI score	10	12	-
Stride length* (m)	0.51 (0.02)	0.50 (0.01)	0.33
Step length (P/NP) ratio *	1.03 (0.07)	0.87 (0.06)	0.01

* Mean (SD) of 5 cycles; P-value of paired t-test (pre vs post).

Sagittal kinematics of the hip, knee, and ankle joints at pre- and post-training assessments are plotted in Figure 6.15. The patient wore a solid AFO for both assessments. The graph of his gait pattern did not show significant changes in hip or knee kinematics on the plegic (right) side between the two assessments, and he continues to require a solid AFO for ambulation.

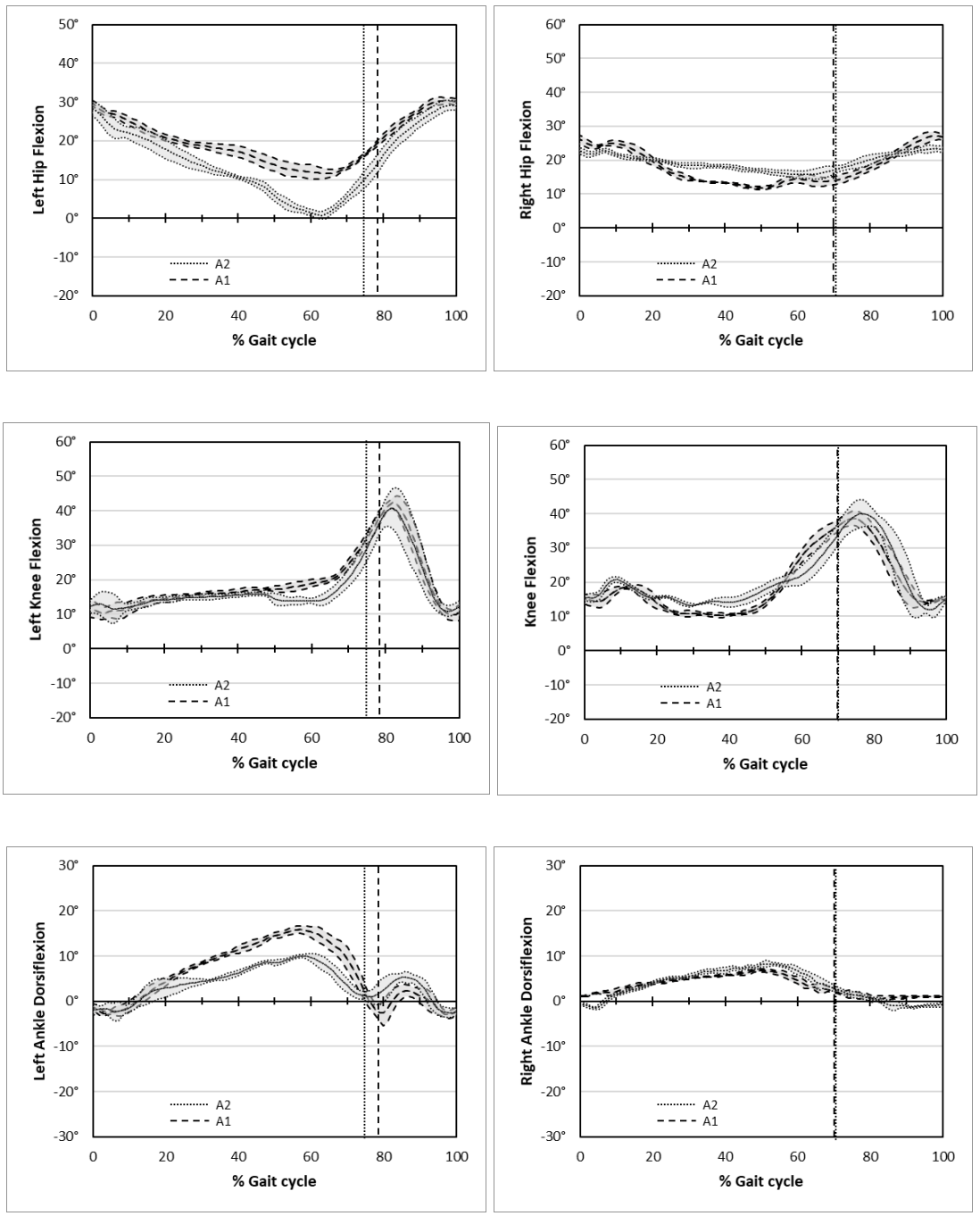


Figure 6.15: Joint kinematics (Mean ± SD) of case 5 at pre-treatment (A1) and post-treatment (A2) assessment (N = 5 cycles for both assessments).

6.2.6. Case 6

Case 6 was a 47-year-old male presenting with left hemiplegia due to having a right MCA infarction within 12 months. At the enrolment, he still had severe muscle weakness in the upper limb on his plegic side, but moderate muscle power was found in the plegic leg. He was able to ambulate on a level surface independently with the use of a single-leg walking stick and a posterior leaf spring AFO. At the pre-training assessment, his walking speed and RMI score were measured as 0.67 m/s and 10, respectively.

Training programme

Due to caregiver availability, case 6 received enhanced treadmill training once per week; equivalent to his existing rate of rehabilitation therapy before participating in this study. He attended 5/6 training sessions of the present study and did not receive other sessions of physiotherapy in the hospital during this time. His treadmill speed ranged from 0.40 to 0.55 m/s on fixed-pace mode. He did interval training and used the support of the front bar of the treadmill while walking on the treadmill. He received FES to the pretibial muscle only, which was applied in all 5 training sessions. He did not report any adverse events throughout the duration of the study. The time spent for each session was 20 min, and the distance covered ranged from 420 to 589 m (Figure 6.16).

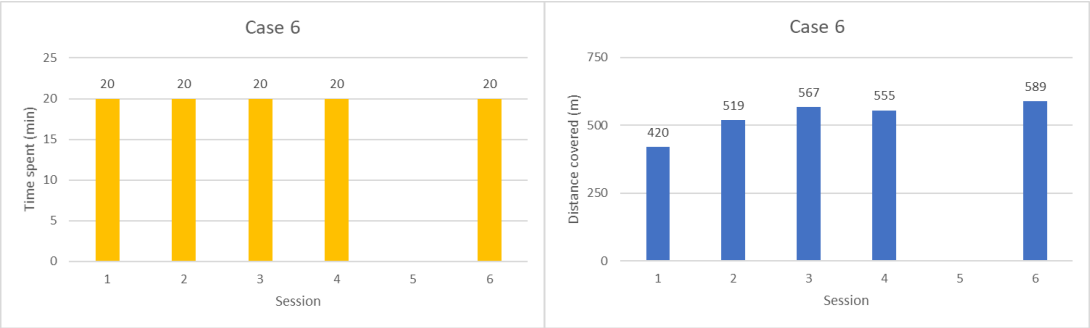


Figure 6.16: The time spent and distance on the treadmill of case 6.

Immediate effect of FES

According to the graph in Figure 6.17, it may be noted that the patient did not have a foot drop problem during swing phase although FES to the pretibial muscle was not used. Moreover, walking with and without FES showed very similar patterns of sagittal ankle kinematics. Nevertheless, FES was applied to the pretibial muscle during every session to ensure that he would not develop a foot drop problem while performing enhanced treadmill training.

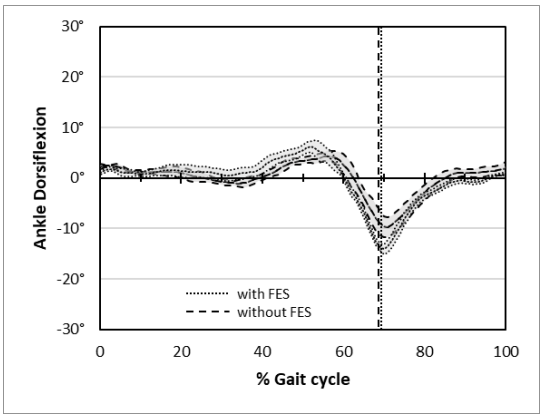


Figure 6.17: Sagittal kinematics of ankle on plegic (left) side (Mean ± SD) of case 6, walking with and without FES to the pretibial muscle (N = 5 cycles for both conditions).

Therapeutic effect of enhanced treadmill training

Pre- and post-training assessments of his over-ground walking speed, RMI score, stride length, and step length ratio are detailed in Table 6.7. He wore his own AFO for the pre-training assessment, but did not use it for the post-training assessment. Improved stride length and step length ratio were observed in the post-training assessment. Stride length increased by 0.15 m (95% CI: 0.13 to 0.18) and step length ratio reduced from 1.31 to 1.02. However, over-ground walking speed was not improved.

Table 6.7: Walking speed, RMI score, stride length, and step length ratio of case 6 at pre- and post-training assessments

Outcomes	Pre-training	Post-training	P-value
walking speed (m/s)	0.67	0.62	-
RMI score	10	12	-
Stride length* (m)	0.59 (0.04)	0.74 (0.02)	<0.001
Step length (P/NP) ratio *	1.31 (0.20)	1.02 (0.08)	0.007

* Mean (SD) of 5 cycles; P-value of paired t-test (pre vs post).

The sagittal kinematics of the hip, knee, and ankle joints at pre- and post-training assessments are provided in Figure 6.18. The patient had good hip excursion on both sides at both assessments. There were no significant differences in the maxima of hip extension on the plegic (left) side between both assessments. However, there was a significant improvement of peak knee flexion during swing phase, which increased by 15.13 degrees (95% CI:

13.35 to 16.91). Moreover, although a posterior leaf spring AFO was not used, no foot drop problem was observed in the post-training assessment.

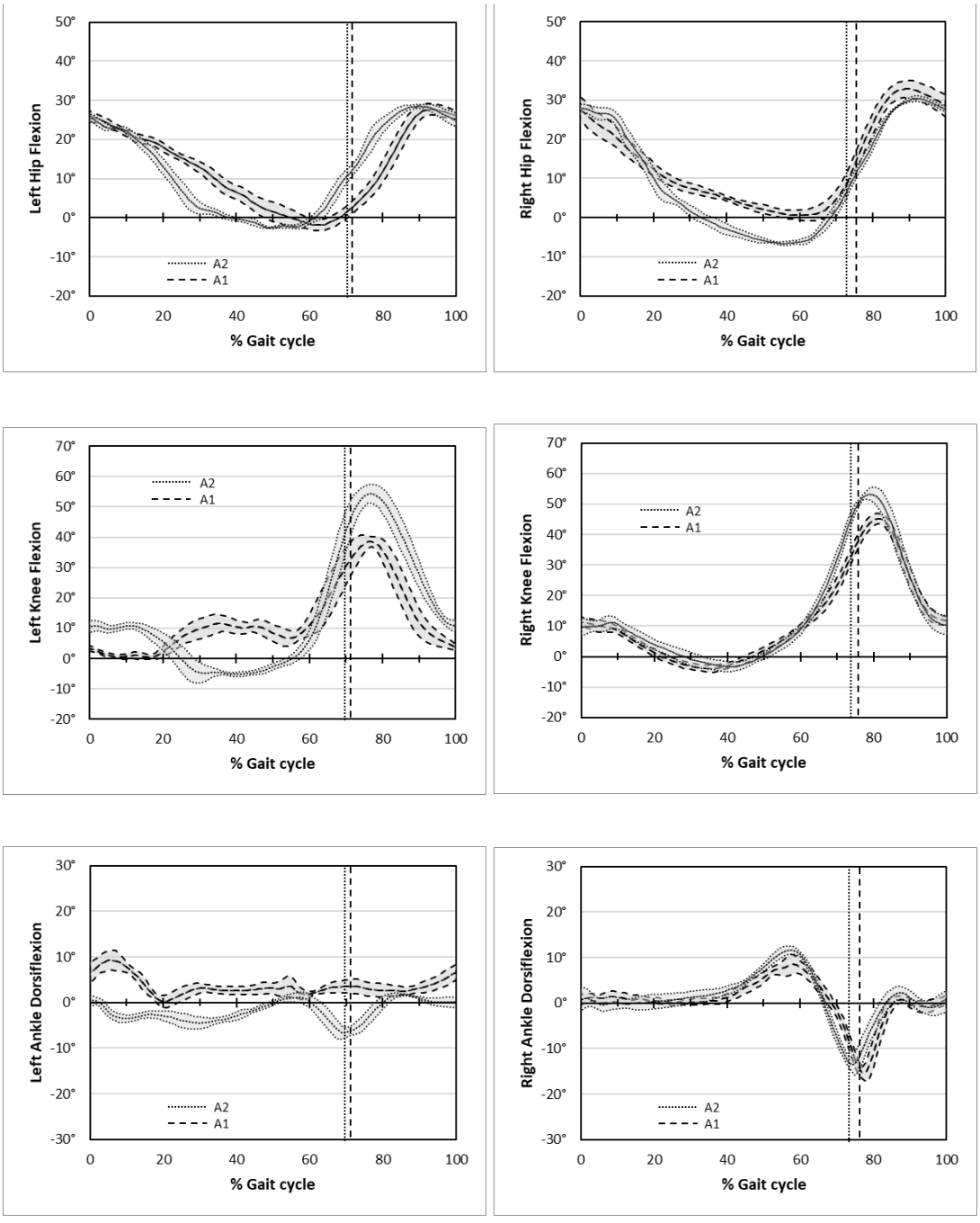


Figure 6.18: Joint kinematics (Mean ± SD) of case 6 at pre-treatment (A1) and post-treatment (A2) assessment (N = 5 cycles for both assessments).

6.2.7. Case 7

Case 7 was a 43-year-old male with right spastic hemiplegia due to left basal ganglion haemorrhage that occurred 2 months before the study. At enrolment, he had moderate motor recovery of both the upper and lower extremities. He was able to ambulate on a level surface, walk up and down stairs independently and safely, but needed a single-leg walking stick and rebound foot-up orthosis for long-distance walking. An occupational therapist provided him with hand function rehabilitation. At the pre-training assessment, his walking speed and RMI score were 0.58 m/s and 14, respectively.

Training programme

Case 7 had 7 appointments over 4 weeks because he planned to visit his home country before the end of the study. He attended all (7/7) training sessions and did not receive other physiotherapy sessions in the hospital during this time. His treadmill speed ranged from 0.45 to 0.52 m/s on fixed-pace mode. He did not need interval training, but required a little support from the side bar of the treadmill during training. There were 4 training sessions with FES applied only to the pretibial muscle, and 3 training sessions with FES applied to pretibial and gastro-soleus muscles. He did not report any adverse events during the study period. The time spent for each session was 20 min, and the distance covered ranged from 530 to 585 m (Figure 6.19).

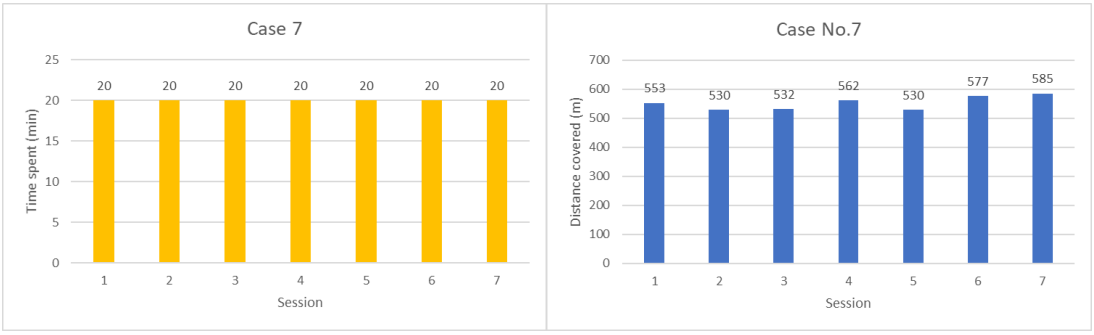
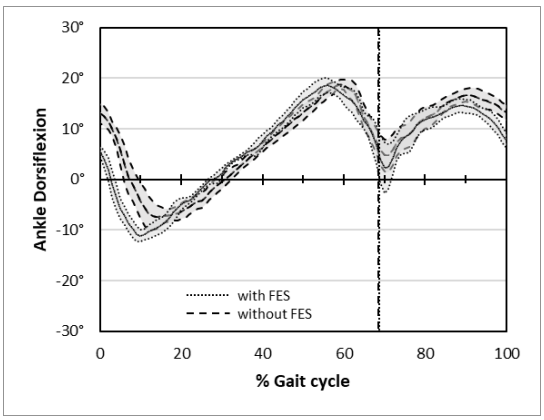
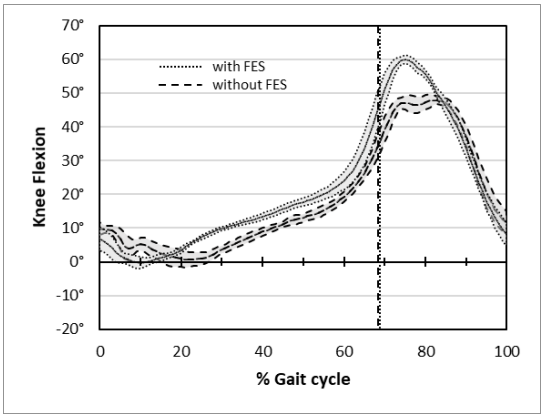


Figure 6.19: The time spent and distance on the treadmill of case 7.

Immediate effect of FES

The graphs plotted in Figure 6.20 display data from the patient walking with and without FES applied to their pretibial and calf muscles. The patient had no foot drop problem during swing phase when walking without FES. In addition, it seems that he intended to perform ankle dorsiflexion during swing phase for foot clearance. Hence, there was no significant difference in ankle motion between the two conditions. However, FES to the pretibial muscle was still used for every training session to prevent any foot drop problems during swing phase emerging. The application of FES to calf muscles while walking appeared to improve peak knee flexion during swing phase compared with walking without FES, with a mean difference of 11.27 degrees (95% CI: 10.82 to 11.71). This increase was not caused by hip motion because there was no significant difference in hip kinematics during that time period (70% – 80% of gait cycle).





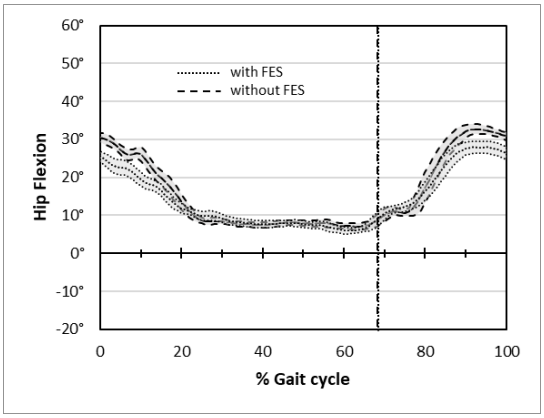


Figure 6.20: Sagittal kinematics of ankle, knee, and hip on plegic (right) side (Mean ± SD) of case 7, walking with and without FES to pretibial muscle (N = 5 cycles for both conditions).

Therapeutic effect of enhanced treadmill training

His over-ground walking speed, RMI score, stride length, and step length ratio during pre- and post-training assessments are shown in Table 6.8. The patient wore a rebound foot-up orthosis for the pre-training assessment, but did not use it for their post-training assessment. At the post-training assessment, walking speed, stride length and step length ratio were found to be significantly improved. Over-ground walking speed reached the level of a community ambulator (more than 0.8 m/s). Stride length increased

by 0.26 m (95% CI: 0.23 to 0.30), and step length ratio was in the normal range.

Table 6.8: Walking speed, RMI score, stride length, and step length ratio of case 7 at pre- and post-training assessments

Outcomes	Pre-training	Post-training	P-value
walking speed (m/s)	0.58	0.82	-
RMI score	14	14	-
Stride length* (m)	0.64 (0.04)	0.90 (0.01)	<0.001
Step length (P/NP) ratio *	1.24 (0.13)	1.04 (0.03)	0.01

* Mean (SD) of 5 cycles; P-value of paired t-test (pre vs post).

The sagittal kinematics of the hip, knee, and ankle joints during the pre- and post-training assessments are plotted in Figure 6.21. There were significant improvements in hip and knee kinematics on both plegic and non-plegic sides by the end of training programme. The patient had an increased peak hip extension on his plegic (right) side, with a mean difference of 19.26 degrees (95% CI: 18.90 to 19.62), and on his non-plegic side, with a mean difference of 8.85 degrees (95% CI: 8.23 to 9.47). Moreover, improved peak knee flexion was found on both sides. Peak knee flexion in the post-training assessment increased by 12.11 degrees (95% CI: 8.82 to 15.41) on his plegic (right) side, and by 10.39 degrees (95% CI: 9.66 to 11.13) on his non-plegic side, compared with those measured in the pre-training assessment. Concerning ankle kinematics on the plegic side, it seems that he intended to perform ankle dorsiflexion during the swing phase at both assessments.

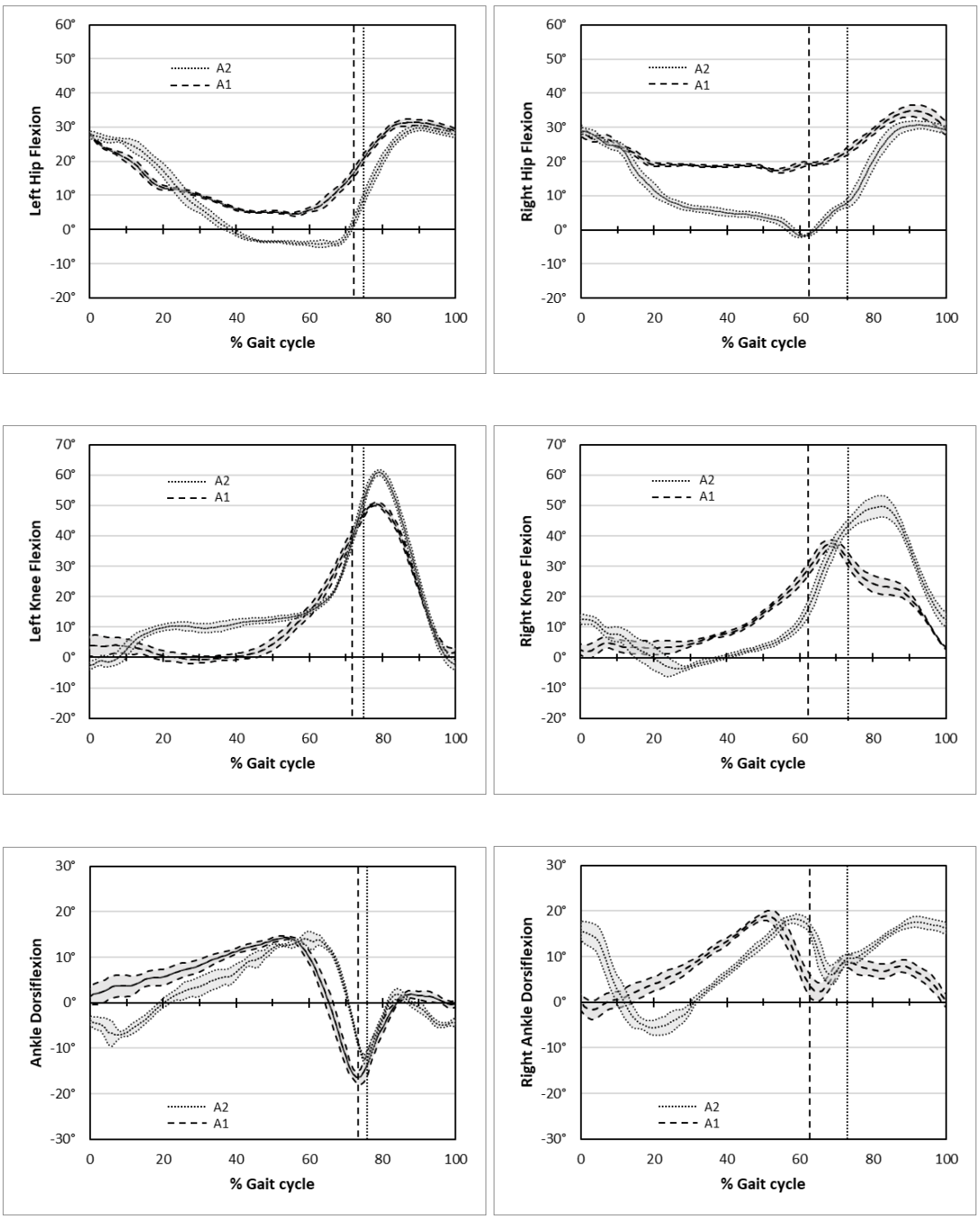


Figure 6.21: Joint kinematics (Mean ± SD) of case 7 at pre-treatment (A1) and post-treatment (A2) assessments (N = 5 cycles for both assessments).

6.2.8. Case 8

Case 8 was a 45-year-old male who had suffered from poor muscle coordination mainly on the right side for 5 months due to cerebellar infarction. He withdrew from the study at the pre-training assessment because treadmill walking aggravated the soreness of his hip.

6.2.9. Case 9

Case 9 was a 64-year-old male who had suffered from left spastic hemiplegic and severe shoulder subluxation for 4 months due to right MCA infarction. At enrolment, he had no motor recovery in his upper extremity, but some motor recovery in his lower extremity. He required an arm sling to support his shoulder subluxation. He also needed a solid AFO and a single-leg walking stick to ambulate safely on a level surface. During the pre-training assessment, his walking speed and RMI score were measured as 0.48 m/s and 12, respectively.

Training programme

Due to the availability of an ambulance service, case 9 received enhanced treadmill training twice per week. This was the same rehabilitation schedule as before he participated in the present study. He attended 10/12 training sessions of the present study, and no other sessions of physiotherapy were received during this time. His treadmill speed ranged from 0.20 to 0.22 m/s on fixed-pace mode. He needed interval training and support from the front bar of the treadmill while walking. There were 4 training sessions with FES applied only to the pretibial muscle, and 6 training sessions with FES applied to pretibial and quadriceps muscles. He did not report any adverse events throughout the study period. The time spent and distance walked ranged from 7 to 12 min and 149 to 343 m, respectively (Figure 6.22).

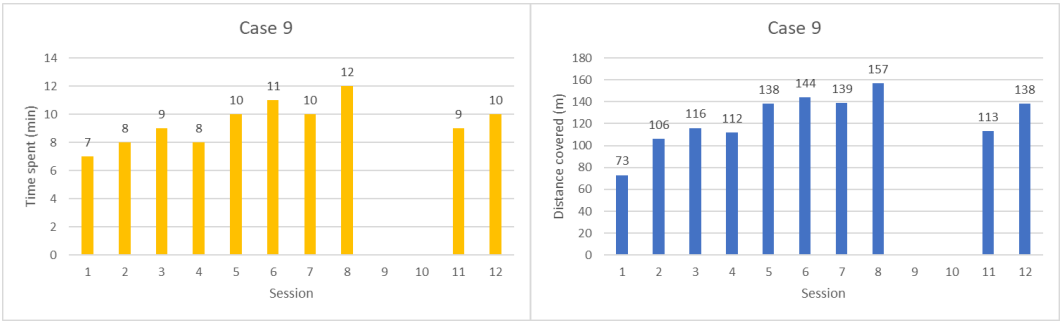


Figure 6.22: The time spent and distance on the treadmill of case 9.

Immediate effect of FES

According to the graph in Figure 6.23, which displays the patient's gait while provided with FES to pretibial and quadriceps muscles, it was found that he had no foot drop problem during swing phase when no using FES. In addition, both conditions had a similar ankle kinematic pattern. However, FES was still applied to the pretibial muscle during every training session to prevent the occurrence of any foot drop problems during swing phase. In relation to the quadriceps muscle, it appears that walking with and without the application of FES did not greatly affect the kinematic pattern of the knee.

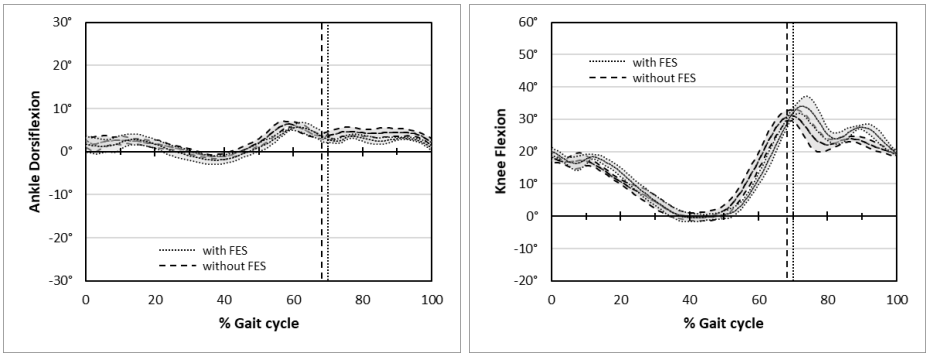


Figure 6.23: Walking speed, RMI score, stride length, and step length ratio of case 9 at pre- and post-training assessments

(N = 5 cycles for both conditions).

Therapeutic effect of enhanced treadmill training

Case 9's over-ground walking speed, RMI score, stride length, and step length ratio measured in pre- and post-training assessments are provided in Table 6.9. The patient wore a solid AFO for both assessments. This patient did not demonstrate any improvement in primary outcome measures, although a statistically significant change in stride length was observed between the two assessments.

Table 6.9: Walking speed, RMI score, stride length, and step length ratio of case 9 at pre- and post-training assessments

Outcomes	Pre-training	Post-training	P-value
walking speed (m/s)	0.48	0.49	-
RMI score	12	12	-
Stride length* (m)	0.32 (0.03)	0.37 (0.02)	<0.001
Step length (P/NP) ratio *	0.58 (0.06)	0.64 (0.11)	0.07

* Mean (SD) of 5 cycles; P-value of paired t-test (pre vs post).

The sagittal kinematics of the hip, knee, and ankle joints at pre- and post-training assessment are shown in Figure 6.24. The patient wore a solid AFO during both assessments. It may be noted that the post-training gait pattern is similar to the pre-training pattern, particularly knee hyperextension during midstance and poor knee flexion during swing phase.

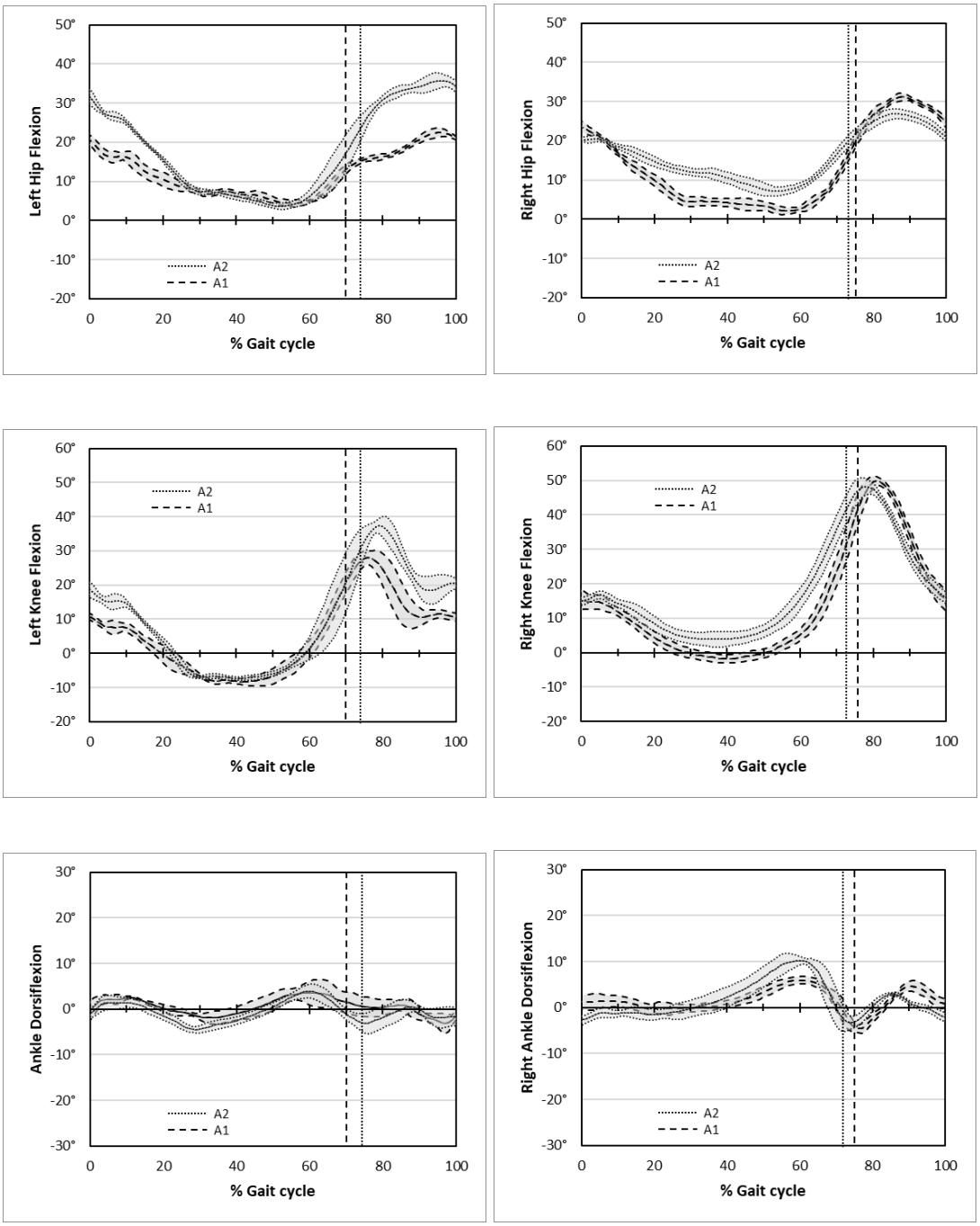


Figure 6.24: Joint kinematics (Mean ± SD) of case 9 at pre-treatment (A1) and post-treatment (A2) assessment (N = 5 cycles for both assessments).

6.2.10. Case 10

Case 10 was a 45-year-old female who had suffered from left spastic hemiplegia for 4 months due to right MCA infarction. She withdrew from the study at the pre-training assessment because she felt nervous about walking on a treadmill.

6.3. Feasibility and acceptability of enhanced treadmill training

Analysis of retention rate, attendance rate, number of completed training sessions, and adverse events was performed to determine the feasibility of enhanced treadmill training for use in clinical practice. The immediate effects of MFES on lower limb kinematics were also considered. Additionally, feedback was gathered from participants and physiotherapists involved in this study to evaluate the practical acceptability of the enhanced treadmill training system.

As shown in Table 6.10, eight out of initial participants were able to fully complete their training programme. Two participants withdrew from the study at the baseline assessment due to aggravated hip soreness caused by treadmill walking (case 8) and being nervous with treadmill walking (case 10). In total, from the eight participants who completed their programmes, 67 sessions of enhanced treadmill training were carried out. The number of training sessions for each participant ranged from 5 to 20. It can be seen that enhanced treadmill training had a good attendance rate. Cases 1 and 3 were each absent from one training session due to health issues, while cases 5

(one session), 6 (one session), and 9 (two sessions) encountered absences due to transportation issues.

Importantly, no serious adverse events occurred during this study. Three participants reported non-serious adverse events. Case 1 reported increased toe flexor spasticity; possibly due to the natural course of stroke recovery, and not directly caused by the research intervention. Case 3 felt shoulder pain on her plegic side, which was reported to occur before a training session; therefore, she requested to terminate the training session after 14 minutes. Case 4 reported on one occasion that he had fallen at home due to spasticity of his plegic leg. However, he proceeded to receive his training programme as usual without suffering any further adverse events.

The developed MFES system was used in 63 training sessions (It was not used for the last 4 training sessions of case 1). Stimulation of the pretibial muscle was able to reduce the magnitude of plantarflexion angle during swing phase among patients with foot drop problems (cases 1, 2, 3, 4, and 5). One patient (case 7) who received FES to their calf muscle showed improved peak knee flexion during swing phase. Two patients (cases 4 and 5) received FES to their quadriceps muscles; however, resulting changes in knee kinematics were only observed from case 4.

Table 6.10: Attendance rate, time spent, and distance covered of each participant

Case	Attendance rate	Time spent (min) *	Distance covered (m) *
1	11/12	15 (8 – 20)	107 (52 – 149)
2	6/6	11 (9 – 13)	62 (42 – 112)
3	11/12	18 (10 – 20)	278 (149 – 343)
4	12/12	20 (10 – 20)	305 (178 – 330)
5	5/6	15 (15 – 20)	190 (178 – 230)
6	5/6	20 (20 – 20)	555 (420 – 589)
7	7/7	20 (20 – 20)	553 (530 – 585)
8	Withdraw		
9	10/12	9 (7 – 12)	127 (73 – 157)
10	Withdraw		

* Median (Min – Max)

Participants and physiotherapists provided feedback concerning the enhanced treadmill training based on a structured questionnaire. They rated their level of agreement with each statement from strongly agree (5) to strongly disagree (1). Table 6.11 shows the tabulated feedback from each of the participants who completed their training programme; it can be seen that one participant failed to provide feedback. In general, positive feedback was given for enhanced treadmill training. All responders (7/7) thought that the training was enjoyable and easy to understand. In addition, they were all motivated to continue their training and would recommend this training to

other stroke survivors. However, some responders gave negative feedback regarding set-up time (1/7), equipment (1/7), treadmill walking (1/7), and comfort and security of the harness (2/7).

Six physiotherapists who were responsible for treating the participants also provided feedback about the research intervention; although it should be noted that these physiotherapists did not operate or set up the enhanced treadmill training. The feedback from physiotherapists is shown in Table 6.12. They all provided positive feedback on set-up time, equipment and system operation, and agreed that enhanced treadmill training could encourage their patients' motivation. They also expressed their desire to continue using the enhanced treadmill training system after the study ended, and would recommend it to other physiotherapists. Additionally, one physiotherapist provided a specific comment regarding the real-time visualisation feedback, as shown below:

> **"The visual feedback was great motivation for patients especially the stride length + distance travelled parameters"**

Based on this qualitative analysis, it may be concluded that the enhanced treadmill training system that we have developed is feasible and acceptable for gait rehabilitation after stroke in clinical practice.

Table 6.11: Participants' Feedback

Statement	P1	P2	P3	P4	P5	P6	P7	P9
The amount of set up time before each session was acceptable.	2	NG	4	5	4	5	5	5
Walking with all of the equipment set up was not too cumbersome.	4	NG	3	5	2	5	5	5
The treadmill is comfortable to walk on, and easy to get used to.	2	NG	4	5	5	4	5	5
Walking with the harness was comfortable and made me feel safe.	3	NG	2	5	2	5	5	5
The sessions as a whole were enjoyable.	5	NG	4	5	4	4	5	5
The instructions given during the sessions were easy to understand and carry out.	5	NG	4	5	5	4	5	4
I still feel motivated to continue with this training program.	4	NG	5	5	5	4	5	5
I would recommend treadmill training such as this to other stroke survivors.	4	NG	4	5	5	5	5	5

1 = Strongly disagree; 2 = Disagree; 3 = Neutral; 4 = Agree; 5 = Strongly agree

Table 6.12: Physiotherapists' Feedback

Statement	P1	P2	P3	P4	P5	P6
The amount of set up time before each session was acceptable.	4	5	5	5	4	5
Walking with all of the equipment set up was not too cumbersome for this participant.	5	5	5	5	4	5
The enhanced treadmill system was user friendly.	5	3	4	4	4	5
Any inconvenience during the training sessions was unimportant.	4	5	4	4	5	5
This enhanced treadmill training program increases motivation in participants.	5	5	5	5	5	5
I would like to continue using the enhanced treadmill system after the study ends.	5	5	5	5	5	5
I would recommend treadmill training such as this to other therapists working in gait rehabilitation.	5	5	5	5	5	5

1 = Strongly disagree; 2 = Disagree; 3 = Neutral; 4 = Agree; 5 = Strongly agree

6.4. Factors of clinically improved walking ability

The present study was designed as a small series of cases to be used for a feasibility trial. Therefore, any clinically relevant effects of the enhanced treadmill training were not likely to be established, considering that many factors influence gait recovery following stroke. Nevertheless, the present study does provide some insights into the factors that may be associated with positive outcomes in future work. Statistical analysis was conducted using data from the seven participants who had suffered from anterior circulation stroke resulting in muscle weakness. Therefore, case 2 who suffered from a posterior circulation stroke causing ataxia was excluded from the analysis.

The first factor to be considered was the amount of training time. The intensity of physiotherapy in usual service of community hospitals sometimes might be lower than the recommended dosage. In the present study, participants received up to 20 minutes of enhanced treadmill training once or twice a week for 6 weeks (6 – 12 sessions), whereas the previous study provided participants with 20 to 30 minutes of typical treadmill training three times a week for 12 weeks (30 – 36 sessions). It may be interpreted that some participants in the present study received a sub-optimal dosage of gait rehabilitation. However, this reflects a realistic situation in clinical practice due to therapists' workload, caregiver availability, financial problems, or transportation issues.

For this reason, the correlation between total time spent on enhanced treadmill training and increased over-ground walking speed (Table 6.13) was determined using Spearman's rank correlation. The results showed poor

correlation between these two factors (r_s = 0.36), which was not found to be statistically significant (p = 0.43).

Table 6.13: Total time spent on treadmill training and increased over-ground walking speed of seven cases.

Case	Total time spent (min)*	Increased speed (m/s)**
1	175	0.01
3	183	0
4	215	0.15
5	85	0
6	100	0
7	140	0.24
9	94	0.01

* The sum of all training sessions; ** Negative values are replaced with 0.

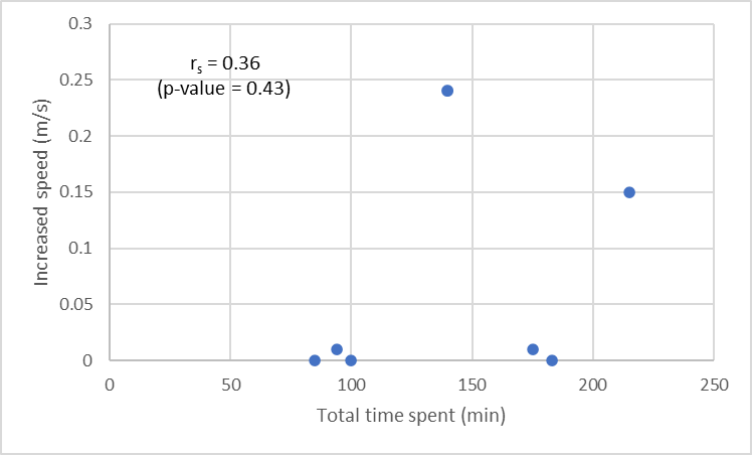


Figure 6.25: Correlation between total duration of enhanced treadmill training and increased over-ground walking speed.

The present study also aimed to determine possible clinical factors that might be associated with clinically relevant improvements in walking speed (increase > 0.14 m/s). The results of this analysis could be beneficial for designing a future randomized controlled trial (RCT), which will require a balance between the numbers of participants with good prognostic indicators in each treatment group. Factors which were examined included sex (male vs female), age (≤ 45 vs > 45 years), stroke onset (≤ 4 vs > 4 months), MCA (large vessel) stroke (No vs Yes), and pre-training walking speed (≥ 0.4 vs < 0.4 m/s). For age, stroke onset, and pre-training walking speed, these factors were categorised according to literature review. Stroke which occurred among individuals whose age ≤ 45 years was commonly defined as stroke in young adults (Smajlovic, 2015). Neurological recovery was usually found within 15 weeks after stroke onset (Jørgensen et al., 1995a). Stroke survivors whose walking speed < 0.4 m/s were classified as household ambulators (Duncan et al., 2011). Two-by-two tables were generated to compare each factor with categorical outcomes of clinically improved speed, and crude association was analysed using Fisher's exact test (Table 6.14). The results showed that absence of an MCA infarction had a statistically significant association with improved clinical outcome. It can be seen in Table 6.15 that cases 4 and 7, both of which exhibited a clinical improvement, had this factor. They both suffered from a stroke at the basal ganglion, which was not caused by an MCA lesion. Other common factors between these two cases were sex, age ≤ 45 years, stroke onset ≤ 4 months, and pre-training walking speed ≥ 0.4 m/s. These factors also may have contributed to the clinical

improvements observed from cases 4 and 7, although it is difficult to draw strong conclusions based on the limited sample size. Data from the present study was unsuitable for multivariate analysis to mitigate the effects of confounds due to having a very modest sample size.

Table 6.14: Association between clinical factors and clinical improvement

Clinical factors		Clinically improved speed; n (%)		P-value
		Yes	No	
Sex	Male	2 (33.7)	4 (66.7)	1.0
	Female	0 (0)	1 (100)	
Age (years)	≤ 45	2 (66.7)	1 (33.7)	0.14
	> 45	0 (0)	4 (100)	
Stroke onset (months)	≤ 4	2 (66.7)	1 (33.7)	0.14
	> 4	0 (0)	4 (100)	
MCA (Large vessel) stroke	No	2 (100)	0 (0)	**0.048***
	Yes	0 (0)	5 (100)	
Pre-training speed (m/s)	≥ 0.4	2 (40)	3 (60)	1.0
	< 0.4	0 (0)	2 (100)	

Table 6.15: Clinical factors of each participant

Case	Sex	Age > 45 years	Onset > 4 months	MCA stroke	speed < 0.4 m/s	Clinical improvement
1	M	Yes	Yes	Yes	Yes	No
3	F	No	Yes	Yes	No	No
4	**M**	**No**	**No**	**No**	**No**	**Yes**
5	M	Yes	Yes	Yes	Yes	No
6	M	Yes	Yes	Yes	No	No
7	**M**	**No**	**No**	**No**	**No**	**Yes**
9	M	Yes	No	Yes	No	No

Chapter 7: Discussion and Conclusion

7. Discussion and Conclusion

7.1. Discussion

Treadmill training is one of the most widely used methods of gait rehabilitation for patients after stroke. However, clinical evidence has shown that its effect on recovering community walking level is not implicitly superior to conventional over-ground gait training. Therefore, the present study aimed to develop a novel treadmill gait training paradigm that might have more clinical benefits than typical treadmill training. The present study consisted of developing a computerised MFES system using a 3D motion capture sensor network to determine the phase of gait cycle, and conducting a clinical feasibility trial of treadmill training augmented with MFES and real-time visual feedback in a clinical setting. We hypothesised that it is feasible and acceptable to use this novel treadmill training system in clinical practice.

7.1.1. Development of 3D motion capture-based MFES

There was some delayed latency of the system, as mentioned previously in chapter 3. Summation of the last 5 frames of the toe marker position (antero-posterior direction) was used to determine the phase of gait cycle. Therefore, the present method had slightly delayed detection of initial contact (IC) and toe-off (TO) events compared with the Zeni's work (Zeni et al., 2008). The delay for both IC and TO detection was 3 frames or 50 ms at a frame rate of 60 Hz. Although this method was quick enough to trigger the MFES system in the feasibility trial, the delayed latency can be reduced by increasing the frame rate; for example, if the frame rate is raised from 60 Hz to 120 Hz, the latency delay will be reduced from 50 ms to 25 ms.

The MFES system was triggered based on toe marker movements that were used to divide the gait cycle into five phases. Stimulation could be started or stopped only at the beginning of the phases; for example, stimulation of the pretibial muscle started at the first frame of Second Double Support and stopped at the first frame of First Double Support. This stimulation pattern was able to correct foot drop during the swing phase. However, this does not reflect the fine motor control of normal muscle activity during a gait cycle, in which the pretibial muscle is activated from late Second Double Support to the end of First Double Support. Hence, other algorithms may be considered to improve this problem; for instance, triggering FES based on the timing of previous gait cycles.

For the future study, some components of the intervention require further development. For instance, wireless connection between D-Flow and Arduino board might be used so patients probably feel more comfortable. In addition, some script of Arduino might need to be improved such as using delay function to adjust the time for triggering FES device to the pre-tibial muscle so the stimulation on this muscle could be stopped at the late First Double Support.

7.1.2. Feasibility trial of enhanced treadmill training

The key result from the feasibility trial was that enhanced treadmill training can be appropriately applied in real clinical situations. Stimulation of the pretibial muscle was able to significantly reduce the degree of ankle plantarflexion during swing phase among patients with foot drop problems;

demonstrating that the system can provide adequate stimulation support at the target time. In addition, one patient who received FES to their calf muscle exhibited better peak knee flexion during swing phase, and one patient who received FES to their quadriceps muscles showed better knee control during early stance phase. Importantly, of eight participants, more than 60 training sessions were carried out in the feasibility trial, and the system was able to run for up to 20 minutes continuously. Additionally, enhanced treadmill training using the research system had low drop-out and good attendance rates, and no serious adverse events were reported. Both participants and physiotherapists gave positive feedback on the intervention. Overall, these findings generally support the hypothesis of this study.

Dynamic biofeedback may potentially be more effective if it involves combined perception and cognition during rehabilitation training, is attractive and motivating, and is easy to understand (Huang et al., 2006). Based on the participants' feedback, they all found the training sessions enjoyable and easy to understand. Moreover, they were all motivated to continue this training programme. The real-time visualisation of dynamic avatar movement and step length/ratio during treadmill training seemed to provide an effective form of biofeedback for stroke rehabilitation. Importantly, in the feasibility trial two participants had a clinical improvement in their walking speed, stride length and step length symmetry.

As mentioned in chapter 4, the Strathclyde cluster model (Millar et al., 2019) was used in the present study because it was straightforward to run with D-Flow software and practical to use in a hospital setting. Patients did

not need to change their clothes, and the trained operator spent just a few minutes to perform an anatomical calibration. Feedback from participants and physiotherapists supported these design decisions. Six out of seven participants who gave feedback on enhanced treadmill training and all six physiotherapists agreed that the set-up time before training sessions was acceptable. One of the participants provided negative feedback regarding the set-up time.

To the best of our knowledge, the present study was the first to provide patients with dynamic avatar for gait kinematic feedback. This visual feedback included step length and step ratio in real-time, which is similar to the Biodex Gait Trainer^{TM} 3. The gait trainer provides patients with visual feedback about the location of their feet on the treadmill and step length of both feet, based on force sensors underneath the treadmill (Druzbicki et al., 2015, Druzbicki et al., 2018). In contrast, the present study determined gait parameters using marker positions measured using the 3D motion capture system. The Druzbicki study of 30 patients with subacute stroke (within 30 days after onset) observed only small improvements in walking speed (10MWT) and distance (2MWT) compared with the control group at the end of a 3-week training programme (Druzbicki et al., 2018). However, the long-term effects of training (e.g. outcome measures 6 months after stroke onset) were not evaluated. Future validation of the enhanced treadmill training system developed in the current study should therefore be achieved by conducting an RCT with a larger sample size of recent stroke patients, and include 6-month follow-up outcome measures.

In combining MFES with treadmill training, the present study is somewhat similar to those of Daly and colleagues (Daly et al., 2006, Daly and Ruff, 2004, Daly et al., 2011). The main differences between our approach and theirs are the types of FES electrode, treadmill, and biofeedback. Daly et al. used implanted electrodes, which require minor surgery to be inserted into or removed from the muscles. The present study used non-invasive surface electrodes, which physiotherapists are able to apply themselves in an out-patient clinic. Additionally, the studies of Daly et al. did not incorporate biofeedback, and the treadmill was operated only in fixed-pace mode.

Some limitations were experienced, as follows. Firstly, identification of the pelvic landmarks (ASIS and PSIS on both sides) for anatomical calibration was difficult for some participants because of obstruction by the harness of the weight-bearing system. The accuracy of hip joint kinematics might be affected by this problem. Secondly, due to the limited space for staff inside the treadmill, there may be difficulty helping patients who require physical support on or off of the treadmill. Thirdly, the surface electrodes used in the present study could cause cutaneous pain or ankle clonus when a high level of stimulation was applied. Fourthly, only self-administered questionnaire was used for qualitative information which has some weaknesses such as misunderstanding in the questionnaire. Subsequently, there might be some differences between visuomotor processes during treadmill and over-ground walking. Next, the study did not assess the feasibility of therapists to provide research intervention. Lastly, there were no

visual tests before enrolment although the study provided participants with visual feedback.

7.1.3. Outcome measures for gait rehabilitation after stroke

It is very important to set goals for rehabilitation that are specific, measurable, and relevant to the patient's condition. Several measures of functional outcome are typically used to set the goals for mobility and gait rehabilitation in clinical practice; for instance, Rivermead mobility index (RMI), 10-meter walk test (10mWT), and 6-minute walk test (6MWT).

The RMI and 10mWT assessments were used in the present study as outcome measures in the feasibility trial, as previously detailed in chapter 5. These two measures are short, simple assessments. No special equipment or additional training is required. Hence, they can easily be conducted in clinical practice. However, RMI uses a series of YES/NO questions to evaluate mobility performance, which is not capable of measuring the speed or extent of stroke survivors' walking rehabilitation. This can be seen in the results of cases 4 and 7 in the feasibility trial. Both of these cases had a good RMI score before receiving the research intervention (pre-training RMI of cases 4 and 7 were 13 and 14, respectively). At the end of their training programmes, their RMI had not changed significantly (post-training RMI of case 4 and 7 were 14 and 14, respectively) but their walking speeds, measured by 10mWT, showed a clinically significant improvement.

The 10mWT has become a common tool for measuring walking speed in gait rehabilitation. A variety of protocols for calculating walking speed have

been explored, but five to ten meters was recommended as the optimum timed distance (Middleton et al., 2015). In the present study, a timed distance of 6 meters with 2-meter acceleration and deceleration phases was chosen because it was considered to be more feasible for clinical practice than longer distance protocols. Walking speed was also used to classify functional ambulation into 3 levels: < 0.4 m/s for household, 0.4 – 0.8 m/s for limited community, and > 0.8 m/s for unlimited community level (Schmid et al., 2007). However, there is an argument that walking speed alone cannot reliably indicate the level of community ambulation (Lord and Rochester, 2005).

The 6MWT is a widely used measure for quantifying submaximal exercise capacity. In this test, the total distance walked along a 100-feet hallway within 6 minutes is measured (Laboratories, 2002). Although the 6MWT is mainly used to assess functional outcome among patients with cardio-pulmonary diseases, it is also used to evaluate walking capacity among stroke survivors (Sullivan et al., 2013). In addition, the study of Fulk and colleagues argued that the 6MWT was a better proxy measure than 10mWT to determine the level of ambulation (Fulk et al., 2017). However, the present study did not use the 6MWT as an outcome measure due to the limited space at the research site; although this test is recommended for use in future studies of enhanced treadmill training.

Using 3D motion capture analysis, outcomes such as temporo-spatial parameters and joint kinematics could also be used for setting goals of gait rehabilitation. With the enhanced treadmill training system, it was shown to

be clinically feasible to use this information as outcome measures for training. Because step length on both sides with their ratio was shown on the screen, therapists and patients were able to see changes in these outcomes in real-time during training. The system was also able to measure the duration of each phase of the gait cycle and calculate the respective percentage of the cycle for each phase; however, this information was only displayed to the system operator on the D-Flow runtime console. Some participants in the feasibility trial set their own goals for each training session based on the distance covered, which was shown on the feedback monitor, motivating patients to achieve their rehabilitation targets.

In the feasibility trial, gait analysis of treadmill walking should be interpreted with caution. Participants who have not had much experience of treadmill walking since their stroke may take several sessions to familiarize themselves with the treadmill. Moreover, one study published in 2019 suggested that healthy subjects needed at least 6 minutes to acclimatise to treadmill walking (Meyer et al., 2019); although there was no comparable data gathered from stroke survivors, their acclimatisation period may be longer. Furthermore, participants in the present study usually spent approximately 3 to 4 minutes for treadmill gait analysis at pre- and post-training assessments, which may not be representative of their best performance.

7.1.4. Clinical factors on the effect of enhanced treadmill training

The present study did not aim to determine the therapeutic effects of enhanced treadmill gait training. However, some of the factors that may be associated with clinically improved walking speed were examined. The statistical analysis was based on only 7 participants who had anterior circulation stroke causing weakness. There were just 2 participants (case 4 and 7) from this group who had clinically improved walking speed (increase > 0.14 m/s). The only associated factor that showed statistical significance was “Not having MCA (large vessel) infarction”, which had a p-value of 0.048. In addition, both stroke onset ≤ 4 months and age ≤ 45 years had p-values of 0.14, approaching the threshold for statistical significance.

Based on the natural history of stroke recovery, most stroke survivors reach their optimum motor recovery within 10 weeks, and it is rare to see further stroke recovery after 6 months post onset (Kwakkel and Kollen, 2013). Therefore, it may be predicted that 4 participants who had chronic stroke: case 1 (6 months); case 3 (12 months); case 5 (10 months); and case 6 (12 months) will show little to no improvement in their over-ground walking speed. Meanwhile, case 9 who had a subacute stroke (4 months) may be expected to show more improvement in their gate if they received greater intensity or longer periods of training.

Not only stroke onset but also stroke classification might contribute to the overall effectiveness of a training programme for gait recovery. A study observing gait recovery among 185 patients with recent stroke admitted to a rehabilitation unit showed that patients who had an incomplete MCA or

lacunar (small vessel) stroke had better gait recovery that those who had a complete MCA stroke (Baer and Smith, 2001). Another study that aimed to develop a predictive model for recovery after stroke based on 1281 patients also showed that stroke classification of lacunar infarction was significantly associated with an excellent outcome, with an odds ratio of 3.1 (95%CI: 1.5 to 6.4) (Adams et al., 1999). This might explain the results of the present study, which found a significant association between stroke type (large vessel vs non-large vessel) and clinically improved outcomes.

The age factor alone is shown to have a small effect on functional outcomes after stroke (Bagg et al., 2002). There is also strong evidence that age combined with severity of acute cerebral infarction measured by the National Institutes of Health Stroke Scale (NIHSS) ranging from 0 (no impairments) to 42 (the most severe impairment) (Brott et al., 1989) can be used to predict gait recovery. A prospective cohort study of 200 patients with stroke reported that a predictive model containing age group and NIHSS was able to forecast the recovery of independent ambulation (ability to walk at least 3 m without assistance while using an assistive device if needed) at 6 months after stroke onset. This model estimated that at NIHSS of 5 (mild stroke), there was around 80%, 97%, and 100% probability to return to independent ambulation among patients in their 80s, 60s, and 40s, respectively; these probabilities reduced to 25%, 75%, and 95% if NIHSS was raised to 15 (severe stroke) (Kwah et al., 2013).

In summary, the clinical gains from enhanced treadmill training are most likely to be found among patients with subacute stroke. Other important

clinical factors that should be considered are age, stroke severity, and stroke classification.

7.1.5. Effective dose of enhanced treadmill training

The present study examined the relationship between training dose and walking speed, but the results showed no significant relationship between these two factors. However, previous studies have suggested that large amounts of training practice might be required for stroke survivors to achieve a clinically significant improvement (Lang et al., 2015, Lohse et al., 2014). National Institute for Heath and Care Excellence (NICE) clinical guidelines for stroke rehabilitation published in 2013 recommend that patients with stroke should accumulate at least 45 minutes of each relevant training for a minimum of 5 days a week (Dworzynski et al., 2013). In 2017, a review of treadmill training with and without body weight support for gait rehabilitation after stroke reported that treadmill training less than 3 times a week did not result in a significant improvement in walking speed or endurance (Mehrholz et al., 2017). Furthermore, as treadmill gait training is a kind of aerobic exercise, the American Heart Association/American Stroke Association recommend that stroke survivors undergo a structured regime of gait training rehabilitation (Billinger et al., 2014). They recommend that stroke survivors should receive 20- to 60-minute training sessions, depending on patient's physical fitness, at least 3 sessions per week, and a series of a short training sessions may be introduced for better exercise tolerance (Billinger et al., 2014).

The present study provided participants with only up to 20 minutes of enhanced treadmill training once or twice a week, which was consistent with the intensity of rehabilitation therapy that they received from hospital services before participating in the present study. This may be considered suboptimal training intensity. Of 3 participants who had suffered a stroke within 4 months and received training twice a week, 2 participants (case 4 and 7) showed a clinical improvement in walking speed. However, it could not be concluded that enhanced treadmill training can improve gait recovery better or faster than normal treadmill training, because the present study had no control group to compare with.

In clinical practice, it may not be feasible to provide a training frequency of 5 days per week, in keeping with the NICE recommendation for outpatient services. Baer and colleagues conducted a feasibility study of treadmill training to improve mobility among patients with subacute stroke in the UK. They found that the average frequency of treadmill training in the clinical setting was only twice per week. In Thailand, based on the researcher's personal experience of working as a rehabilitation physician in a medical school hospital, the frequency of gait rehabilitation after stroke provided in outpatient care is typically 1 to 3 times a week, due to the availability of services and transportation issues. Hence, a frequency of 3 times a week of 20- to 30-minute enhanced treadmill training sessions may be more clinically feasible and in most cases sufficient for gait recovery.

7.1.6. Clinical implications of enhanced treadmill training

Clinical practice does not usually rely on a single intervention. For gait recovery and rehabilitation after stroke, the treadmill can provide stroke patients with skill-specific training to encourage neuroplasticity, and also aerobic training to improve or maintain cardiopulmonary fitness. In addition, handrail support from a treadmill with body weight support system can prevent falls and reduce the fear of falling which is a common problem among stroke survivors (Schmid et al., 2015, Schmid and Rittman, 2007, Watanabe, 2005). Visual feedback can provide an important element of motor relearning training (Belda-Lois et al., 2011, Huang et al., 2006). Functional electrical stimulation on the impaired lower extremities can help to re-educate muscles and may correct gait deficits such as foot drop and poor knee flexion during swing phase, or knee hyper-extension during early stance (Chae et al., 2008, Knutson et al., 2015). Clinicians have used each of these interventions individually in clinical practice for some time. However, combining these interventions, as in the present study, can potentially lower the total duration of training sessions, reduce the overall workload of therapists required to assist patients' movement, and be more effective than applying them individually.

Although the clinical effects of enhanced treadmill training are yet to be established, the system is ready for use in clinical practice because each intervention in enhanced treadmill training already complies with EU safety, health, and environmental requirements (CE marking). Hardware and software of the gait training system were practical and easy to use for

clinicians. Hence no specialist operating staff or technicians are required, and only a few short training sessions are likely to be sufficient for competently operating the system. In addition, this system does not require a large space or special building infrastructure for equipment installation. However, it might be difficult to use this system in primary care services or community settings due to the requirement to use technologically advanced equipment and skilled staff.

7.2. Conclusion

Findings from the present study may be summarized in the following points:

- The 3D motion capture system can be used effectively as network of sensors for coordinating MFES.
- Toe marker trajectory in the AP direction can be used to divide the gait cycle into five phases: 1DS; SS; 2DS; ESW; and LSW.
- An open-source microprocessor (Arduino) is capable of triggering stimulators at the targeted times.
- The motion-capture based MFES system can be integrated with treadmill training system and with biomechanical visual feedback.
- D-Flow software can be used to develop and operate enhanced treadmill training.
- Sixty-seven training sessions of enhanced treadmill training were carried out in the present study.
- No serious adverse events were reported.

- The motion capture-based MFES system can improve gait kinematics during training.
- Participants and physiotherapists generally have a positive experience of this enhanced treadmill training.
- The therapeutic effect of this enhanced treadmill training on gait recovery remains to be established.

In conclusion, the results of the present study suggest that the combined treatment modality (MFES plus biofeedback) is feasible and acceptable for gait rehabilitation after stroke in clinical practice. Ultimately, future work is necessary to establish the clinical effects of this form of enhanced treadmill training.

Chapter 8: Future Work

8. Future work

8.1. Introduction

The main objective of this study was to determine the feasibility of enhanced treadmill training in clinical practice. Hence, this study was not designed as a randomised clinical trial (RCT) to determine the therapeutic benefits of the developed system on walking abilities; leaving the clinical efficacy of this intervention yet to be proven. This chapter presents a proposal for a further study to establish the clinical effect of the described biofeedback and MFES system on neurological and functional outcomes among stroke survivors that require gait rehabilitation.

The proposed future study design is that of a standard RCT to determine whether there is a clinically relevant difference between two treatment groups in the proportion of participants who exhibit an improvement in ambulation at 6 months after incurring a stroke. An improvement in ambulation level is defined as when participants' walking ability progresses from household to limited community ambulator, or from limited to full community ambulator, depending on the initial severity of motor impairment following stroke. The two proposed treatment groups are: 1) enhanced treadmill training (intervention group) including real-time visual feedback and MFES system developed from this research, and 2) normal treadmill training (control group) that receive treadmill training with the same equipment as the first group without visual feedback and MFES during training. Conventional treatment or home exercise is not explicitly included in this proposal, given that previous studies have identified no significant

differences in outcomes between treadmill and over-ground gait training related to the inclusion of home exercise (Duncan et al., 2011, Baer et al., 2018). The proposed study design aims to quantify whether the effect of combined treatment modalities (real-time visual feedback and MFES) for augmented treadmill training can be established as clinically significant. The hypothesis under examination here is that the intervention group will contain a higher proportion of individuals who manage to achieve their target levels of ambulatory improvement after 6 months of training post stroke.

8.2. Study design

The proposed study is a two-group (1:1), assessor-blinded, multicentre RCT that compares enhanced treadmill training with standard treadmill training. The assessors will be blinded to the treatment group of participants to reduce measurement bias. The participants will be aware of their treatment groups, given the inherent difficulty in blinding them to the procedural aspects of this intervention. Participants will also be informed of the study plan and measurement of objective outcomes. To balance gait impairment at baseline between intervention and control groups, computer-generated stratified randomisation will be used to allocate the participants equally (1:1) based on their severity of gait impairment. Participants will be categorised into two strata based on their functional ambulation category (FAC) for randomisation: ambulators requiring continuous manual contact or continuous/intermittent light touch from a therapist (an FAC level of 1 or 2) and ambulators requiring supervision on level or non-level surfaces (an FAC level of 3 or 4). Because of the moderately large sample size requirement (calculation will be

explained later), a multicentre trial is recommended to efficiently limit the duration of the study. Outcome measures will be assessed before starting training, after 8-weeks of training, and at 6 months after stroke onset. The CONSORT diagram of this proposed study is shown in Figure 8.1.

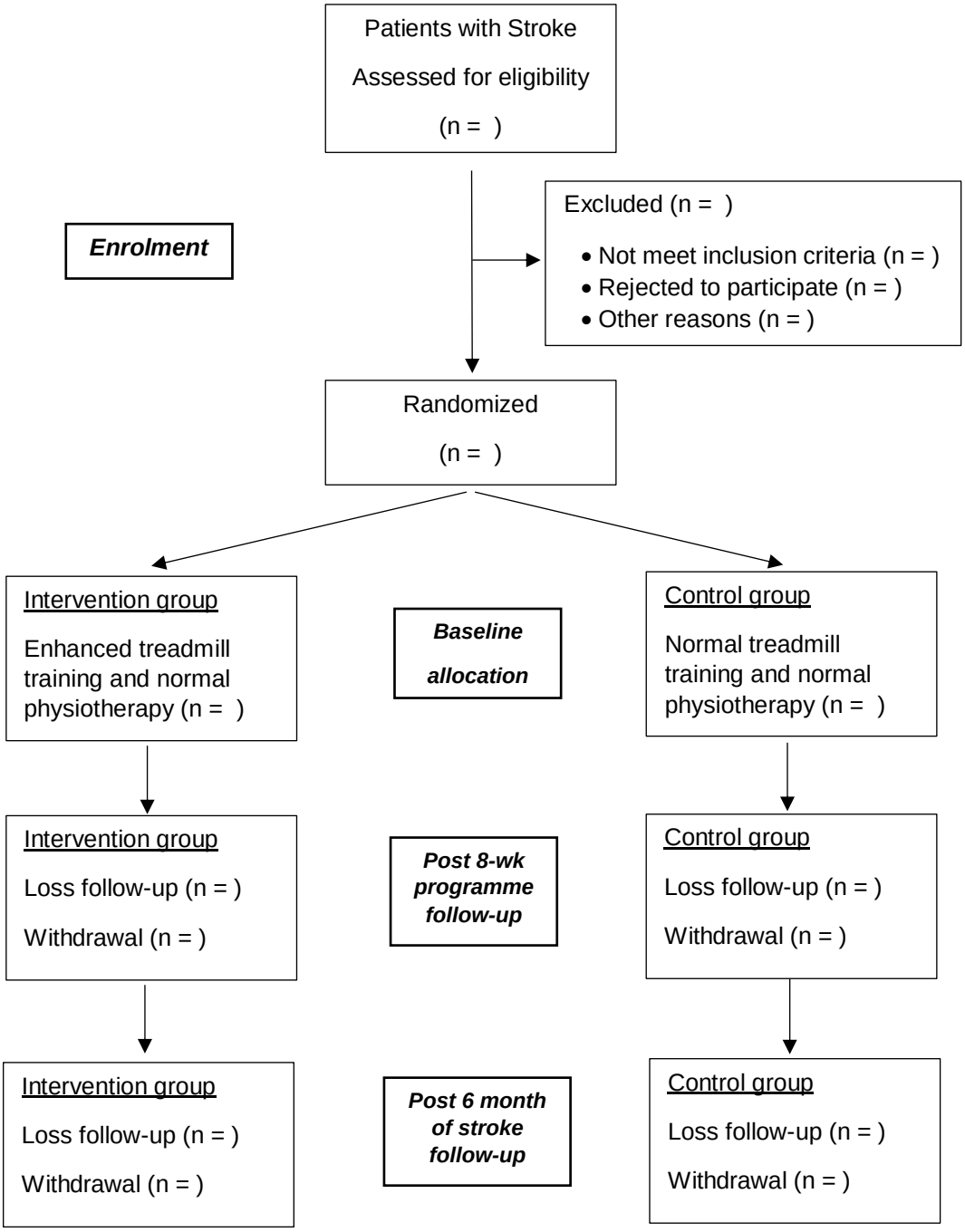


Figure 8.1: CONSORT diagram of the proposed future study

8.3. Participants

Inclusion criteria for the proposed study:

1. an age of 18 years or older
2. first episode of anterior circulation stroke
3. stroke onset within 60 days before study enrolment
4. unilateral hemiplegic stroke
5. remaining weakness in the hemiplegic leg
6. an FAC level of 1 to 4
7. ability to follow a 3-step command
8. medically stable and fit for gait rehabilitation

Exclusion criteria for the proposed study:

1. contracture of hip, knee, or ankle which prevents walking
2. walking difficulty or dependency before the stroke
3. contraindication for using FES such as cardiac pacemaker; skin/vascular problem on stimulation sites
4. visual impairments which may affect visual feedback
5. severe neglect, communication, depression, or cognition problems that may interfere with training
6. body weight over 120 kg or height over 190 cm
7. spasticity resulting in uncontrollable and painful muscle contraction
8. anxiety about walking on a treadmill
9. pain on lower extremities affecting gait training

This study inclusion criteria are designed to select for patients with subacute stroke because results of previous feasibility trials showed that patients with chronic stroke did not improve their walking ability after the training programme (Phongamwong et al., 2019). Additionally, this set of criteria excludes stroke patients with an FAC of 0 (non-functional ambulators) or 5 (totally independent ambulators). This is because a previous study showed that at 1 to 2 months after stroke onset, none of the patients who started with an FAC level of 0 could achieve the community ambulation standard at a 6-month follow-up, whereas all of the patients who had an FAC level of 5 were able to reach this standard (Mehrholz et al., 2007). For exclusion criteria, spasticity resulting in uncontrollable and painful muscle contraction, anxiety about walking on a treadmill, pain on lower extremities will be used based on the findings in this feasibility study.

8.4. Intervention and training programme

All equipment and technology used will be based on the previous study (Phongamwong et al., 2019). Both groups will receive up to 30 minutes of treadmill training followed by 15-minutes of conventional physiotherapy and gait training; for example, strengthening, movement control, balance, weight transfer, stepping, and walking up and down stairs for 3 sessions per week for 8 weeks (24 sessions). This training regimen should be sufficient to achieve the maximal effect of training in both groups (Rose et al., 2017). While walking on the treadmill support from a front or side bar is allowed, and interval training may be necessary if requested. In the intervention group, any ankle-foot orthoses (AFO) will be removed and exchanged for the FES to be

applied on the pretibial instead, while participants in control group will be allowed to use their AFO. However, if patients in the intervention group need to terminate FES support (e.g. case 1 in the feasibility trial who developed increased spasticity), they may resume using their AFO. The MFES system can provide participants with stimulation on four different muscles: pretibial, gastro-soleus, quadriceps and hamstring (Phongamwong et al., 2019). Clinicians will decide which muscles require FES to optimize gait training.

Participants who want to discontinue the assigned intervention due to adverse events, intolerability, poor efficacy, or inconvenience will not automatically be withdrawn from the study. They will instead have the opportunity to continue receiving conventional physiotherapy and gait training until the end of their programme. Home exercises and additional physiotherapy sessions at other hospitals or clinics will also be allowed and monitored. Table 8.1 shows the description of enhanced treadmill gait training based on the TiDIER checklist (Hoffmann et al., 2014).

Table 8.1: Intervention description based on the TiDIER checklist

Item No.	Item	Detail
1	Brief name	Treadmill augmented real-time visual feedback and functional electrical stimulation
2	Why	Combination of these 3 interventions might have synergistic beneficial effect on gait recovery after stroke
3	What: Materials	6-camera motion capture system, Strathclyde Cluster Marker model, N-Mill treadmill, PneuMex body-weight supported system, a large TV, Dual-channel surface electrical stimulators (NeuroTrac® Rehab)
4	What: procedures	Camera and Subject calibration for motion capture system, FES set-up, system operation using D-Flow application
5	Provider	A physiotherapist
6	How	Enhanced treadmill gait training will be delivered individually.
7	Where	Physiotherapy room
8	When and How much	Intensity: comfortable speed, Training duration: up to 30 minutes per session, Training frequency: 3 sessions a week, Programme duration: 8 weeks
9	Tailoring	Increasing training duration every 2 week until reaching 30 minutes. A series of short training can be used if needed. Side view of avatar is the primary view of visual feedback.
10	Modifications	Subjects can use AFO if they cannot tolerate FES. In addition, they can receive conventional or normal treadmill training instead If they want to discontinue assigned intervention,
11	How well: Planned	Each subjects receive at least 20/24 sessions to determine the effect of enhanced treadmill gait training
12	How well: Actual	Attendance rate, training duration, treadmill speed will be recorded and reported.

8.5. Outcome measures

Characteristics of participants to be collected during study enrolment include sex (male or female); age (years); onset of stroke (days); hemiplegic side (right or left); stroke type (large vessel infarction, lacunar infarction, or haemorrhage) and severity; and whether there are any comorbidities (e.g. diabetes, cardiovascular disease, or chronic kidney disease).

The primary outcome measurement of interest is the overall level of improvement in ambulation 6 months after the onset of stroke. Walking speed (10-meter walk test) and endurance (6-minute walk test; 6MWT) will be used to classify participants' ambulation into one of 3 levels: household, limited community, or full community ambulator. In this context, improvement will be defined as a participant increasing their level of ambulation to the next level by the final assessment. The proportion of participants who have achieved an improvement in enhanced training (intervention) and non-enhanced training (control) groups will be compared to determine the overall efficacy of the novel gait rehabilitation system.

Most of the previous studies in walking rehabilitation of stroke patients have used comfortable walking speed (CWS) to define home and community ambulation levels (Duncan et al., 2011, Perry et al., 1995, Schmid et al., 2007, van de Port et al., 2008). However, several studies have argued that walking distance is also an important factor for determining community ambulation level (Fulk et al., 2017, Andrews et al., 2010). In 2017, Fulk and colleagues conducted a diagnostic study to examine factors that could determine home and community walking activity after stroke (Fulk et al.,

2017). They found that both CWS and 6MWT can be used effectively to discriminate between the 3 levels of ambulation. To discriminate between household and community ambulators, CWS ≥ 0.49 m/s has sensitivity of 87%, specificity of 61%, and overall accuracy rate of 76%, whereas 6MWT ≥ 205 m has sensitivity of 71%, specificity of 79%, and overall accuracy rate of 74% (Fulk et al., 2017). To discriminate between limited and full community ambulators, CWS ≥ 0.93 m/s has sensitivity of 60%, specificity of 80%, and overall accuracy rate of 76%, whereas 6MWT ≥ 288 m has sensitivity of 68%, specificity of 77%, and overall accuracy rate of 75% (Fulk et al., 2017).

Hence, in the proposed RCT, the level of ambulators will be defined according to the following metrics:

1. CWS ≥ 0.9 m/s “AND” 6MWT ≥ 300 m as a full community ambulator
2. CWS ≥ 0.5 m/s “AND” 6MWT ≥ 200 m as a limited community ambulator
3. CWS < 0.5 m/s “OR” 6MWT < 200 m as a household ambulator

Moreover, changes in FAC level, Fugl Meyer Assessment for Lower Extremity (FMA-LE), Berg Balance Scale (BBS), and Barthel Index (BI) at the end of the training programme and 6 months after stroke onset will be assessed as secondary outcome measures. Firstly, the FAC level is a clinical gait assessment commonly used to categorise walking ability into 6 classes based on the amount of physical assistance required (Holden et al., 1984). This assessment has been shown to demonstrate excellent test-retest and

interrater reliability, with kappa of 0.95 and 0.91, respectively, and good correlation with distance measured in 6MWT as well as walking speed (Mehrholz et al., 2007). Secondly, the FMA-LE is a validated and reliable index designed to assess the degree of neurological impairment specifically in stroke survivors (Fugl-Meyer et al., 1975). However, only the motor function component of the FMA-LE is recommended for this proposal; measured from a total score ranging from 0 to 34, where lower numbers indicate greater impairment. Next, the BBS is the most commonly used test in post-stroke balance assessment, with excellent validity and reliability (Blum and Korner-Bitensky, 2008). It has a 14-item scale used to measure static and dynamic balance. The total score ranges from 0 to 56 points, where a higher score signifies better balance. Lastly, the BI is one of the most popular scales used to rate the level of competency in various daily living activities including feeding, bathing, grooming, dressing, bowel function, bladder function, toilet use, transfer, mobility, and traversing stairs among patients with neurological conditions including stroke (Hsueh et al., 2002, Kwon et al., 2004, Green et al., 2001). The total BI score ranges from 0 to 100 points, with higher scores reflecting greater ability to function independently.

All participants will receive an assessment of primary and secondary outcome measures before and after their rehabilitation programme, and at 6 months after stroke onset. Table 8.2 presents a summary and scheduled time points of all outcome measures.

Table 8.2: Summary and timing of all outcome measures

Outcome	Pre-training (week 0)	Post-training (week 9)	6 months after stroke onset
Walking speed (m/s)	x	x	x
6MWT (m)	x	x	x
FAC level (1 – 4)	x	x	x
FMA-LE (0 – 34)	x	x	x
BBS (0 – 56)	x	x	x
BI (0 – 100)	x	x	x

The proposed study design recommends that final outcome measurements are taken at 6 months after stroke onset because it has been found that, on average, stroke recovery plateaus approximately 6 months after onset (Kwakkel and Kollen, 2013).

8.6. Sample size calculation

A study with 80% power and a threshold for significance (alpha value) of 0.05 should be able to detect a 20% difference in the proportion of participants who improve their functional ambulation status: e.g. from a household to limited community ambulator, or from a limited to full community ambulator (Duncan et al., 2011). Based on the results of Duncan and colleagues' study, approximately 50% of the participants in the non-enhanced training (control) group are expected to achieve an improvement in their ambulation level (Duncan et al., 2011). The sample size calculation below shows that a

minimum of 182 participants (91 per group) are required to produce the desired statistical power to identify meaningful differences between intervention and control groups.

$$n = \frac{p1\ (1 - p1)\ +\ p2(1 - p2)}{(p1 - p2)^2} \times c$$

(Whitley and Ball, 2002)

where $p1$ = 0.5; $p2$ = 0.7; c for p-value of 0.05 and power of 80% = 7.9

However, a dropout rate of 15% may be assumed, given that this is a longitudinal study design; therefore, a total of 214 participants (107 in each group) are recommended for inclusion in the proposed study.

8.7. Safety

Adverse events may be defined as any undesired signs, symptoms or diseases occurring during the study; including recurrent stroke, myocardial infarction, fracture, pneumonia, muscle soreness/pain persisting for more than 48 hrs, skin irritation or blisters, dizziness, or fainting, falling, and increased spasticity. Adverse events that result in death, are life-threatening, cause a requirement for hospitalization or prolongation of existing hospitalization, or result in persistent or significant disability/incapacity are considered to be serious adverse events and should be reported to the sponsors immediately.

8.8. Analysis plan

This proposal for a future study suggests using intention-to-treat analysis which the results are based on the treatment initially assigned and not on the treatment eventually received to evaluate the effect of treatment assignment.

This approach should be robust to variations in participants' compliance, protocol deviations, or the treatment group to which they are assigned. As a result, this analysis should maintain the balance of prognostic factors among treatment groups initially achieved using the stratified randomization procedure. This should provide an unbiased analysis of treatment effect. In addition, this represents a realistic situation that may occur in clinical practice due to the regular occurrence of non-compliance and protocol deviations.

Data collected from longitudinal studies is frequently incomplete, potentially containing many missing values, as a result of the reasons given above. In a review of 73 articles from top medical journals (BMJ, JAMA, Lancet, and New England Journal of Medicine), Bell and colleagues reported that the most common methods of analysing data with missing values are complete-case analysis (45%), simple imputation (27%), model-based (19%) and multiple imputation (8%) methods (Bell et al., 2014). The proposed study plans to conduct complete case analysis whereby participants with missing outcome measures are excluded, and the last-observation-carried-forward method (single imputation) can be used to replace missing values in the analysis.

Characteristics of participants among the two treatment groups will be compared using a chi-square test or unpaired t-test. The primary outcome measure (i.e. the proportion of participants who succeed in improving their community ambulation level) will be compared between groups using a logistic regression model. Unadjusted data and participants' characteristics-adjusted data analyses should be performed. For the secondary outcome

measures which are continuous variables the mean value across 3 assessments will be analysed using repeated ANOVA to simultaneously examine the overall effects of treatment group (between-subjects factor) and treatment duration (within-subjects factor).

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Appendix 1: Participant Information Sheet

Study title: Enhanced Treadmill Gait Training After Stroke (ENTRES)

Invitation

You are being invited to take part in research which is being undertaken by two PhD students; Karen Chase and Chanwit Phongamwong. Before you decide, it is important that you understand what the study involves and what will be required. We ask that you read this document carefully and take your time about deciding. You may wish to discuss it with your family or friends first. Please ask if anything is not clear or you would like other information. Participation is completely voluntary and confidential. If you choose to participate, nothing which could identify you will be shared outside of the research team involved.

What is the purpose of the study?

The aim of this study is to investigate whether people are happy using the enhanced treadmill training system.

Do you have to take part?

You do not have to take part in this study, whether you take part is entirely up to you. If you decide not to take part it will not affect the standard of your care. If you do decide to take part, you are free to withdraw at any time.

Why have you been invited to take part?

You have been asked to take part because you:

1. Are over 18 years old.
2. Have had a diagnosed stroke.
3. Had your stroke between 1 week and 12 months ago.
4. Are attending Coathill Hospital (NHS Lanarkshire) for stroke rehabilitation which includes gait training.
5. Have weakness on one side of your body (hemiplegia).

6. Are medically stable.

7. Can follow simple, verbal instructions in English, or in another language if an appropriate translator is available.

8. Can provide informed consent.

We will also check the following points to ensure that you are fit and able to use the system.

1. You are not considered by the GP or NHS clinicians to be unsafe to do mild exercise for the duration of time required (about 20 minutes).

2. You do not have tightening of the hip, knee or ankle which prevents walking.

3. You do not have any skin irritation on the leg or foot.

4. You do not have a heart pacemaker.

5. You do not weigh more than 19 stone (120kg) as this is the limit of the equipment.

6. You are able to understand and follow the whole process (assessed by the clinicians responsible for each volunteer).

7. You did not have problems walking before your stroke (e.g. severe arthritis)

What will you do in the project?

Each session will consist of walking on a treadmill with a screen in front of you showing a moving scene, such as a country walk or your own movement. In addition, while you walk, you may either receive a mild electric stimulation to your weak leg muscles (which will be kept within comfortable limits), or a plastic splint covering your foot and ankle. Which of these you receive will be decided by the research team with advice from the physiotherapist, before you begin, however, if you are not suitable for one (for example skin problems on your foot that prevent the use of the splint) you will be offered the alternative. Small areas of leg hair may have to be shaved by the researcher to attach the sensors and electrodes. Throughout the session,

your movement will be recorded using special cameras. This will require markers to be worn on your legs and lower back during the sessions. We will ask you to wear comfortable shorts for each of the sessions (which we will provide if you don't have any), we will also ask you to bring the shoes you normally wear for walking so that they can be used during all the walking activities.

We will ask you to attend Coathill hospital 3 times a week for 8 weeks, with a follow-up assessment 3 months later. If you require transport, this can be arranged through the hospital. Each rehabilitation session will take around an hour, with up to 20 minutes of treadmill walking in place of your normal walking training. We will also ask you some questions about what you thought of the session. All sessions will be supervised by the NHS physiotherapists, and a safety harness will be worn to prevent falls. If you lose the ability to consent during the study, we will withdraw you from the study, but your information and all data collected up to that point will be kept.

Along with these training sessions we will carry out some simple tests of your walking ability on the treadmill, indoors and outdoors. These will be carried out before your first session, then during weeks five and eight and finally a month after you have completed the treadmill training. The outdoor walking assessment will last for approximately 5 minutes in which you will walk around a short course in the area immediately outside the physiotherapy gym at Coathill hospital. You will be free to use your normal mobility aid during this walk and one of the research team will accompany you. We will also ask you to wear a small sensor on your thigh for 48 hours which will record the time you spend being active at home and ask you some questions about your walking habits.

We will record details on your stroke (type, severity, location, onset of stroke attack and rehabilitation), cognition function, and co-morbidities from your medical record. We will also record details of your height, weight, and age. Also, your GP will be informed that you are participated in the study.

What are the potential risks to you in taking part?

The possible risks are:

1. You will receive up to 20 minutes of continuous walking and you may feel mild muscle and joint discomfort during and after walking. You will be allowed to rest during the session, if required.
   If after a rest you are unable to continue, the session will be stopped, and you will be taken home after being checked by the clinical physiotherapist.
2. You will walk on the treadmill so there may be a risk of falling. To prevent an incident, a safety harness will be worn. There is also an emergency stop button on the treadmill.
3. You will receive a plastic splint or electrical stimulation. Both treatments may cause mild skin irritation, which we will check for.

What are the possible benefits of taking part?

Repetitive walking on a treadmill has been shown to improve walking ability, using our enhanced system may further improve your walking in the community. The outcomes of this study will help us to better understand if this system can be used with people who have had a stroke and ways of improving the experience.

What happens to the information in the project?

All data collected from this investigation will be treated confidentially. Your personal details will not be included in the stored data. In the short term, data will be stored on an encrypted and password secured hard-drive. This information will then be transferred to the University. At all times, only the named investigators will have access to this information.

The anonymised results of this study may be submitted for presentation at scientific and clinical conferences and may be submitted for scientific and clinical peer-reviewed publication. Moreover, the results from this study will be included in the research students' PhD theses. Any research publications or presentations resulting from this work will only discuss group results and

will not report on each participant individually. At no time will any personal or identifiable information be released.

What happens next?

If you are happy to participate in this study please complete and sign the consent form on the next page at your next meeting with the person who gave you this sheet. If you do not wish to participate now you just need to tell us and accept our thanks for taking the time to read this information. If you have any questions/concerns, before, during or after the study then please contact the researchers using the details below. The University of Strathclyde is registered with the Information Commissioner's Office who implements the Data Protection Act 1998. All personal data on participants will be processed in accordance with the provisions of the Data Protection Act 1998.

Who is organising and funding the research?

This study is being carried out by Dr. Andy Kerr (Chief Investigator) in conjunction with Professor Philip Rowe and two PhD students (Karen Chase and Chanwit Phongamwong) who are all based at the University of Strathclyde. The study is sponsored by the University of Strathclyde, United Kingdom.

The study has been reviewed by an NHS ethics committee (West of Scotland REC 5) who have decided that there are no unacceptable risks and the study may go ahead.

Contact details

Chief Investigator: Dr Andy Kerr. email: a.kerr@strath.ac.uk

PhD students: Karen Chase, email: karen.chase@strath.ac.uk Chanwit Phongamwong, email: chanwit.phongamwong@strath.ac.uk

Appendix 2: Consent form

Title of Project: Enhanced Treadmill Gait Training with Lower Limb Support After Stroke (ENTRES)

Name of Researcher: Please Initial Box

1. I confirm that I have read the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant section of my medical notes and data collect during the study, will be looked at by individuals from research team where it is relevant to my taking part in this research. I give my permission for these individuals to have access to my record. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree for photo to be taken and anonymised ☐

6. I agree to take part in the above study. ☐

……..... ……..... …….....

Name of Patient Date Signature

……..... ……..... …….....

Name of Person Taking consent Date Signature

Appendix 3: Rivermead Mobility Index

The Rivermead Mobility Index

Name: _____

Topic and Question:							
Day							
Month							
Year							
Turning over in bed: Do you turn over from your back to your side without help?							
Lying to sitting: From lying in bed, do you get up to sit on the edge of the bed on your own?							
Sitting balance: Do you sit on the edge of the bed without holding on for 10 seconds?							
Sitting to standing: Do you stand up from any chair in less than 15 seconds and stand there for 15 seconds, using hands and/or an aid if necessary?							
Standing unsupported: (Ask to stand) Observe standing for 10 seconds without any aid							
Transfer: Do you manage to move from bed to chair and back without any help?							
Walking inside: (with an aid if necessary): Do you walk 10 meters, with an aid if necessary, but with no standby help?							
Stairs: Do you manage a flight of stairs without help?							
Walking outside: (even ground): Do you walk around outside, on pavements, without help?							
Walking inside: (with no aid): Do you walk 10 meters inside, with no caliper, splint, or other aid (including furniture or walls) without help?							
Picking up off floor: Do you manage to walk five meters, pick something up from the floor, and then walk back without help?							
Walking outside: (uneven ground): Do you walk over uneven ground (grass, gravel, snow, ice etc) without help?							
Bathing: Do you get into/out of a bath or shower and to wash yourself unsupervised and without help?							
Up and down four steps: Do you manage to go up and down four steps with no rail, but using an aid if necessary?							
Running: Do you run 10 meters without limping in four seconds (fast walk, not limping, is acceptable)?							
Total							

Appendix 4: Participants' feedback form

For the following statements answer with **Strongly Agree, Agree, Neutral, Disagree or Strongly Disagree,** and comment if you wish.

1. The amount of set up time before each session was acceptable. _____

2. Walking with all of the equipment set up was not too cumbersome. _____

3. The treadmill is comfortable to walk on, and easy to get used to. _____

4. Walking with the harness was comfortable and made me feel safe. _____

5. The sessions as a whole were enjoyable. _____

6. The instructions given during the sessions were easy to understand and carry out. _____

7. I still feel motivated to continue with this training program. _____

8. I would recommend treadmill training such as this to other stroke survivors. _____

Further comments on the system, and possible ways to improve it:

Appendix 5: Physiotherapists' feedback form

For the following statements answer with **Strongly Agree, Agree, Neutral, Disagree or Strongly Disagree,** and comment if you wish.

1. The amount of set up time before each session was acceptable. _____

2. Walking with all of the equipment set up was not too cumbersome for this participant. _____

3. The enhanced treadmill system was user friendly. _____

4. Any inconvenience during the training sessions was unimportant. _____

5. This enhanced treadmill training program increases motivation in participants. _____

6. I would like to continue using the enhanced treadmill system after the study ends. _____

7. I would recommend treadmill training such as this to other therapists working in gait rehabilitation. _____

Further comments on the system, and possible ways to improve it:

Appendix 6: Arduino sketch to control electrical stimulators

```
const int fes1 = 6;     // FES1 for pre-tibial

const int fes2 = 4;     // FES2 for gastro-soleus

const int fes3 = 2;     // FES3 for hamstring

const int fes4 = 3;     // FES4 for quadriceps


int incomingKey;      // a variable to read incoming serial data (1=1DLS;
                          2=SLS; 3=2DLS; 4=ESW; 5=LSW)

int last_incomingKey;

int incomingKey2;      // a variable to read incoming serial line feed and
carridge return

int last_incomingKey2;


int writeState1; // digital write HIGH OR LOW

int last_writeState1;

int writeState2;

int last_writeState2;

int writeState3;

int last_writeState3;

int writeState4;

int last_writeState4;


int fesState1 = 0; // 0 = non-stim, 1 = stim

int fesState2 = 0;

int fesState3 = 0;

int fesState4 = 0;


void setup() {

 // initialize serial communication:
```

```
 Serial.begin(57600);
 // initialize the LED pin as an output:
 pinMode(fes1, OUTPUT);
 pinMode(fes2, OUTPUT);
 pinMode(fes3, OUTPUT);
 pinMode(fes4, OUTPUT);
 Wire.begin();
  seg.init();
  seg.printInt(0);
}

void loop() {
 // see if there's incoming serial data:
 if (Serial.available() > 0) {
   // read the oldest byte in the serial buffer:
   incomingKey2 = Serial.read();
if (incomingKey2>47){
  if (incomingKey2<54) {
    incomingKey= incomingKey2;
    Serial.println(incomingKey-48);
    seg.printInt(incomingKey-48);
  }
}
 }
delay(5);
if (incomingKey != '0'){
if  (incomingKey != last_incomingKey) {
```

```
if (incomingKey == '1' && last_incomingKey == '5'){
  if (fesState1 == 1) {writeState1 = HIGH;} else {writeState1 = LOW;}
  writeState2 = LOW;
  writeState3 = LOW;
  writeState4 = LOW;
  }
if (incomingKey == '2' && last_incomingKey == '1'){
  writeState1 = LOW;
  if (fesState2 == 0) {writeState2 = HIGH;} else {writeState2 = LOW;}
  if (fesState3 == 1) {writeState3 = HIGH;} else {writeState3 = LOW;}
  if (fesState4 == 1) {writeState4 = HIGH;} else {writeState4 = LOW;}
  }
 if (incomingKey == '3' && last_incomingKey == '2'){
  if (fesState1 == 0) {writeState1 = HIGH;} else {writeState1 = LOW;}
  writeState2 = LOW;
  writeState3 = LOW;
  writeState4 = LOW;
  }
 if (incomingKey == '4' && last_incomingKey == '3'){
  writeState1 = LOW;
  if (fesState2 == 1) {writeState2 = HIGH;} else {writeState2 = LOW;}
  writeState3 = LOW;
  writeState4 = LOW;
  }
 if (incomingKey == '5' && last_incomingKey == '4'){
  writeState1 = LOW;
  if (fesState2 == 1) {writeState2 = HIGH;} else {writeState2 = LOW;}
  if (fesState3 == 0) {writeState3 = HIGH;} else {writeState3 = LOW;}
  if (fesState4 == 0) {writeState4 = HIGH;} else {writeState4 = LOW;}
```

```
    }
}
if (last_incomingKey == incomingKey){
  writeState1 = LOW;
  writeState2 = LOW;
  writeState3 = LOW;
  writeState4 = LOW;
  }
}

if (incomingKey == '0'){
  if (fesState1 == 1) {writeState1 = HIGH;} else {writeState1 = LOW;}
  if (fesState2 == 1) {writeState2 = HIGH;} else {writeState2 = LOW;}
  if (fesState3 == 1) {writeState3 = HIGH;} else {writeState3 = LOW;}
  if (fesState4 == 1) {writeState4 = HIGH;} else {writeState4 = LOW;}
}

last_incomingKey = incomingKey; // save current state as last state for next
loop

if (writeState1 == HIGH && last_writeState1 == LOW){
    fesState1 = 1 - fesState1;  // changing stage when LOW --> HIGH
   }
   last_writeState1 = writeState1;  // save current state as last state for next
loop

if (writeState2 == HIGH && last_writeState2 == LOW){
    fesState2 = 1 - fesState2;
   }
   last_writeState2 = writeState2;
```

```
if (writeState3 == HIGH && last_writeState3 == LOW){
    fesState3 = 1 - fesState3;
   }
   last_writeState3 = writeState3;

if (writeState4 == HIGH && last_writeState4 == LOW){
    fesState4 = 1 - fesState4;
   }
   last_writeState4 = writeState4;

   digitalWrite(fes1, writeState1);
   digitalWrite(fes2, writeState2);
   digitalWrite(fes3, writeState3);
   digitalWrite(fes4, writeState4);
}
```

Appendix 7: Confirmation of ethical approval

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 8SJ

Date 04 January 2018

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

Dr Andrew Kerr
Department of Biomedical Engineering
University of Strathclyde
859, Graham Hills Building
40 George Street, Glasgow
G1 1QE

Dear Dr Kerr

Study title: **The Design and Testing of an Enhanced, Treadmill Based Training Program for Post-Stroke Gait Rehabilitation, through Co-Production with Users; Incorporating Visual Flow, Ankle Foot Orthosis and Functional Electrical Stimulation.**
REC reference: **17/WS/0245**
IRAS project ID: **236335**

Thank you for responding to the Committee's request for further information on the above research by submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

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 opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

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

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 NHS permission for research is available in the Integrated Research Application System, 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 within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

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, 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).

Approved documents

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

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Employers liability]		15 July 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Professional Indemnity]		15 July 2017
GP/consultant information sheets or letters [Letter to GP]	1	10 October 2017
IRAS Application Form [IRAS_Form_09112017]		09 November 2017
Letter from sponsor [Insurance letter]		09 November 2017
Non-validated questionnaire [Therapists' Questionnaire]	1	10 October 2017
Non-validated questionnaire [Feedback form]	1	10 October 2017
Non-validated questionnaire [Session form]	1	10 October 2017
Non-validated questionnaire [Demographic information form]	1	10 October 2017
Other [Confirmation email re A77+A78]		16 November 2017
Participant consent form [Consent form version 2]	2	19 December 2017
Participant information sheet (PIS)	2	19 December 2017
Research protocol or project proposal [Protocol]	1	09 October 2017
Summary CV for Chief Investigator (CI) [CV for chief investigator]		09 January 2017
Summary CV for student [Karen Chase CV]		05 October 2017
Summary CV for student [CV Chanwit]		03 October 2017
Summary CV for supervisor (student research) [CV Professor Rowe]	1	15 November 2017
Validated questionnaire [community walking habits]		
Validated questionnaire [Mobility index]		
Validated questionnaire [Cognitive assessment]	7.1	

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.

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/

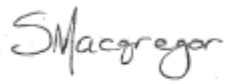
HRA Training

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

17/WS/0245	**Please quote this number on all correspondence**

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

Yours sincerely



for
Canon Matt McManus
Vice-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. Louise McKean, University of Strathclyde
Mr Raymond Hamill, NHS Lanarkshire

West of Scotland REC 5

Attendance at Sub-Committee of the REC meeting

Committee Members:

Name	*Profession*	*Present*	*Notes*
Professor Doreen McClurg	Reader	Yes	
Canon Matt McManus	Parish Priest (Vice-Chair)	Yes	
Mrs June Russell	Retired (Research Chemist)	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Sharon Macgregor	REC Manager

Appendix 8: Confirmation of R&D approval

NHS Lanarkshire

Dr Andrew Kerr
Lecturer
University of Strathclyde
Department of Biomedical Engineering
859, Graham Hills Building
40 George Street
Glasgow
G1 1QE

R&D Department
Corporate Services Building
Monklands Hospital
Monkscourt Avenue
AIRDRIE
ML6 0JS

Date 3rd May 2018
Enquiries to Elizabeth McGonigal,
Senior R&D Facilitator
Direct Line 01236 712459
Email elizabeth.mcgonigal@lanarkshire.scot.nhs.uk

Dear Dr Kerr

Project title: The Design and Testing of an Enhanced, Treadmill Based Training Program for Post-Stroke Gait Rehabilitation, through Co-Production with Users; Incorporating Visual Flow, Ankle Foot Orthosis and Functional Electrical Stimulation

R&D ID: L16008

NRS ID Number: NRS18/236335

I am writing to you as Chief Investigator of the above study to advise that R&D Management approval has been granted for the conduct of your study within NHS Lanarkshire as detailed below:

NAME	TITLE	ROLE	NHSL SITE TO WHICH APPROVAL APPLIES
Dr Mark Barber	Consultant Geriatrician	Principal Investigator	Coathill Hospital Monklands Hospital

For the study to be carried out you are subject to the following conditions:

Conditions

- You are required to comply with Good Clinical Practice, Ethics Guidelines, Health & Safety Act 1999 and the Data Protection Act 1998.

- The research is carried out in accordance with the Scottish Executive's Research Governance Framework for Health and Community Care (copy available via the Chief Scientist Office website: http://www.cso.scot.nhs.uk/ or the Research & Development Intranet site: http://firstport2/staff-support/research-and-development/default.aspx
- You must ensure that all confidential information is maintained in secure storage. You are further obligated under this agreement to report to the NHS Lanarkshire Data Protection Office and the Research & Development Office infringements, either by accident or otherwise, which constitutes a breach of confidentiality.
- Clinical trial agreements (if applicable), or any other agreements in relation to the study, have been signed off by all relevant signatories.
- You must contact the Lead Nation Coordinating Centre if/when the project is subject to any minor or substantial amendments so that these can be appropriately assessed, and approved, where necessary.
- You notify the R&D Department if any additional researchers become involved in the project within NHS Lanarkshire
- You notify the R&D Department when you have completed your research, or if you decide to terminate it prematurely.
- You must send brief annual reports followed by a final report and summary to the R&D office in hard copy and electronic formats as well as any publications.
- If the research involves any investigators who are not employed by NHS Lanarkshire, but who will be dealing with NHS Lanarkshire patients, there may be a requirement for an SCRO check and occupational health assessment. If this is the case then please contact the R&D Department to make arrangements for this to be undertaken and an honorary contract issued.

I trust these conditions are acceptable to you.

Yours sincerely,

Raymond Hamill – Senior R&D Manager

cc.

NAME	TITLE	CONTACT ADDRESS	ROLE
Dr Mark Barber	Consultant Geriatrician	Mark.barber@nhs.net	Principal Investigator

Ms. Louise McKean		ethics@strath.ac.uk	Sponsor Contact
Professor Philip Rowe	Professor of Rehabilitation Science	philip.rowe@strath.ac.uk	Other
Derek Esson Lyndsey Forsyth	Clinical Trials Nurse Clinical Trials Nurse	Derek.Esson@lanarkshire.scot.nhs.uk Lyndsey.Forsyth@lanarkshire.scot.nhs.uk	Named Contact